Under-nutrition in vascular surgery patients: Development of a malnutrition screening tool to identify those at risk.

by

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Abbreviations

25(OH)D	25-hydroxyvitamin D
AA	Aortic Aneurysmal Disease
ALST	Appendicular lean skeletal tissue
aOR	Adjusted Odds Ratio
APD	Accredited Practising Dietitian
AUC	Area under the curve
AWMA	Australian Wound Management Association
BIS	Bioelectrical impedance spectroscopy
BMI	Body Mass Index
CALHN	Central Adelaide Local Health Network
CAMA	Corrected arm muscle area
CEAP	Clinical Etiological Anatomical Pathophysiological (Classification system for chronic venous disorders)
CHD	Coronary Heart Disease
CHSA	Country Health South Australia
CI	Confidence Interval
CLI	Critical Limb Ischaemia
CRP	C-Reactive Protein
CT	Computed tomography
CVD	Cardiovascular Disease
CVI	Chronic Venous Insufficiency
DEXA	Dual energy x-ray absorptiometry
DFD	Diabetic Foot Disease
DFU	Diabetic Foot Ulcer
DM	Diabetes Mellitus
DoH	Department of Health
EFA	Exploratory Factor Analysis
EQ5D-5L	EuroQoL 5-dimension quality of life questionnaire
EQVAS	Vertical visual analogue scale component of the EQ5D-5L
EVAR	Endovascular aneurysmal repair
EWGSOP	European working group on sarcopenia in older people
FFM	Fat free mass
FFMI	Fat-free mass index
FM	Fat mass
GLM	Generalised Linear Modelling
GNRI	Geriatric Nutrition Risk Indicator
HR	Hazard ratio
HRQoL	Health related quality of life
IC	Intermittent Claudication
IQR	Interquartile Range
LEA	Lower extremity amputation
LOS	Length of stay
MBS	Medicare Benefits Scheme
MNA	Mini Nutritional Assessment

MNA-SF	Mini Nutritional Assessment-Short Form
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NALHN	Northern Adelaide Local Health Network
NHMRC	National Health and Medical Research Council
NO	Nitric Oxide
NPV	Negative Predictive Value
NRS-2002	Nutrition Risk Screen-2002
Oacis	Open architecture clinical information system
OR	Odds ratio
PAD	Peripheral Arterial Disease
PBS	Pharmaceutical Benefits Scheme
PG-SGA	Patient-Generated Subjective Global Assessment
PMA	Psoas Muscle Area
PPV	Positive Predictive Value
QOL	Quality of Life
ROC	Receiver Operating Characteristics
RR	Risk ratio
SAHREC	Southern Adelaide Clinical Human Research Ethics Committee
SALHN	Southern Adelaide Local Health Network
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SGA	Subjective Global Assessment
SMA	Skeletal Muscle Area
SMI	Skeletal Muscle Index
SMM	Skeletal Muscle Mass
Sn	Sensitivity
Sp	Specificity
SPPB	Short physical performance battery
SSI	Surgical site infection
T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischaemic Attack
TPA	Total psoas muscle area
TPAI	Total psoas muscle area index
VLU	Venous leg ulcer
VMST	Vascular Malnutrition Screening Tool

Thesis Summary

The prevalence of vascular disease and the requirement for vascular surgery services in increasing. Concerning rates of undernutrition and associated poorer outcomes in this patient population are being reported in the literature, hence a comprehensive review of the literature was conducted and is presented in **chapter 2**. Results of the review showed that undernutrition is prevalent in vascular patients which is linked to poorer outcomes. Micronutrient deficits are prevalent which is of great concern when many have key roles to play in vascular health and wound healing. Identification of undernutrition is a challenge with the literature review highlighting that there are no validated screening tools for vascular surgery patients.

An observational study was conducted with the aims to (1) investigate the prevalence of undernutrition and the impact on patient outcomes in a heterogenous sample of vascular surgery inpatients and (2) to examine the validity of commonly used and researched screening tools in this patient group.

There was a high prevalence of undernutrition in the study sample, in particular micronutrient deficits with >44% of participants having suboptimal zinc, iron, vitamin D or vitamin C status (**chapter 4**). Overall, 75% were deemed undernourished which was associated with several poorer outcomes on discharge. Four commonly used screening tools (MST, MUST, MNA-SF and NRS-2002) and a nutrition assessment tool (PG-SGA) were not valid in the study sample (**chapter 5**) which lead to the conclusion that a screening tool specific for vascular surgery patients was warranted.

Exploratory Factor Analysis and k-fold cross validation techniques were utilised to develop a malnutrition screening tool (VMST) specifically for use within the vascular surgery population (**chapter 6**). The new tool has good sensitivity (87%), fair diagnostic accuracy and consistency

which were all improved compared to the tools that were examined. The VMST also has improved discriminant and convergent validity whilst being predictive of a number of discharge outcomes.

Chapter 7 explores the health care costs and clinical outcomes of the study participants at 12-months post discharge, with results showing significant health care spending that varied across the types of vascular disease. Participants deemed 'at risk' of malnutrition on the VMST were more likely to have experienced poorer outcomes and have incurred higher costs.

This research is the first to conduct a comprehensive assessment of nutritional status in a heterogenous sample of vascular surgery patients and to examine the validity of malnutrition screening tools in identifying those at risk. The VMST is the first screening tool to be developed using robust methodology that has good validity and predictive ability both at discharge and 12-months. This research is also the first to explore health care costs and whether a malnutrition screening tool can predict higher health care costs. Future research will focus on translation of this research into clinical practice to determine whether the implementation of the screening tool would work in the environment for which it was developed and to determine what conditions or factors impact on whether implementation is successful or unsuccessful.

Summary of Publications Contributing to this Thesis Including Author Contributions

1. **Thomas, J.,** Delaney, C., Suen, J., Miller, M. (2019) Nutritional status of patients admitted to a metropolitan tertiary care vascular surgery unit. *Asia Pacific Journal of Clinical Nutrition*, 28(1) p 64-70.

   This study was conceived by JT, MM and CD. JT and JS were responsible for data collection and JT was responsible for the analyses. JT drafted the initial manuscript and MM, JS and CD provided critical review and feedback. All authors read and approved the final manuscript.

2. **Thomas, J.,** Kaambwa, B., Delaney, C., Miller, M. (2019) An evaluation of the validity of nutrition screening and assessment tools in patients admitted to a vascular surgery unit. British Journal of Nutrition, 122(6) p689-697.

   This study was conceived by JT, MM, BK and CD. JT was responsible for the data collection and data analysis and drafted the initial manuscript. MM, BK and CD provided critical review and feedback. All authors read and approved the final manuscript.

Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text. An editing service was not employed in the preparation of this thesis.

Disclaimer

When reference to research is made using 'I' the research was undertaken by myself as a component of this PhD under the supervision of Professor Michelle Miller, Associate Professor Billingsley Kaambwa and Dr Christopher Delaney.

Signed:

Jolene Thomas

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Chapter 1 An overview of Vascular Surgery and Malnutrition Screening – what is it and why is it a concern?

Vascular Surgery is a surgical specialty area in which diseases of the vascular system, or arteries and veins, are managed by medical therapy, minimally invasive catheter procedures and surgical reconstruction. Several specific conditions are managed under the vascular surgery specialty, however in the present thesis, the conditions of focus are occlusive disease encompassing peripheral arterial disease (PAD, encompassing aorto-iliac and infra-inguinal disease) and cerebrovascular disease (carotid and vertebral arterial disease), aneurysmal disease, venous disease and diabetic foot infection, with other conditions grouped together under the term of 'other vascular conditions'.

1.1 Occlusive disease

While occlusive vascular disease refers to the involvement of all blood vessels, including coronary arteries, vascular surgery is focussed on the assessment and management of the peripheral and extra-cranial cerebral vasculature. While occlusive disease can include vasculitis and aneurysmal disease, which will be discussed later in this chapter, the focus in occlusive disease is atherosclerotic disease.

Atherosclerosis is the accumulation of fat- and cholesterol-containing plaque on the inside of artery walls, which over time leads to narrowing, and hardening of the blood vessels (1).

Inflammation is an important component of atherosclerosis initiation and progression with increased inflammatory markers such as C-reactive protein, fibrinogen and plasma homocysteine being implicated as important risk factors (2). The mechanisms of action

include increased adverse endothelial and smooth muscle function and remodelling, platelet dysfunction and increased vascular inflammation (1, 2).

1.1.1 Peripheral Arterial disease

Peripheral arterial disease (PAD) is the obstruction of large arteries as a result of atherosclerosis resulting in reduced blood flow and oxygenation of the muscles which leads to symptoms and consequences of claudication. PAD can range in severity from asymptomatic, progressing to intermittent claudication (muscle pain) with walking, critical limb ischaemia (CLI) with pain at rest and in severe cases it can result in ulceration, gangrene and tissue loss (amputation) (3).

Clinical Features and classification

A large proportion (20-50%) of individuals with PAD can be asymptomatic, despite the National Health and Nutritional Examination Survey (NHANES) findings that 15% of men and 5% of women with asymptomatic PAD had 50% or greater artery stenosis during autopsy (4). Evidence is also available to suggest that progression of PAD is similar regardless of whether the individual is symptomatic or not and that 5-year outcomes, in particular limb morbidity, cardiovascular morbidity and mortality are similar to those observed in individuals with claudication which accounts for a third of individuals with PAD (4). At the extreme end of the PAD spectrum is CLI, accounting for 1-3% of the PAD population which presents with rest pain and/or tissue loss. Outcomes for CLI patients are poor, with approximately 25% mortality at one-year and a 30% amputation rate (4).

Several categorisation systems exist for PAD however the system used in this study and routinely in the clinical care of PAD patients is the Rutherford Classification (3). The Rutherford Classification is similar to its predecessor the Fontaine Classification, a four-

category classification based on clinical symptoms, however it includes both clinical symptoms and objective diagnostic criteria (5). Table 1 displays the Rutherford's classification which is utilised and referred to throughout this thesis.

Table 1: Rutherford's Classification of Peripheral Vascular Disease

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic – no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperaemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise >50mmHg but at least 20mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise <50mmHg
II	4	Ischaemic rest pain	Resting AP <40mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP , 30mmHg
III	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischaemia	Resting AP<60mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP<40mmHg
	6	Major tissue loss – extending above the TM level, functional foot no longer salvageable	Same as category 5

AP: Ankle pressure, PVR: pulse volume recording, TM: transmetatarsal, TP: toe pressure

Risk factors for PAD

The cause of atherosclerosis and PAD is multifactorial, with both modifiable and non-modifiable risk factors implicated in the initiation and progression of the disease. Non-modifiable risk factors include Increasing age and being of male gender with the male: female ratio of PAD overall being reported as 2:1, and 3:1 for CLI specifically (6). Ethnicity also plays a role, with results from the NHANES study showing African Americans are almost three times more likely (OR 2.83 (95%CI 1.48-5.42) to develop PAD compared to Caucasian counterparts (7). In Australia, recent research found that Indigenous Australians presented with PAD at a younger age and had an almost 5-fold greater risk of cardiovascular disease (CVD) events (adjusted hazard ratio 4.72 [95% confidence intervals 1.41-15.78], p=0.012)

compared to non-indigenous Australians (8). The variations in PAD based on ethnicity supports the evidence suggesting multi-gene involvement in PAD development and progression (9).

Smoking is the most powerful modifiable independent risk factor for PAD with a four-fold increase in risk of PAD amongst smokers observed in NHANES (7). While smoking rates have decreased, there has been a concomitant rise in the prevalence of other risk factors (10), which has provided for an overall steady increase in PAD and PAD intervention over recent years (11).

Diabetes is an important risk factor for PAD and progression of PAD is more rapid in those with diabetes with a 5-10 times greater likelihood of major amputation compared to patients without diabetes (6). A meta-analysis in 2004 of 13 studies revealed a 26% increase in risk of PAD development with every 1% increase in glycated haemoglobin (7), while Greg et al (12) found a significantly higher prevalence of PAD in adults with diagnosed and un-diagnosed type 2 diabetes mellitus (T2DM) compared to those without diabetes. Data from the Framingham Heart Study also implicated hypertension and hyperlipidaemia as risk factors for developing PAD (13). It was found that a blood pressure of greater than 160/95mmHg resulted in a 2.5 times increased risk of developing intermittent claudication (IC) (Rutherford's stages 1-3) in men and 4 times increased risk in women. A fasting cholesterol level of >7mmol/L resulted in double the risk of claudication (13).

Burden of Disease

In Australia, PAD is an increasing health problem affecting approximately 1 in 8 of the elderly population, affecting men more than women (10). While there is no national data available for the prevalence of PAD in Australia studies have indicated a prevalence of 10.3-

16% (14, 15). Internationally, it has been cited that worldwide prevalence is estimated to be 10%, rising to 15-20% in those aged 70 years and above with approximately 27 million people affected in Europe and North America (6). Prevalence in the NHANES was 4.3%, equating to approximately 5 million people in the United States of America (USA) in 2000 (7). The Global Burden of Disease Study 2013 reported that PAD was responsible for over 40,000 deaths in 2013, a 155% increase from 1990 (2). In Australia there were 25,796 hospitalisations for PVD in 2007-08, with an average length of stay being 10.8 days. Five percent resulted in death which was reduced compared to 6.4% in 1993-94. PVD was the cause of 2160, or 1.6% of all deaths in Australian in 2007 (16).

Physical and psychological impact of PAD

The impact of PAD on the individual is significant, particularly as the disease progresses and symptoms worsen. Reduced exercise tolerance, functional impairment (17, 18), and poorer psychological/mental health (19, 20) have all been linked with PAD. Evidence is available indicating there is a link between PAD and the development of depression, however a causal link is unclear (19-21). Studies that have investigated quality of life (QoL) in PAD patients have found significantly lower SF-36 scores compared to population norms predominantly due to the functional limitations caused by IC (22-24). In addition to health-related burden, a study was located examining work productivity in PAD patients. Marrett et al (25) conducted a study in approximately 1500 PAD patients in the USA and Europe to investigate the burden of PAD in Europe and the USA as the authors recognised that previous studies had failed to control for demographics. The results of the survey found a significantly higher proportion of absenteeism (percentage of work missed over past 7 days: 12.08 ±27.68% vs 3.65±15.16), presenteeism (percentage of impairment experienced at work: 30.05±27.42%

vs 13.77±21.30%) and overall work productivity lost (36.63±33.33% vs 16.26±24.73%) compared to those age-matched individuals without PAD. Results were similar in both Europe and USA.

1.1.2 Cerebrovascular Disease

Occlusive disease can also encompass stenosis or narrowing of the extra-cranial carotid and vertebral arteries leading to cerebrovascular disease. Common clinical manifestations include transient ischaemic attack (TIA), stroke and amaurosis fugax (transient loss of vision in one or both eyes) (26). Like PAD, cerebrovascular disease can also be asymptomatic.

Clinical Features and management.

Clinical features of cerebrovascular disease vary depending on which arteries are affected. Carotid stenosis is usually asymptomatic until a clinical manifestation occurs such as a TIA or stroke. Both are characterised by symptoms including weakness or numbness, communication difficulties, changes in vision through to loss of consciousness depending on the site and severity of the brain ischaemia (26). Vertebral artery disease can include additional symptoms such as vertigo and tinnitus (26).

Management of cerebrovascular disease is multifactorial, including medication and lifestyle changes to address the atherosclerosis through to vascular interventions such as carotid endarterectomy, angioplasty and stenting. Vascular interventions are performed to either remove the atherosclerotic plaque (atheroma) as occurs in an endarterectomy, or to widen arteries to restore blood flow as occurs in angioplasty and stenting (26).

Risk factors

Risk factors for cerebrovascular disease are like those for PAD. Modifiable risk factors include smoking, inadequate physical activity and suboptimal dietary practices, along with excessive alcohol intake (27). There appear to be differences in the incidence of stroke between the genders, with males being more likely to have a stroke than females (149 and 113 per 100,000 capita), however there death rates from stroke are similar across both genders (28). Age is also a risk factor with approximately 67% of strokes occurring in adults 65 years or over. The highest proportion is in those 85 years and older, which had a three times higher rate that the 65-74 years age group (15% and 5% respectively) (28).

Burden of Disease

In Australia from 2010-2012, cerebrovascular disease, specifically stroke, was the fifth leading cause of premature death (27). In 2015 approximately 394,0000 Australians had suffered a stroke at some time in their life. In the same year, stroke caused over 8400 deaths accounting for 5% of all deaths and 18% of CVD deaths, a 25% decrease since 1985 (28). Stroke accounted for more than 77,500 hospitalisations in Australia in 2015-16. In terms of financial burden, total health system expenditure for stroke was $881 million in 2012, with a further $4.1 billion in non-health related costs (including lost productivity, carer costs, aids and modifications) (29).

Physical and Psychological Impact

The impact of cerebrovascular disease on the individual will vary depending on the extent of disease and its clinical manifestation with most of the focus being on stroke. Stroke has the potential to have the largest impact, particularly in cases where large or significant areas of the brain have been affected. Physical consequences can include apraxia, visual spatial

perceptual disorders and paresis with other consequences including communication disorders and emotional disorders (30). Stroke has been shown to have an impact on quality of life and mental health with degree of disability, affected brain area and other co-morbidities being some of the influencing factors (31). A study of sixty-two stroke survivors found that twenty nine percent were suffering depression three months post stroke (32). Low mean QoL scores were also observed in another study of seventy stroke survivors, also at three months post stroke (31).

1.2 Aneurysmal disease

The development of aneurysmal disease is complex with multiple mechanisms involved. A true aneurysm is an outward ballooning of the arterial wall that involves all three layers of the wall. False or "pseudoaneurysms", also managed by vascular surgeons, are characterised by a blood-filled cavity which forms between the two outer layers of the artery wall. They usually form as a result of an injury to the blood vessel which then leaks into the space between the two layers rather than exiting the blood vessel (33). Aneurysmal disease has been shown to be attributable, at least in part, to the atherosclerotic process which is supported by the overlap in risk factors for aneurysmal disease and atherosclerosis (34). Aortic aneurysmal (AA) disease is characterised by a loss of elastin, smooth muscle cell apoptosis and collagen deposition as a compensatory measure, resulting in dilatation of all layers of the artery wall (35). Inflammation and degradation of the matrix within the vasculature is critical for the development of AA disease, with reactive oxygen and nitrogen species and oxidative stress implicated in the pathogenesis of the disease (35). Over time, the artery is unable to sustain the tensile strength from blood flow through the artery and hence an aneurysm forms (35).

Clinical Features and Management

Aneurysmal disease is often asymptomatic until it progresses to a size large enough to cause localised pain (chest for thoracic AA, abdomen and lower back for abdominal AA). Symptoms of a leaking or ruptured AA are more severe including dizziness, tachycardia, shortness of breath, loss of consciousness and death (36). Death occurs in around 80% of people with a ruptured AA either before reaching hospital or during emergency surgery (36). The management strategies for AA include medical management for CVD risk reduction including antiplatelet therapy, and anti-hypertensive and lipid lowering medications, and smoking cessation (37). Surgical management of AA has evolved in recent years with the development of endovascular aneurysmal repair (EVAR). Data from 2016 shows that 21.5% of elective and 69% of ruptured AAA repairs in Australia were open procedures with mortality rates of 3.4% and 34.9% respectively (37). EVAR, in the form of bifurcated stent-graft aorto-iliac exclusion of the aneurysm sac, has been shown to have a lower 30-day mortality rate compared with open repair at 1.3-1.7% in the USA in unruptured AA (37). Management with EVAR requires long-term surveillance for complications and potential re-intervention in the situation where there is an endo-leak, graft occlusion or migration (37).

Risk Factors

Results from the Tromso study in Norway found significant relationships between the presence of an AA and increasing age, reduced physical activity, dyslipidaemia, smoking and increased waist: hip ratio. In men, a significant relationship was also found between increased BMI and AA presence (38). Later work from the same researchers investigated the risk factors for the incidence of AA in approximately 4300 adults over a 7-year follow-up

period and found that being male and increasing age were significant risk factors for AA development. Other risk factors were smoking (OR = 13.72, 95% CI 6.12 to 30.78), hypertension (OR=1.54, 95% CI 1.03 to 2.30), hypercholesterolemia (OR=2.11, 95% CI 1.23 to 3.64) and low high-density lipoprotein cholesterol (OR=3.25, 95% CI 1.68 to 6.27) (39). In 2013, 16.9% of the total harm (years of healthy life lost) caused by aortic aneurysm world-wide was attributed to dietary risk factors (39).

Burden of Disease

The prevalence of AA has been reported between 4-8% (40-42). An Australian study found the prevalence of AAs (> 30 mm) rose from 4.8% in men aged 65-69 years to 10.8% in those aged 80-83 years in over 12000 men who underwent screening for AA (43). In 2007-08 there were over 4600 hospital admissions for AA in Australia, 18% of all admissions for arterial disease, with nearly 700 deaths (16). Males were over five times more likely to be hospitalised with an AA compared to females and 89% of all AA hospitalisations were aged 65 years or above (16). More recent literature from the USA found that there were approximately 2.3 million cases of AA in 2013 resulting in 41,371 deaths. Interestingly, while females accounted for just 21.1% of cases, they had a disproportionately higher percentage of the deaths at 45.2% (44).

Psychological Impact of AA

The psychological impact of AA diagnosis has been explored in several studies, which all show that AA diagnosis negatively affects individuals. A Danish study exploring the psychological consequences of AA screening and conservative management observed a lower QoL score in men with a small AA compared to controls, and that the score declined further during conservative treatment, mainly due to decline in health perception and

psychosomatic distress scores. Following surgery, all scores improved to the same level as the controls (45). Similarly, a study conducted in the UK also investigated the effects of AA diagnosis on mental and physical quality of life (QoL) in men. They observed a reduction in mental QoL scores following diagnosis, however it was transient returning to baseline levels after 12 months. Meanwhile, physical QoL was consistently lower in the AA cohort compared with controls (46). Whilst there are at least 5 studies exploring the psychological impact of AA, a recent systematic review concluded that while there was an impact, it was difficult to allow a precise estimation of the severity and frequency of the psychological harm as the available quantitative evidence was insufficient, requiring more sensitive measures (47).

1.3 Venous disease (Venous insufficiency/Chronic venous disease)

Clinical Features and Management

Chronic venous disease is a progression of an early-stage condition termed venous insufficiency, a condition where blood flow through the veins in the lower limbs is inadequate, causing blood to pool in the legs. Venous insufficiency syndromes can be caused by valvular incompetence in the low-pressure superficial venous system but may also be caused by valvular incompetence in the deep venous system (or, rarely, both). In addition, they may result from the congenital absence of venous valves (48).

If left untreated, venous insufficiency progresses to a syndrome known as chronic venous insufficiency (CVI) which can lead to chronic life-threatening infections of the lower extremities. Pain, especially after ambulation or prolonged standing, is a common symptom of the disease (48). Along with pain, CVI causes skin characteristic changes, called lipodermatosclerosis, which can lead to eventual skin ulceration (49).

Venous leg ulcers (VLUs) are the most common type of leg ulcer and usually develop on the inside of the leg just above the ankle. They are associated with localised pain, itchiness and swelling and are susceptible to infection (50). Most VLUs will heal if optimal treatment is followed which involves pain management, treatment of infection, appropriate dressings and compression therapy to promote venous return, reduce venous pressure and prevent venous stasis (51). VLUs have a high likelihood of recurrence, with rates between 22-70% cited in the literature and hence ongoing compression therapy and optimal skin care is important in preventing recurrence and managing the underlying venous disease (51).

Venous disease is assessed and classified using the Comprehensive Classification System for Chronic Venous Disorders (CEAP) which incorporates clinical, aetiological, anatomical and pathophysiological assessment (51). The CEAP has 7 levels of classification that describe the severity of venous disease (51). Table 2 below displays the CEAP Classification and clinical characteristics of each level.

Table 2: The CEAP classification system for venous disease

CEAP Level	**Clinical Characteristics**
0	No signs of venous disease
1	Telangiectasias or reticular veins
2	Varicose veins
3	Presence of oedema
4 a	Eczema or pigmentation
4 b	Lipodermatosclerosis or atrophy blanche
5	Evidence of a healed VLU
6	Active VLU

Risk Factors

Risk factors for venous disease include high intravenous pressure due to standing for long periods, a sedentary lifestyle, pregnancy, female gender, and family history (52). Smoking in men has also been shown to be a risk factor (53). While obese people with venous disease are more symptomatic and have a higher complication rate, obesity itself is usually not classed as a risk factor (54).

Burden of Disease

Studies in Europe and the UK have found that prevalence of chronic venous disease increases with age. In the UK, it is estimated that the prevalence is 20-40% in adults (52), increasing to 55% in the 50-64 years age group (55). In the USA, active venous ulceration affects less than 1% of the population, its prevalence slightly increases to 3% in individuals older than 65 years (56). In Australia, the prevalence is difficult to estimate, however the Australian Wound Management Association (AWMA) estimates that VLUs affect 3 in every 1000 Australia adults with 99% of them being in adults aged 60 or above (51). With an ageing Australian population, and predictions that the proportion of the population aged over 65 years is set to increase from 13% in 2007 to between 23% and 25% in 2056 (51), the financial, health and personal burden of VLUs is, and will become more, significant.

Physical and Psychological Impact

A study of 6009 patients across Belgium and Luxembourg (52) found that 75.2% had chronic venous disease, with 25.9% having CVI and 0.9% having an active venous ulcer. Symptoms were present in 64.7%, with pain and heaviness in the legs being the most commonly reported symptoms. A significant inverse relationship ($p<0.001$) was found between CEAP classification and quality of life, with worsening QoL as CEAP class increased. The impact of

venous disease on the patients was further explored finding that 2.1% of patients had made changes to their professional activities as a result of their leg problems and that 9.4% had needed hospitalization. Loss of workdays was also an issue for 10.4% of patients, with 30.2% of these losing between 1 week and 1 month of workdays. In Europe and the UK, available data regarding direct health care costs of chronic venous disease shows significant burden with direct costs exceeding 10 million Euros per million inhabitants per year in Belgium (57) and the UK (58) in the 1990's.

1.4 Diabetic Limb Infections/Diabetic Lower Limb Ulcers

Clinical Features and Management

Diabetic foot infections and ulcers are a serious complication of diabetes progression and with the rising incidence of diabetes and increasing life span of individuals with diabetes (59), diabetic foot ulcers (DFU) and infections are likely to increase worldwide. Diabetic foot ulcers and infections usually arise from either a wound resulting from a trauma or from an ulcer resulting from PAD and peripheral neuropathy (59). Wounds can become colonised, and if not managed effectively local tissue damage can ensue which can spread to deeper tissues and eventually bone.

Several classification systems exist for diabetic foot ulcers, including the University of Texas classification and the Wagner grading system. The University of Texas classification uses a combination of wound grade and stage to categorise wounds by severity. Wounds are graded 0 (pre- or post-ulcerative site) through to 3 (wound penetrate to bone or into the joint) based on depth and within each grade there are four stages from A (non-ischaemic, clean wound) through to D (infected, ischaemic wound). Both clinical and laboratory data are used in this system (60). The Wagner classification is commonly used and assesses

wound depth and presence of osteomyelitis or gangrene (61). A grade from 0 (foot at risk) through to grade-V (gangrene of entire foot) is assigned and recommendations for prevention and management are included for each stage (61).

Risk factors for the development of DFU include poor glycaemic control, smoking, PAD, anatomical foot deformities, prior history of a foot ulcer or lower limb amputation and diabetic nephropathy (62). Patho-physiologically, DFU have both neuropathic and vascular components with both components arising from hyperglycaemia-induced oxidative stress and cellular changes (62). Neural cell damage in the motor neurons can lead to foot musculature changes and anatomical deformities while damage to autonomic nerves can impede sweat gland function leading to decreased foot moisture and skin breakdown. In addition to the ulcer development, individuals with diabetes can have reduced peripheral sensation and hence foot wounds/ulcers can go unnoticed and untreated in their early stages (62). Vascular changes also play a role in the DFU process. Endothelial dysfunction as a result of hyperglycaemia-related changes in the peripheral arteries of the lower limb, can lead to vasoconstriction and hypercoagulation in the peripheral arteries due to a reduced presence of vasodilators and increased plasma thromboxane A2 levels. This in turn can induce lower limb ischaemia and increased risk of ulceration (62).

Burden of Disease

In 2011, over 16 million people in the USA had diabetes with predictions that this was underestimated by one-third (63). It is expected that 10-15% will suffer a DFU at some stage (63) and that these ulcers lead to over 80,000 amputations per year in the US (62). In 2014-15 there was approximately 1.2 million Australian adults living with diabetes (64), however the prevalence is likely to be higher as many individuals with diabetes are un-

diagnosed. Every year there are approximately 10,000 hospital admissions for diabetes related limb ulcers, with 4100 lower limb amputations in 2014-2015 due to diabetes, 75% of which were in males and 57% in individuals aged 65 years or above (64). Hospitalisation rates for amputations secondary to diabetes have remained stable in Australia between 2000-01 and 2014-15 however the rates for major amputations have declined (65). Likely as a result of changes in vascular surgery techniques, such as the increasing use of endovascular interventions. A recent study exploring trends in vascular surgery in Australia found that the types of interventions have changed significantly between 2001 and 2015. Whilst, there has been an increase in the volume of endovascular revascularisation and minor extremity amputations, there has been a significant decrease in open revascularisation procedures and major amputations over the 15 year time period (11). This data is supported by a study in Western Australia which examined the rates of both major and minor lower limb amputation in people with diabetes and found that overall amputation rates declined by approximately 3% each year between 2000-2010 in both type 1 and 2 diabetes as a result of a reduction in major amputations in those with type 2 diabetes. However, while major amputation rates fell, recurrent minor amputation rates increased by 3.5% (95%CI 1.3%, 5.7%) in those with type 2 diabetes, suggesting effective intervention to prevent major amputations (66). In the Indigenous population of Australia, 98% of amputations were attributable to diabetes with the rate of minor amputations amongst those aged 25-49 years being 27 times higher than in the non-Indigenous population and 38 times higher for major amputation (67).

Diabetic foot disease has a large impact on health care costs. In the USA, DFU is estimated to cost between $US9-13 billion annually, in addition to the costs associated with diabetes management (68). In Australia, costs associated with diabetic foot disease are estimated to

be approximately $AU875 million per year (69). Diabetic Foot Australia quoted an estimated cost of $AU350 million per year for hospitalisations in public hospitals, however this is likely to be a gross underestimate as costs for surgical procedures and hospital costs for patients where diabetic foot disease wasn't the primary reason for admission weren't included (70). When considering health care costs, costs outside of the hospital setting is also an important consideration. Data in Australia is limited, however a recent study conducted in the UK found that costs associated with the health care of ulceration and amputation in diabetes from 2014-2015 was approximately £837-962 million (approximately $AU1.6-1.8 billion), of which 60% was associated with care in the community, outpatient and primary care settings (71). This would equate to approximately $AU309 million in Australia when accounting for differences in the size of the populations between Australia and the UK.

With the increasing prevalence of diabetes, health care costs associated with DFU is likely to also increase and hence prevention and effective management is crucial.

Physical and Psychological Impact

The impact of DFU and infections on the individual are substantial. A cross-sectional study conducted in Norway investigated HRQoL in those with a DFU compared with participants with diabetes but without ulcers and the general population. A significantly ($p<0.001$) poorer HRQoL was found in the DFU participants compared to both the general population and the non-ulcer participants, particularly in the physical functioning, role limitations-physical and the role limitation-emotional domains (72). Similar results were found when comparing patients with healed versus non-healed DFU (73).

Diabetic foot ulcers also have an impact on mortality in people with diabetes. A population

study in Norway, investigated mortality rates in individuals with a history of a diabetic ulcer (HFU) compared to individuals with diabetes but without a history and the general population over a period of 10 years. They found that having a HFU was associated with more than a twofold (HR 2.29 [95% CI 1.82–2.88]) risk for mortality compared with that of the general population group. In comparing individuals with diabetes, with and without a HFU, a HFU was associated with 47% increased mortality (HR 1.47 [95%CI 1.14–1.89]). All analyses were controlled for comorbidity and depression scores (74).

Differences in mortality were also observed in a restrospective cohort study of individuals with diabetes with and without foot ulcers. In this study, survival at 3 years was 72% for the foot ulcer patients versus 87% for a group of age- and sex-matched patients with diabetes but without foot ulcers ($P < 0.001$) (75).

1.5 Other Pathologies Managed by Vascular Surgery

Whilst there are conditions and pathologies synonymous with the vascular surgery clinical specialty, vascular surgeons also manage a range of other clinical pathologies that are not encompassed within the conditions already discussed in this chapter. In this thesis, this range of pathologies has been termed “other vascular surgery conditions” which is heterogeneous in nature and includes the following conditions;

I. Renal access patients: Patients admitted for the formation of an arteriovenous (AV) fistula or AV graft in preparation for haemodialysis.
II. Thoracic outlet syndrome: a group of disorders where blood vessels or nerves between the collarbone and first rib (thoracic outlet) are compressed. Surgical intervention can include the removal of the first rib and/or decompression/removal of the scalene muscles and/or brachial plexus.

III. Ulcers of mixed or unknown aetiology: Ulcers that are attributable to both venous and arterial pathologies or those that have an unknown pathology.

IV. Lower limb infection not attributable to occlusive disease or diabetes.

1.6 Nutritional Health in Vascular Surgery

Malnutrition, by definition refers to 'deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients' and therefore encompasses 2 conditions; (1) overweight and obesity; and (2) undernutrition which includes underweight and wasting and/or micronutrient deficiencies or insufficiencies (76). In clinical practice, malnutrition tends to be synonymous with undernutrition which will be the focus of the research presented in this thesis.

Malnutrition is a common condition amongst hospitalised patients with prevalence rates as high as 50% overall and 47% in surgical patients (77). The impact of undernutrition is significant to both the individual and the health care system with increased mortality, higher incidence of infections, slower wound healing, increased risk of falls and poorer mobility, longer hospital admissions and increased rates of hospital readmission (78-81). In vascular patients, high rates of malnutrition have been observed ranging from 61-90% depending on the type and severity of disease and the method employed to define malnutrition (82-84). Studies have also demonstrated poorer outcomes in vascular patients with nutritional deficits such as increased risk of amputation in PAD patients (85), and more severe amputation in DFU (80). Malnutrition has also been shown to be predictive of longer hospital admission and 12-month mortality (86).

When discussing malnutrition, it is important to consider the following parameters that either contribute to nutritional health or are markers of nutritional health: (1) body

composition including weight status, muscle and fat mass and (2) micronutrient status/stores. Similarly, poorer micronutrient status has been observed in the literature (87-89) with poorer outcomes in those with deficits (85, 90, 91).

Sarcopenia

When discussing nutritional health, it is important to consider body composition as a key component of nutritional health. Body composition refers to the proportion of fat mass, muscle/ lean body mass and bone of an individual's body and can be indicative of chronic disease risk. Changes in body composition are common and are a natural occurrence of the ageing process with increased fat mass and a reduction in lean body mass with increasing age, however a sedentary lifestyle, less than optimal diet and certain pharmacological therapies also play a role (92). Changes in body composition can have negative consequences. Reduced lean muscle mass can lead to impaired ability to carry out activities of daily living (92), and a reduced ability to respond to stresses such as illness and injuries (93). Increased body fat and fat distribution is associated with the development of chronic disease such as T2DM (94), CVD (95) and some cancers (96, 97).

There is a plethora of literature to support the prevalence of and the relationships between obesity/increased fat mass in the development of vascular diseases (98, 99). However, research in the area of sarcopenia and reduced muscle mass and vascular disease is in its early stages.

Sarcopenia is a decline in muscle function or strength in the presences of low muscle mass and is a major contributor to frailty (100). Diagnosis, based on consensus, is made when both lower muscle mass and low muscle function are present (92, 101) and can exist in the presence of or without obesity (sarcopenic obesity) (102). Various assessment techniques

exist to measure muscle mass and function (strength and performance) with all having their positive aspects and their challenges in terms of accurate measurement. Several methods are available to measure muscle mass however cost, availability and ease of use can determine their acceptability and whether they are applicable to the research or clinical setting. Computed tomography (CT Scan), Magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DEXA) are very precise methods of measuring muscle mass with CT and MRI being the gold standard methods for research. However, both methods are high cost, involve radiation and access to CT and MRI equipment is limited. DEXA has been shown to be an appropriate alternative method in both the clinical and research setting (92). Portable methods are also available such as bioelectrical impendence analysis (BIA) and anthropometric measurements (e.g. corrected arm muscle area (CAMA)) which are more portable, inexpensive and non-invasive in the clinical setting however they are less reliable and more prone to error (92).

Similarly, there are several techniques to determine muscle strength and function. Hand grip strength is a valid and reliable method of measuring muscle strength (103). Low hand grip strength has been shown to be a clinical marker of poor mobility which correlates strongly with lower limb muscle power and is a predictor of clinical outcomes (92). Other methods for measuring strength include knee flexion techniques and peak expiratory flow however the applicability of these measures is limited by the need for specific equipment and training (92).

Muscle function or physical performance is the third component of defining sarcopenia with a range of measurement techniques available, all of which involve measuring the individual's ability to complete one or more physical tasks. Single task measures include usual gait speed which is a predictor of adverse health events and can be used as a single

measure or as part of a composite measurement test such as the short physical performance battery (SPPB) (104). Other techniques include the timed get up and go test and the stair climb power test both of which can be utilised to measure muscle performance (92).

With numerous measurement techniques, cut-off points with appropriate reference standards are crucial to define suboptimal values for sarcopenia. The European Working Group on Sarcopenia in Older People (EWGSOP) recommends the use of normative reference populations with cut-off points at 2 standard deviations below the mean reference value (92). What is clear when considering sarcopenia is that there are several methods of defining and measuring sarcopenia and it is challenging to reach a consensus on one definition and diagnosis algorithm hence making comparisons and drawing conclusions from the literature can be challenging.

In the vascular disease setting, the disease itself already places individuals at increased risk of poor mobility and function (105). The presence of sarcopenia has the potential to further exacerbate the consequences of vascular disease and may also play a role in the development of disease and its progression.

Micronutrient Status

Micronutrient status is another area of interest in the vascular surgery population mainly due to the role of various micronutrients in the prevention of atherosclerosis development and progression, wound healing, skin and epithelial integrity, as well as their antioxidant capabilities. Particular micronutrients of interest are vitamins A and C (106), D and E (89, 107-111), the B group vitamins (folate and vitamin B12 in particular) (112, 113) and the trace elements iron, zinc and selenium (106, 114-116).

The role of micronutrients in wound healing has been well studied as many are co-factors in enzymatic processes involved in the healing of wounds (117). Vitamin A has been shown to have an anti-inflammatory effect by increasing monocytes and macrophages within wounds as well as altering the activity of epithelial cells, endothelial cells and other cells involved in skin/tissue integrity (117). Vitamin C has a role in collagen formation, within immune response and also acts as an anti-oxidant and hence is involved in tissue healing but also within the inflammatory response (117) which is also pertinent to atherosclerosis, given its inflammatory component (118). Serum levels of vitamins A and C have been shown to have an inverse relationship with inflammatory markers, adhesion molecules and flow-mediated dilatation leading to a possible protective effect on atherosclerosis (119). Vitamin D plays a role in wound healing through the induction of anti-microbials (117) but has also been shown to have vaso-protective effects through improving endothelial dysfunction, down-regulation of the inflammatory process and acting on vascular smooth muscle cells to inhibit proliferation and migration (120). Vitamin E is more controversial as large-scale studies have indicated that vitamin E supplementation can be atherogenic which contradicts its known natural anti-oxidative ability. It is now hypothesized that the type of tocopherol (form of vitamin E) is relevant. Alpha-tocopherol has been found to enhance nitric oxide (NO) production which is crucial in the functioning of the vascular endothelium. It has also been shown to modulate the inflammatory response. Gamma-tocopherol also has these properties (121). The controversy is more observed in supplementation studies (alpha-tocopherol), whereby some studies observed an increase in cardiovascular outcomes in certain population groups, but others observed reduced cardiovascular outcomes. This has resulted in more focus on other types of vitamin E (121).

Minerals, particularly selenium and zinc, are crucial as enzyme structural factors and metalloenzymes. Zinc is contained in over 200 enzymes, including superoxide dismutase. All act as antioxidants, modulate cell replication, assist in tissue repair and growth. Low levels of zinc and selenium have been implicated in reduced immunity, impaired collagen synthesis and down-regulation of fibroblast proliferation (117). The evidence regarding iron is less clear with iron deficiency resulting in reduced inflammatory response, however iron supplementation has been shown to increase inflammation (117). Iron does play a role in oxygen transport; hence low levels inhibit wound healing.

Identifying Nutritional Risk

A crucial factor in optimising nutritional health is the identification of those who are at risk of suboptimal nutritional health to enable appropriate assessment and nutritional intervention where indicated. Identifying malnutrition and/or nutritional risk in the clinical setting is a challenge, due to several factors. Firstly, a number of studies have highlighted that there is a lack of knowledge with respect to dietary requirements amongst hospital staff (122) and that even amongst medical physicians there is reduced awareness likely as a result of insufficient nutrition education in their tertiary education (123). Nutrition can be viewed as a lower priority by some nursing staff compared to other patient care activities (124) and similar to medical staff, nursing staff do not always have sufficient knowledge regarding nutrition (125, 126). In addition to knowledge and awareness within hospital staff, there is also a lack of consensus on how to identify malnutrition and/or nutritional risk. However, the Dietitians Association of Australia evidence-based practice guidelines for the management of malnutrition in adults specifies that routine screening for malnutrition using a validated screening tool should be implemented across care settings (127).

Nutrition screening is a process to enable early identification of individuals with nutritional characteristics that would benefit from further assessment and expedite nutrition intervention where necessary or to predict poor clinical outcomes related to malnutrition (128). Over the years numerous nutrition screening tools have been developed and implemented across the continuum of care some of which have been endorsed by international nutrition societies while others are used more widely in certain countries rather than world-wide (128). The majority of screening tools contain parameters such as anthropometry measurements, appetite changes, unintentional weight loss and changes in oral intake (128, 129). A 2014 systematic review of screening tools in the hospital setting identified 32 screening tools across 83 studies and while the results were variable in terms of validity, the Malnutrition Universal Screening Tool (MUST), The Nutrition Risk Screen-2002 (NRS-2002) and the Mini Nutritional Assessment – Short Form (MNA-SF) were the better performers across hospitalised patients (128). Whilst, screening tools have been examined in hospitalised patients, it isn't clear whether any have been examined in vascular surgery patients which is a clear gap in nutrition research within this patient group.

1.7 Conclusion

In conclusion, vascular diseases are prevalent in western countries, including Australia. With an ageing population and increasing prevalence of risk factors, the problem is likely to escalate. Vascular diseases cause heavy burden to the individual and the health care budget, hence research into optimising the health and outcomes of individuals with vascular disease is crucial. Given the increasing prevalence of vascular disease and the evidence that undernutrition is a major concern in this patient group, it is appropriate to

explore the extent of nutritional issues in vascular surgery patients and the impact on outcomes. To assist in identifying appropriate instruments for nutrition screening it is important to explore tools that have been investigated in vascular patients if available, or in surgical patients more broadly to determine whether there are suitable tools for implementation.

Chapter 2: Nutrition in Vascular Disease.

As discussed in chapter 1, the vascular surgery population encompasses a range of clinical conditions and aetiologies and as such, the nutritional health of vascular surgery patients is also heterogeneous with individuals across the spectrum of nutritional status from undernutrition to overnutrition. In order to further understand the nutritional status of vascular surgery patients and the impact nutritional status has on outcomes in this patient group a review of the literature was necessary. In addition, whilst many malnutrition screening tools are available for hospitalised patients, a review of the literature to determine whether any tools are valid and/or reliable for use in vascular surgery patients specifically was important. Therefore, a narrative review was undertaken to answer the following questions

1. What is the prevalence of malnutrition in vascular disease patients and how does it affect clinical outcomes?
2. Are individuals with vascular disease at risk of poor micronutrient status?
3. What malnutrition screening tools are valid and/or reliable for use in patients with vascular disease?

2.1 Methods

Methods used to conduct this literature review were in accordance with those recommended in an article by Green et al which describes the process of writing a narrative literature review for publication in peer-reviewed journals (130) and the Evidence Analysis Manual of the American Dietetic Association (131)

A search of the literature was conducted in December 2017 and updated in January 2019 in the following electronic databases; Medline, Cochrane, Scopus, CINAHL and Psychinfo. Prior to commencing the literature search, the selection of databases, search terms and inclusion criteria were determined by the PhD candidate in consultation with an experienced medical librarian. Search terms and limits for each of the three literature review question are shown in Appendix 1. For example, key search terms were a combination (using OR) of synonyms for body composition such as *"body mass index"* or *"lean body mass"* combined with the Medical Subject Heading (MeSH) "*vascular diseases*" including related MeSH headings such as "*aneurysm*" and "*peripheral vascular disease*" combined (using OR). MeSH terms were common to the 3 literature review questions, other key search terms differed for each question and are displayed in the relevant search strategy in appendix 1.

Articles were included if they met the following selection criteria: 1) humans aged ≥18 years old, 2) published in English, 3) focused on individual's with vascular disease and 4) reported patient outcomes quantitatively. Systematic reviews were identified, and reference lists were hand-searched with relevant articles included for review. Reference lists of included articles were also hand-searched for relevant articles. A summary of the screening process is shown in appendix 2, including the number of records located, screened and included. Data was extracted into study summary tables which are included in the review (Tables 4-6). All literature searches, screening and data extraction was conducted by the PhD candidate.

When included articles were determined, each study was assessed for methodological quality using the Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary

Research (131) by the PhD candidate. The checklist consists of key validity questions for a publication resulting in an overall rating of positive, negative or neutral. Levels of evidence were determined using the National Health and Medical Research Council (NHMRC) evidence hierarchy (132). The quality assessment and level of evidence for each included article is available in appendix 3. The findings of the included studies were then summarised and discussed, including the limitations and implication for practice.

2.2 Results

2.2.1 What is the prevalence of malnutrition in vascular surgery patients and how does it impact on clinical outcomes?

The literature search across the five databases yielded 3610 articles for consideration. Following the removal of duplicates (n=58) and screening by title and abstract, 166 remained. Full text screening resulted in 16 articles for inclusion in the review. The articles were grouped into (1) those examining undernutrition and (2) those examining sarcopenia/low muscle mass. The groupings were based on the research question of the articles, with two clear foci, (1) undernutrition defined using a variety of parameters and (2) sarcopenia defined using muscle mass. Further details of the screening process can be viewed in Appendix 2.

Undernutrition in vascular disease patients and the impact on outcomes

Five studies were located that examined undernutrition and its impact on outcomes in vascular disease participants. A summary of the studies is available in Table 3. Sample sizes varied from 122 (133) to 7595 (134). Two were retrospective in design (133, 134) with the remainder being prospective studies (80, 135, 136). One was conducted in venous leg ulcer patients (133), two in diabetic foot ulcer patients (80, 136), and two were in PAD patients

(134, 135). A variety of methods were used to determine undernutrition including low body mass index (BMI), the Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA) or a range of parameters.

Using the National Health and Medical Research Council (NHMRC) evidence hierarchy (132) based on the 'Aetiology' classification, two studies were classified as level III-2 evidence (133, 134), and three were level II evidence (80, 135, 136). Four studies were of neutral quality (80, 133-135) with the remaining one being of negative quality (136). The consistent areas of poor quality and risk bias were unclear or poor reporting of subject selection, unclear representation of the relevant population, lack of blinding of outcome assessment and unclear or poor reporting of the research question and aims (appendix 3).

Venous Disease

In the one study conducted in venous ulcer patients, undernutrition was more prevalent in those with ulcers compared to those without ulcers. Finlayson et al (133) defined undernutrition as a BMI≤20kgm^2 and investigated its effects on ulcer recurrence. They found a higher proportion of undernourished participants in the ulcer recurrence group versus those with no recurrence (21% vs 5% $p<0.05$) but that a BMI≤20kgm^2 was not predictive of recurrence (OR 3.59, 95%CI 0.14-93.5 p=0.44) when entered into logistic regression analyses. The authors did note that they had a relatively small number of participants with a BMI≤20kgm^2 (16%), which could explain the difficulty in reaching statistical significance. No rationale was provided as to why the BMI cut-off was at 20kgm^2 and as participant age wasn't reported it is difficult to make inference as to whether it was an appropriate cut-off for the study population. A significant proportion of participants (72%) were receiving the aged pension which implies the majority were older adults. There

is literature to indicate that a normal body mass index (BMI) in those aged 65years and older is 22-27kgm^2 (137) or even 23-31kgm^2 (138), in which case this study would be under-estimating the prevalence by using the lower cut-off.

This study was classified as level III-2 evidence and of neutral quality due to unclear representativeness of the sample and a lack of blinding of outcome assessments and hence this should be considered when drawing conclusions.

Diabetic Foot Disease/Ulcers

Two studies were located involving diabetic foot disease participants with both being of evidence level II according to the NHMRC levels of evidence (132). Gau et al (80) was rated as neutral quality as there was no reporting of outcome assessment blinding and no consideration of clinical significance of findings. Zhang et al (139) was rated as negative quality as reports of exclusion and inclusion criteria were unclear as well as representativeness of the sample and differences in the study groups were not accounted for in the analyses. There were no reports of blinding and potential funding and conflicts of interest were not clearly reported. Hence the study has a high risk of bias based on what was reported in the article.

Malnutrition was prevalent in those with more severe disease in both studies and poorer clinical outcomes were observed in the malnourished participants. Gau et al (80) assessed the nutritional status of 478 Taiwanese DFU patients using the Mini Nutrition Assessment (MNA), revealing that 14.8% of participants were malnourished and a further 70% were at risk of malnutrition. The participants were separated into those who had a major lower extremity amputation (LEA), minor LEA and non-LEA and a significant difference was found in mean MNA score across the 3 groups with lower scores (poorer nutritional status) as the

severity of amputation increased (Non-LEA: 21.1±3, Minor LEA: 20.0±3.4, Major LEA: 17.9±3.8 ($p<0.001$)). Multivariate analysis also showed an association between MNA score and major LEA (aOR 0.81, 95% CI 0.67-0.98, $p=0.027$) and minor LEA (aOR 0.9, 95%CI 0.81-1, $p=0.042$) indicating that higher MNA scores confers lower risk of amputation. The nature of the study design doesn't allow causality to be determined, however it is possible that the more well-nourished participants have less severe disease and hence lower risk of amputation. Conversely, those with more severe disease and increased likelihood of amputation have multiple factors that contribute to a lower MNA score (worse nutritional status) such as poorer mental health (19), poorer mobility and reduced lower limb musculature (105) (measurements of calf circumference can be included in the MNA).

Zhang et al (136) used the Subjective Global Assessment (SGA) as well as other parameters to determine nutritional status in 192 hospital patients with DFU (Wagner's grade 1-5) and 60 without ulcers (Wagner's grade 0). Outcomes were investigated over six months according to nutritional status based on SGA, it is unclear how the other parameters of measuring nutritional status listed in the methods were incorporated or utilised. Similar to Gau et al (80), a higher prevalence of malnutrition was observed in those with DFU (62% vs 11.7%, $p<0.001$) and the proportion of ulcers not healed was much higher in the poorly nourished participants (SGA-B&C vs SGA-A: 69.6% vs 17.8%, $p<0.001$.). Other results showed a significant association between nutritional status and severity of infection (B value 0.47, $p<0.001$) and whether an ulcer was healed at 6 months (B value 0.28, $p<0.001$). Poor outcomes were significantly higher in the SGA-C group compared to other groups ($p<0.001$) with higher rates of non-healing (69.6%), amputations (7/23) and death (4/23).

Both studies indicate that malnourished patients with diabetic foot disease have poorer outcomes, however the level of evidence is low (III-2) and the quality of the studies also needs to be considered. The studies used two different assessment tools to classify nutritional status and while there are differences in the parameters included in the two methods, both are widely used and validated for the age of the participants and in hospital patients.

Occlusive Disease

Two studies were included that examined PAD patients. One study was level III-2 evidence (134) and the other was level II (135). Both were of neutral quality mainly attributed to unclear representativeness of the sample (135), lack of blinding (134, 135) or unclear outcome measures and no report of funding sources and declarations of conflicts. Both studies used BMI classification to determine malnutrition.

Giles et al (134) utilised a national database, the National Surgical Quality Improvement Program (NSQIP) to analyse the difference in post-operative mortality at thirty days and incidence of surgical site infections (SSI). Seven thousand five hundred and ninety-five bypass procedures were included in the analysis. BMI was classified into five levels; underweight, normal, overweight, obese and morbidly obese using the National Institute of Health (NIH) definitions (Underweight BMI ≤ 18.6kgm^2, normal weight 18.7-25kgm^2, overweight 25.1-30kgm^2, obese class I 30.1-35kgm^2, obese class II 35.1-40kgm^2, obese class III >40kgm^2). Multivariate analysis showed that participants in the underweight category had 3.5 times the risk of 30-day mortality compared with combined overweight and obese (OR 3.5 95% CI 2.1-5.9 p<0.001). Normal weight also had a higher 30-day mortality risk compared to the combined overweight and obese category but to a lesser extent (OR 1.7 95%CI 1.2-2.4 p<0.01). These results lend support to the phenomenon of the "obesity

paradox" whereby a better prognosis is observed in the overweight and obese population of CVD sufferers compared to those of normal and underweight status (140).

Senda et al (135) also used BMI (World Health Organisation definitions) to determine undernutrition in 441 Japanese patients with IC (CLI were not included). Eighty-one per cent were male and the median (IQR) age was 74 (67-80) years. All-cause and cardiovascular death, non-fatal myocardial infarction (MI), heart failure needing hospitalisation, stroke and major bleeding were examined over a mean follow-up of 3.5±1.9 years. Kaplan Meier analyses revealed a significantly higher rate of all-cause death in underweight compared with normal weight participants (77.1 vs 33%, $p<0.001$) and a higher rate of cardiovascular deaths (43.3 vs 14.4%, $p<0.001$). No differences were found in the other outcomes. Multivariate analyses showed that underweight status was a predictor for all-cause death (HR 2.57 95% CI 1.58-4.18. $p<0.001$).

Aneurysmal Disease

No studies were located that examined the prevalence of malnutrition and how it affects outcomes in patients with aneurysmal disease as part of this literature review and hence is an under-explored sub-group of patients with vascular disease.

Conclusion

While the five studies used varying methods to determine nutritional status, the collective results highlight that undernutrition is prevalent across the types of vascular disease patients that have been studied (15-62%) and that being undernourished is associated with negative consequences on clinical outcomes, including mortality, ulcer infections, recurrence and poor healing and severity of amputation. All studies were either level II or level III-2 evidence and either neutral or negative in quality which needs to be considered

when drawing conclusions. Future studies should address selection bias and blinding of assessment outcomes to improve overall methodological quality and reduce risk of bias.

Table 3: Summary of the literature on the prevalence of malnutrition and the impact on outcomes in vascular patients

Study (author, year) Aim	Participants	Method of assessing nutritional status	Relevant outcome measure	Results	Comments
Venous Disease					
Finlayson et al, 2009 Aim: to examine the relationship between leg ulcer recurrence and factors (including nutrition)	Patient survey and retrospective chart review of 122 community living patients with VLUs which had healed between 12-36 months prior to the survey. 49% male, 16% of sample had BMI ≤ 20kgm2	• BMI ≤ 20kgm2	• Ulcer recurrence • Time to recurrence	• **Proportion of participants with BMI ≤ 20kgm2** recurred vs no recurrence: 17 (21%) vs 2 (5%) p<0.05. • **Multivariate analysis**: BMI≤ 20kgm2 as a predictor for recurrence OR 3.59, 95%CI 0.14-93.5 p=0.44	There was a higher prevalence of underweight status in the participants with ulcer recurrence; however, BMI≤ 20kgm2 does not independently predict recurrence on multivariate analysis. Relatively small numbers with BMI≤ 20kgm2 in the study noted to be a limitation. Also, no rationale for the chosen BMI cut-off. Age of participants wasn't reported.
Diabetic Foot Disease					
Gau et al, 2016 Aim: to investigate the nutritional status of patients	478 Taiwanese DFU patients. Mean age 65.4 ±13.1 years.	• Mini-nutritional assessment (MNA) by a dietitian.	• Prevalence of malnutrition. • Limb-preservation	• MNA Status for whole sample: Well-nourished 15.2%, at risk 70%, malnourished14.8% • Mean MNA Score 20.6±3.4	Poor nutritional status as measured by MNA is associated with

with limb threatening DFUs and the impact on treatment outcomes	56.9% male. Mean BMI 25.6±4.6kgm2 (overweight for Taiwanese). Patients in 3 groups: 1. Major lower extremity amputation (LEA) 2. Minor LEA 3. Non-LEA	• Nutritional status determined as per standard scoring system of the MNA. • "Well nourished" (score, 24–30), "at risk of malnutrition" (score, 17–23.5), or "malnourished" (score, <17)		• MNA score according to level of extremity: Non-LEA: 21.1±3.2 Minor LEA: 20.0±3.4 Major LEA: 17.9±3.8 (p<0.001) • **Multivariate analysis**: MNA vs Major LEA: aOR 0.81, 95% CI 0.67-0.98, p=0.027 MNA vs minor LEA: aOR 0.9, 95%CI 0.81-1, p=0.042 • Poorer outcomes found as nutritional status worsened (p<0.001 for trend)	poorer outcomes for DFU patients.
Zhang et al, 2013 Aim: to analyse indicators correlated with nutritional status and outcomes to investigate their relationship in DFU patients. Study Design: Prospective cohort study.	192 hospitalised patients with T2DM and DFU of Wagner stages 1-5. 60 patients with Wagner's grade 0. 155 (80.7%) male with mean age 68.6±11.3 years.	• Subjective Global Assessment (SGA): rating of A, well nourished; B, moderately malnourished; or C, severely malnourished. • Anthropometry: BMI • Biochemistry: total protein, albumin, Haemoglobin, total cholesterol. • Physical exam. • Nutritional status was evaluated from all of these variables but no further details on how BMI, biochemistry were used in addition to the SGA	Outcomes over 6 months: • Healing (ulcer healed). • Deferment (did not heal). • Recurrence. • Above-ankle amputation. • Mortality.	**Proportion of SGA-B&C in Wagner 0 group vs Wagner 1-5**: 11.7% vs 62%, p<0.001. **Proportion of ulcers not healed**, SGA-B&C vs SGA-A: 69.6 vs 17.8%, p<0.001. **Correlation between SGA and severity of infection**: r=0.64, p<0.001. Correlation between SGA and healing: r=0.37, p<0.001. **Association between deferment and malnutrition**: OR 0.6 95%CI 4.1-28, p<0.001. **Multiple regression**: Nutritional status and severity of infection: B value 0.47, p<0.001. **Nutritional status and healed ulcer at 6 months**: B value 0.28, p<0.001. **SGA-C**: 69.6% non-healing, 7/23 had amputations, 4/23 died. Significantly higher than in the other groups (p<0.001)	Higher prevalence of malnutrition in DFU patients compared to T2DM without ulcers with higher rates of poor healing in the malnourished participants. Significant associations between worsening nutritional status and poorer ulcer outcomes.

Occlusive Disease					
Study (author, year) Aim	**Participants**	**Method of assessing nutritional status**	**Relevant outcome measure**	**Results**	**Comments**
Giles et al, 2010 Aim: to examine lower extremity bypass by graft origin and BMI to analyse the difference in post-op mortality (30 days) and surgical site infections (SSI)	Retrospective study of 7595 bypass procedures within the NSQIP database.	• BMI classification was assigned based upon NIH definitions • Underweight (BMI ≤18.6 kg/m2), normal weight (18.7-25 kg/m2), overweight (25.1-30 kg/m2), obese class I (30.1-35 kg/m2), obese class II (35.1-40 kg/m2), and obese class III (>40 kg/m2). • Obesity was defined as obese class I through III and morbid obesity was defined as obese class III.	• 30-day mortality • Occurrence of SSI or graft failure.	**Multivariate analysis** Underweight vs combined overweight, mild and moderate obese (mortality): OR 3.5 95% CI 2.1-5.9 p<0.001 Normal weight vs combined overweight, mild and moderate obese (mortality): OR 1.7 95%CI 1.2-2.4 p<0.01 Underweight not predictive of SSI.	Underweight status associated with 3.5 times risk of 30-day mortality compared to overweight and obese. Normal weight is also associated with mortality but to a lesser extent. Underweight status was not predictive of SSI.
Senda et al, 2018 Aim: to evaluate whether underweight status is associated with poor prognosis in inpatients with PAD with claudication	441 Japanese claudicants (CLI excluded). Sub-analysis of larger cohort study 84 (19%) female. Median age (IQR) 74 years (67-80). Median BMI 22.7kgm2	• Sample divided into 4 groups based on WHO BMI categories • Underweight (BMI<18.5) • Normal (BMI >18.5 <25) • Overweight (BMI ≥25 and <30) • Obese (BMI≥ 30)	• All cause death • CV Death, non-fatal MI, Heart failure needing hospitalisation, Stroke, major bleeding.	**All cause death**: (Kaplan Meier) 77.1 vs 33% (underweight vs norm weight) p<0.001 **CV deaths**: 43.3 vs 14.4% (underweight vs norm weight) p<0.001. No differences in other outcomes. **Predictors of all-cause death** (multivariate): Underweight HR 2.57 95% CI 1.58-4.18. p<0.001	When haemodialysis patients were excluded, underweight was still predictive of all-cause death. Use of WHO BMI categories in Japanese participants must be considered as a potential limitation.

Sarcopenia and muscle mass in vascular disease patients

Twelve studies were located during the literature search that examined sarcopenia and/or reduced muscle mass in vascular patients. A summary of each study is available in Table 4. Whilst all studies used the term 'sarcopenia', all studies examined muscle mass only and did not measure muscle function or strength which are important for the diagnosis of sarcopenia [112]. Hence, all studies examined the impact of low muscle mass on outcomes and for the remainder of this review, the terms low, reduced or suboptimal muscle mass will be used. Four studies (141-144) were conducted in aneurysmal patients, five in PAD patients (145-149), two in diabetic foot patients (150, 151) and one in a heterogenous group of vascular patients (152). All studies investigated the links between low muscle mass and various clinical outcomes in the short and/or long-term. Studies were a mix of prospective and retrospective design with sample sizes ranging from 64 to 1105. The methods for measuring muscle mass varied across the studies with ten employing CT imagery (141-147, 149, 151, 152), and two using DEXA (148, 150). Cut-offs to determine suboptimal muscle mass varied depending on the measure used such as skeletal muscle area, total psoas muscle area and skeletal muscle index. While there are variations in patient type, method of measuring and defining low muscle mass, the results are consistent across the studies that have been studied with a significant prevalence of reduced muscle mass that is linked to poorer outcomes.

According to the NHMRC levels of evidence (132) one study was classified as level II evidence (147), two studies were classified as level IV evidence (148, 150), with the remainder being of level III-2 evidence. One study (147) was of positive quality where seven studies were of neutral quality (141-144, 148-150), and four studies were of negative quality

(145, 146, 151, 152). The consistent areas of risk bias and poor quality were unclear or poor reporting of subject selection, lack of blinding of outcome assessment and unclear or poor reporting of the research question. Within the negative studies, methods of measuring low muscle mass were not clearly reported in two studies (145, 146) and study limitations and biases were not considered or unclearly addressed in the conclusions of three studies (145, 146, 152). In two studies, outcome measures were not clearly described (145, 152).

Aneurysmal Disease

The impact of low muscle mass was examined in aneurysmal patients in four studies which were all retrospective in design (141-144) and employed CT imagery to determine muscle mass. In all CT imagery studies, determination of muscle mass (either psoas muscle or total skeletal muscle mass (summation of abdominal wall, paraspinal, psoas muscle groups)) was conducted using standard protocol and equipment at either the L3 or L4 level using a single slice CT image.

Hale et al (141) studied two hundred patients with AA (mean age 74 ± 7.5 years) to determine the impact of low muscle mass on mortality over 15 years following endovascular aneurysm repair (EVAR). Twenty-five (12.5%) were assessed as having low muscle mass (skeletal muscle area <114.0 cm^2 (men) or <89.8 cm^2 (women)). Results showed that participants with low muscle mass had a significantly higher all-cause mortality rate compared to those with adequate muscle mass (76% vs 48%; p=0.016) with multivariate logistic regression showing an OR (95%CI) of 3.17 (1.20, 9.54). One limitation to note in this study (apart from the retrospective nature and selection bias) was that participant aspirin or statin use wasn't measured and hence could not be included as a confounder in the regression analysis which may have some impact on results given the links between aspirin and statin use and reduced risk of CVD events and death (153, 154).

Like Hale et al (141), Newton et al (143) used total psoas muscle area via CT imagery to determine muscle mass, however they used a cut-off at the lower tertile as a working definition (<2406mm^2) which appears to be higher than in Hale et al. The authors investigated differences in prolonged length of stay (LOS) (LOS >2 days) and mortality over five years of follow-up. Prevalence of low muscle mass was 33.3%, higher than that in Hale et al (141) due to differences in cut-off, however no difference in prolonged discharge was observed (39.4% (n=13) vs 33% (n=33) p=0.41) between patients with and without low muscle mass. A significant relationship was found between low muscle mass and 5-year mortality with multivariate analysis, with a 3.9 increased risk of mortality (OR 3.9, CI 1.2-12.9; p=0.027) in those with low muscle mass.

Tanaka et al defined low muscle mass according to total psoas area index (TPAI) which was derived from measures of total psoas area and body surface area (142). A cut-off of <6.5cm^2/m^2 was used to investigate associations between low muscle mass and adverse events, discharge other than home, or death within 30 days. One hundred and fifty-four (54.6%) of 282 participants with aneurysmal disease were classified as having low muscle mass. The participants were grouped into those managed with open surgery (OSR) and those managed with EVAR with outcomes investigated according to whether low muscle mass was present or not. In both groups the incidence of adverse events was statistically significant with higher incidence in the participants with low muscle mass (EVAR: 41% vs 16%, p=0.020, OSR 49% vs 32%, p=0.012). Associations between TPAI and adverse events and long-term mortality were also significant with low muscle mass being associated with poorer outcomes (adverse events: OR 0.829 95%CI 0.726-0.946; p=0.0053. Long term mortality: Parameter estimate 0.36, p=0.003). Poorer short-term outcomes relating to low muscle mass were more prevalent in the OSR group. The method of using TPAI to

determine low muscle mass requires consideration as higher body surface area values results in lower TPAI. This is important when considering the prevalence of overweight and obesity in vascular patients and the impact that this would have on the prevalence of lower TPAI values. Unfortunately, the authors did not report any details on anthropometry, including body surface area, hence it is difficult to make any inferences about the effect of body weight and body size on the prevalence of low muscle mass in this study, but an affect is likely.

Indrakusuma et al also investigated survival rates in AA patients (n=228) undergoing repair (n=124) or conservative management (n=104) with and without low muscle mass (144). CT imagery was again the method employed, and like Newton et al, (143) this study used psoas muscle area (PMA) to measure muscle mass. Suboptimal/poor muscle mass was defined as PMA at the level of the lowest tertile (<14.56cm^2) of study participants. The authors acknowledged that this method of selecting a cut-off is dependent on the study sample and that it was a limitation to the study. This is evident when you compare the cut-off used by Newton et al (143) derived via the same method at <2406mm^2 which is much higher than that used in this study. The results of this study were contradictory to those by Hale (141), in that low PMA did not have any effect on survival time in either conservatively (p=0.512) or surgically (p=0.311) managed AA patients. This study did have some limitations in addition to the selection of cut-offs. It was noted that different CT scanners were used across the participants, selection bias was important to note due to the retrospective nature and only being able to include patients who had CT imagery available. The authors also noted that measurement of PMA could have been improved by using all available CT data to measure the entire PMA instead of relying on single slice CT.

While there were differences in methods used to measure muscle mass, there was a negative association with most outcomes studied. All studies except for one (144) found that low muscle mass was associated with negative effects on mortality over follow-up and shorter term outcomes. These results suggest that low muscle mass in aneurysmal patients is detrimental to outcomes and that diagnosis and management may improve outcomes, however given the nature of the studies, a causative relationship is unable to eb determined.

Occlusive Disease

Five studies investigated the prevalence and/or impact of low muscle mass on outcomes in PAD patients. Four (145-147, 149) employed CT imagery with the remaining study (148) using DEXA. The first four studies mentioned above investigated mortality and adverse outcomes whereas the remaining study (148) investigated functional status via treadmill test, 6-minute walking distance and a walking impairment questionnaire. All studies found that low muscle mass had a negative impact on the outcome measures studied.

Addison et al studied 108 men with PAD to determine the prevalence of low muscle mass and whether it impacted on functional status (148). DEXA was used to measure appendicular lean mass which was converted to skeletal muscle index (SMI). A SMI $<7.26 kgm^2$ was considered as suboptimal which resulted in a prevalence of 25.9% (n= 28/108). In a subgroup matched sample (42 PAD and 42 controls) the prevalence was higher in the PAD group (10/42 (23.8%) vs non-PAD: 1/42 (2.4%), $p<0.05$). A possible reason for low muscle mass in PAD patients could be muscle atrophy secondary to disuse which was highlighted by McDermott et al (105) on CT examination of calf muscle. This atrophy may extend to the psoas muscle which has been noted in other patient groups with impeded mobility (155) and hence it appears reasonable to expect PAD patients to exhibit

psoas muscle atrophy. Low muscle mass was also found to affect some of the functional outcomes examined. The PAD patients with low muscle mass had a shorter claudication onset time (149±23.7 vs 185±14.2 seconds, $p<0.05$), longer claudication recovery time (592±97.9 vs 395±28.5 seconds, $p<0.05$) and shorter 6-minute walking distance (326±18.8 vs 380±9.7 meters, $p<0.05$) compared to those with adequate muscle mass. There were no differences in peak walking time or the walking impairment questionnaire scores.

The remaining four studies all employed CT imagery and were conducted retrospectively. Juszczak et al investigated associations between total psoas area (TPA) in quartiles and complication rates, length of stay (LOS) and survival after limb revascularisation (149). Survival at 1- and 2-years post-surgery was less likely in the lowest quartile of TPA compared to other quartiles (TPA in 1st quartile vs TPA in 2nd, 3rd and 4th quartile: 0.74 and 0.66 vs 0.90, 0.83; log-rank test, $p<0.001$). Cox-regression analysis revealed TPA was independently associated with mortality (TPA quartile HR 1.89, CI 1.07-3.35; $p=0.028$). There was no association between TPA and complication rates ($p>0.05$) or prolonged hospital stay ($p>0.05$) but median (IQR) LOS in the first quartile of TPA was longer than in the 4th quartile (9 days (4, 28) vs 6 days (4-9); $p=0.022$). Limitations were evident including the retrospective methodology and selection bias based on availability of CT imagery. BMI wasn't collected on all participants and was omitted from data analysis hence it wasn't included as a covariate in regression analyses. BMI is known to have an influence on mortality and other outcome measures and hence results may have been affected by its omission.

The impact of low muscle mass in patients with CLI was explored in two studies conducted in Japan by Matsubara et al with a focus on low muscle mass as a risk factor for cardiovascular events and as a prognostic factor for survival (145, 146). Both studies were

retrospective in nature, investigating 64 (145) and 114 (146) patients undergoing revascularisation with Fontaine stage 3 or 4 PAD. Low muscle mass was determined by skeletal muscle area measured by lumbar-3 level CT scan of <114.0cm^2 and 89.8cm^2 in men and women respectively which was based upon a level of <5th percentile of the standard value in healthy adults. The prevalence of low muscle mass was similar in both studies at 43.8% (145) and 46.5% (146) which is higher than that observed by Addison et al (148), but similar to studies conducted in AA patients using CT imagery. In the earlier study, there was a significant difference in 5-year overall survival between those with and without low muscle mass at 23.5 ± 0.18% vs 77.5 ± 0.09% (p=0.001) with multivariate analysis showing a significant association between low muscle mass and overall survival (HR 3.22, 95% CI 1.24-9.11, p=0.02) (145). Similar observations were made in the second study with a lower proportion of 3-year CVD event-free survival in the patients with low muscle mass compared to those with adequate muscle mass (43.1 % vs 91.2%, p<0.01) (146). Multivariate analysis showed an association between low muscle mass and 3-year CVD event-free survival of HR 3.07, 95%CI 1.56-6.29, p<0.01). The number of CVD deaths in the low muscle group was significantly higher with 15 deaths vs 4 in those with adequate muscle mass (p<0.01).

The final study in PAD patients also used CT imagery to determine psoas muscle area and CT value to examine the relationship between muscle mass and major adverse CVD and limb events (MACLE) (147). This study was prospective and involved 327 patients over a follow-up period of 2500 days. MACLE (CVD death, rehospitalisation due to stroke, acute coronary syndrome, heart failure or amputation) was the end point. Psoas muscle CT value was stratified into tertiles. MACLE overall, major CVD events and amputations all increased with decreasing mean psoas muscle CT value over the follow-up period (p=0.0082, 0.021, 0.0236

respectively). Mean psoas muscle CT value was found to be predictive of MACLE on univariate analysis (HR 0.525 95%CI 0.428-0.657; p<0.001) and in multivariate analysis (2 models - HR 0.784 95%CI 0.617-0.955; p=0.045 and HR 0.699 95%CI 0.548-0.889; p=0.003). These results further support that reduced muscle mass is associated with more negative outcomes and is an independent predictor of adverse outcomes.

Diabetic Foot Disease

Two studies were located in participants with diabetic foot disease. One study (150) used DEXA to measure muscle mass, whereas Kim et al used CT scan at L3 to allow calculation of skeletal muscle area (151). Both studies derived a skeletal muscle index (SMI) with cut-offs to diagnose low muscle mass. Cheng et al (150) set the cut-off at <7kgm^2 (men) or 5.4kgm^2 (women) as per the consensus report of the Asian Working Groups for Sarcopenia (AWGS) (156) which is an adaptation of the Consensus of the European Working Group on Sarcopenia in Older People (92). Kim et al (151) used cut-offs of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women which were developed statistically in a study of oncology patients in Canada investigating sarcopenic obesity utilising CT imagery (157). Given the study by Kim et al (151) was conducted in Korean participants without cancer, the appropriateness of the cut-offs used is questionable. Cheng et al (150) examined shorter-term clinical outcomes whereas Kim et al (151) examined mortality over 5 years.

The study by Cheng et al involved 1105 patients with type 2 diabetes, of which 120 had newly diagnosed diabetic foot disease (DFD - active diabetic foot problem: ulceration (number and severity, spreading infection, critical ischaemia, gangrene, suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain) (150). Prevalence of low muscle mass across the whole sample was 18.5% (204 cases) with

the percentage of low muscle mass in DFD patients more than double than that observed in patients without DFD (35.3% vs. 16.4%, P < 0.001). DFD patients with low muscle mass were more likely to have multiple ulcers (p=0.022) and larger mean ulcer size (p=0.003) and had a higher rate of amputation (21.4% vs 7.8%; p=0.044) compared to DFD patients with adequate muscle mass. Multivariate logistic regression (fully adjusted model) found that low muscle mass was independently associated with DFD (OR 2.06, 95%CI 1.08,3.95, p = 0.029. This study provides an indication that low muscle mass is associated with DFD and that DFD patients with poor muscle mass have a worse prognosis however it is unclear as to whether the low muscle mass is associated with worsening disease or whether it is a result of the disease process.

Kim et al also observed negative outcomes were associated with low muscle mass in 167 patients who underwent amputations for diabetic foot complications (151). Low muscle mass was prevalent at 67.1% (n=112) of participants. Across the whole sample, 5-year mortality rates were higher in the participants with low muscle mass (60.7% vs 36.4%; p=0.006) which was also a predictor of mortality (HR 1.747 [95%CI 1.008-3.027] p=0.047). When the participants were examined according to their level of amputation, 5-year mortality rates were higher in the patients with low muscle mass who underwent minor LEA (57.7% vs 37.0%, p=0.007) and major LEA (67.6% vs 33.3%, p=0.061). It is important to note the limitations of the study including the retrospective methodology and hence selection bias and the presence of infection or PAD was not recorded and therefore couldn't be included in the multivariate analyses. Despite this, the results are in line with those found in the study by Cheng et al (150) whereby outcomes are worse in diabetic foot patients with low muscle mass.

Mixed Vascular Patients

The remaining study by Heard et al examined the effects of low muscle mass in 314 patients with either occlusive or aneurysmal disease (152). Short-term outcomes (hospital LOS, procedures during admission and discharge destination) were examined as well as mortality at three years. The prevalence of low muscle mass was 41.1% (n=129), however unlike other studies it did not impact on any of the outcomes studied and was not predictive of time to death (HR 0.887 95%CI 0.595, 1.321. p=0.55) or in predicting discharge to nursing home/death in hospital vs discharge to home (OR: 1.352 CI: 0.720, 2.541. p=0.35). This study was also retrospective in nature and hence selection bias is a potential limitation. The other methodological difference between this study and the others that have used CT imagery to determine muscle mass is that Heard et al derived a skeletal muscle index (SMI) by normalising skeletal muscle area (SMA) at the L3 level for height. A SMI cut-off was then used that was based on studies in oncology patients to determine sarcopenia whereas the other studies that used CT imagery used SMA. There is the possibility that the cut-offs used were not appropriate for the study population and hence may have impacted on the number of participants diagnosed with sarcopenia.

Conclusion

When examining the literature surrounding muscle mass in vascular disease patients, in all studies except one (152), patients with poorer status had an increased risk of poorer clinical outcomes. However, these studies employ varying methods of determining muscle mass and varying cut-off values for determining low muscle mass which renders comparisons between studies more challenging. The majority of studies were of level III-2 evidence and

either neutral or negative quality except for one positive study (147) with most studies having a high risk of selection bias and lack of blinding.

Future research needs to address the methodological flaws present in the current literature and to also derive clearer definitions of low muscle mass to enable comparisons across the literature. Including measures of muscle strength or function would enable a more robust diagnosis of sarcopenia as current literature extrapolates measures of muscle mass only to diagnose sarcopenia.

Table 4: Summary of the literature on the prevalence of reduced muscle mass and the impact on outcomes in vascular patients

Study (author, year) Aim, Study Design	Participants	Method of diagnosing sarcopenia/reduced muscle mass	Relevant outcome measure	Results	Conclusion
Aneurysmal					
Hale et al, 2016 Aim: To determine the impact of sarcopenia on mortality following EVAR. Study design: retrospective cohort study	200 AAA patients who underwent EVAR repair. 175 males mean age 74±7.5 years. Median follow-up of 8.4 yrs. (IQR, 5.3-11.7).	• CT Scan measurement of third lumbar vertebral body (L3). • Muscle area was determined by manually segmenting and measuring the muscle groups (abdominal wall, paraspinal, psoas) utilizing a freeform mark-up tool. • The summation of these muscle groups = the total skeletal muscle area (cm2) used for establishing the presence or absence of sarcopenia. • Sarcopenia was defined as having a skeletal muscle area <114.0 cm2 (men) or <89.8 cm2 (women)	• Prevalence of sarcopenia (n,%) • Association between sarcopenia and • Time to death Likelihood of death during follow-up	**Prevalence of sarcopenia**: 25/200 (12.5%). **Prevalence in deceased vs living**: 18.5% vs 6.19%, p=0.016. **Mortality rate** (sarcopenic vs non-sarcopenic): 76% vs 48%, p=0.016. **Likelihood of death during follow-up**: Logistic regression analysis (multivariate): OR 3.17, 95% CI 1.2-9.54.	Sarcopenia is an independent risk factor of long-term mortality in patients treated with EVAR. Limitations: retrospective study. Did not measure aspirin or statin use which may impact on outcomes.
Indrakusuma et al, 2018. Aim: to assess the association between psoas muscle area (PMA) and survival in	228 patients, 104 were managed conservatively and 124 underwent AAA repair.	• PMA was defined as the cross-sectional area of the psoas muscle on a single CT slices using a standard protocol by	• Differences in survival rates over 10 years by Kaplan-Meier analysis	At the follow-up 110 patients had died (48.2%). **Difference in survival time in conservatively managed**: low PMA vs without low PMA: p=0.512	Low PMA did not affect survival time in conservatively or surgically managed AAA patients. Limitations:

patients with an asymptomatic AAA. Study Design: Retrospective cohort study.		two independent researchers. • The PMA cut-off was defined as the lower tertile of all patients (≤ 14.56cm^2). PMA was dichotomised. • Survival was deemed at 1 time point almost 4 years post last patient measures. • Survival time was examined in conservatively managed and surgically managed patients separately.		**Difference in survival time in surgically managed:** low PMA vs without low PMA: p=0.311	Retrospective study. Different CT scanners used throughout the study. Single slice measure of PMA could be improved with using all available CT data to measure entire PMA. Method of selecting PMA cut-off dependent on the study sample.
Newton et al, 2018 Aim: to evaluate psoas muscle size as a predictor of outcomes in patients undergoing endovascular aortic aneurysm repair (EVAR). Study Design: Retrospective cohort study.	. 135 males who underwent EVAR. Median (IQR) age of 70 (65, 76) years.	• Measurements of the left and right psoas muscles were obtained from pre-operative CT imaging from the axial CT slice immediately inferior to the 4th lumbar (L4) superior end plate. Total psoas muscle area (TPA) = the cross-sectional area of the left and right psoas muscles. • Patients were divided into tertiles with lowest tertile used as a working definition of sarcopenia (<2406mm^2)	• Prolonged LOS (>2 days) • Mortality over 5 years	**Prevalence** of sarcopenia: 45/135 (33.3%) **Prolonged discharge sarcopenic vs non-sarcopenic**: 39.4% (n=13) vs 33% (n=33) p=0.41 **Association between sarcopenia and 5-year mortality** (multivariate): OR 3.9, CI 1.2-12.9; p=0.027	A third of participants were sarcopenic however there was no difference in longer LOS between the two groups. There was an association between sarcopenia and longer-term survival with sarcopenic patients being 3.9 times more likely to have died by 5 years.

Tanaka et al, 2018 Aim: to evaluate the effect of preoperative total psoas area index (TPAI) on outcomes after descending thoracic aortic aneurysm (DTAA) repair. Study Design: Retrospective cohort study.	282 DTAA patients undergoing TEVAR or OSR with available pre-operative CT imaging.	Psoas cross-sectional area (cm2) of both right and left psoas muscles on CT images at the level of L3. • Measured psoas cross-sectional area was divided by body surface area (BSA) (m^2) to compute total psoas area index (TPAI). • Sarcopenia defined as TPAI<6.5cm^2/m^2	• Associations between sarcopenia and incidence of adverse events. • An adverse event was defined as a composite endpoint of three or more post-operative multisystem complications (Systems: cardiac, respiratory, gastrointestinal, neurological, renal, bleeding and infection), discharge other than home or death within 30 days.	**Prevalence of sarcopenia**: 154/282 (54.6%). **Incidence of adverse events sarcopenic vs no-sarcopenia:** TEVAR group: 41% vs 16%, p=0.020 OSR group: 49% vs 32%, p=0.012 **Post-op outcomes (sarcopenic vs non-sarcopenic**): **TEVAR:** D/C home 20 (59%) vs 33 (89%) p=0.003 Adverse event 14 (41%) vs 6 (16%) p=0.020 **OSR:** Respiratory: 48 (40%) vs 22 (24%) p=0.016 Renal: 48 (40%) vs 22 (24%) p=0.016 Cardiac: 54 (45%) vs 4 (26%) p=0.006 GI: 53(44%) 27 (30%) p=0.032 Neuro: 28 923%) vs 8 (9%) p=0.005 Multi-system: 23 (19%) vs 6 (7%) p=0.009 LOS: 12 (8-17) vs 9 (7-14) p=0.003 DC home: 65 (54%) vs 62 (68%) p=0.04 **Multivariate analysis for adverse events**: TPAI: OR 0.829 95%CI 0.726-0.946; p=0.0053 **Determinants of long-term mortality:** TPAI: parameter estimate, 0.36, p=0.003	Sarcopenic patients had worse outcomes in both short and long-term after DTAA repair. Poorer short-term outcomes relating to sarcopenia were more prevalent in the OSR group.
Occlusive Disease					
Study (author, year) Aim, study design	**Participants**	**Method of diagnosing sarcopenia/reduced muscle mass**	**Relevant outcome measure**	**Results**	**Conclusion**
Addison et al, 2018 Relevant aim: (1) To determine the prevalence of sarcopenia in older men with PAD; (2)	108 sedentary, community-dwelling men with confirmed PAD. Excluded those with claudication pain at rest.	• Whole body dual-energy x-ray absorptiometry scans were used to determine total body, leg, arm, trunk, and appendicular lean mass;	**Prevalence of PAD (%)** **Functional status:** *Treadmill test:* (1) claudication onset time (COT); (2) peak walking time (PWT),	**Prevalence**: 28/108 (25.9%) of PAD participants. Subgroup matched sample (42 per group): PAD: 10/42 (23.8%) vs non-PAD: 1/42 (2.4%)* **Functional outcomes:**	High prevalence of sarcopenia in PAD patients, which is significantly higher than in control group.

<table>
<tr>
<td>to compare the functional status of those with PAD with and without sarcopenia
Study Design: Cross-sectional Study.</td>
<td>Age: 53-88 (mean 68.7±0.6years)
Mean BMI: 27.8±0.4kgm^2
Mean ABI: 0.62±0.01(moderate severity)</td>
<td>fat mass; and percent body fat.
• The presence of sarcopenia was determined using ALM/ ht^2 (SMI) .
• Sarcopenia was considered to be present when SMI <7.26kg/m^2</td>
<td>defined as the walking time at which ambulation could not continue because of maximal claudication pain; and (3) claudication recovery time (CRT).
• 6-minute walk distance (6MWD)
• Walking impairment questionnaire (WIQ) scores (%)</td>
<td>
<table>
<tr><th>Outcome</th><th>No sarcopenia</th><th>sarcopenia</th></tr>
<tr><td>COT (s)</td><td>185±14.2</td><td>149±23.7*</td></tr>
<tr><td>PWT (s)</td><td>436±24.9</td><td>406±53.3</td></tr>
<tr><td>CRT (s)</td><td>395±28.5</td><td>592±97.9*</td></tr>
<tr><td>6MWD (m)</td><td>380±9.7</td><td>326±18.8*</td></tr>
<tr><td>WIQ distance</td><td>36.4±3.5</td><td>24.5±6.3</td></tr>
<tr><td>WIQ speed</td><td>38.7±3.1</td><td>34.4±6.4</td></tr>
<tr><td>WIQ stairs</td><td>49.5±3.6</td><td>50.0±6.5</td></tr>
</table>
*p<0.05
</td>
<td>Sarcopenia in PAD patients resulted in a faster onset of claudication pain and a longer claudication recovery time. They also had a shorter 6MWD. Indicating that sarcopenia affects physical function beyond that of PAD.</td>
</tr>
<tr>
<td>Juszczak et al, 2018
Aim: to study associations between core muscle mass and complication rates, length of hospital stay, and survival after surgical lower limb revascularization.
Study design: Retrospective cohort study</td>
<td>263 patients considered for surgical lower limb revascularization and underwent cross-sectional imaging. Median (IQR) age 68.9 (61.5, 75.6). 72.2% male. 64.6% were elective patients. 66% were Fontaine stage 3 or 4.</td>
<td>• Total psoas area (TPA) was assessed on CT angiograms used for diagnostic and planning purposes by 2 trained researchers using standard procedures.
• Single slice image corresponding to L4 was used.</td>
<td>• Survival (Kaplan-Meier).
• Effect of TPA and clinical factors on rate of complications and prolonged hospital stay (Logistic regression).</td>
<td>TPA in survivor’s vs patients who died during follow-up:
2041mm^2 [IQR, 1656-2524mm^2] vs 1741mm^2 [IQR, 1415-2129mm^2] p=0.001

Survival at 1 and 2 years:
TPA in first quartile vs TPA in 2nd, 3rd and 4th quartile: 0.74 and 0.66 vs 0.90 and 0.83; log rank test p<0.001

Cox-regression for mortality: TPA quartile HR 1.89, CI 1.07-3.35; p=0.028

TPA not associated with complication rates (p>0.05)

Median (IQR) LOS 1st quartile TPA vs 4th quartile:
9 days (4, 28) vs 6 day (4, 9); p=0.022
TPA not associated with prolonged hospital stay on regression analysis (p>0.05)</td>
<td>TPA lower in patients who died during follow-up. Those in the lowest TPA quartile were less likely to survive to 1 and 2 years compared to the other quartiles of TPA.
TPA was independently associated with mortality but not complications of prolonged LOS.
Limitations: retrospective study and selection bias based on availability of CT scans. Omission of</td>
</tr>
</table>

					BMI data which could not be used as a covariate in regression analyses
Matsubara et al, 2015 Aim: to examine whether sarcopenia is a prognostic factor for CLI patients. Study design: retrospective cohort study.	64 (43 male) CLI patients (Fontaine 3 or 4) who underwent revascularisation with CT imaging available. Mean age - sarcopenic: 73.8±9.6yrs, non-sarcopenic: 69.2±11.8yrs	• Transverse CT image at L3 to determine the cross-sectional areas of the skeletal muscles in the region using standard protocol. • Sarcopenia defined as skeletal muscle area of <114cm2 in men and <89.8cm2 in women.	• Overall survival (Kaplan-Meier). • Hazard rations (HR) for overall survival in uni- and multi-variate analyses.	**Prevalenc**e of sarcopenia: 28/64 (43.8%) **5-year survival**: Sarcopenic: 23.5 ± 0.18% vs non-sarcopenic: 77.5± 0.09% (p=0.001) **Univariate analyses**: presence of sarcopenia (HR, 4.24; 95% confidence interval [CI], 1.69-11.7; P =0 .002). **Multivariate analysis**: sarcopenia (HR, 3.22; 95% CI, 1.24-9.11; P=0.02)	Sarcopenia was prevalent in the sample with the sarcopenic patients having poorer outcomes in terms of 5-year survival. Limitations: retrospective and selection bias.
Matsubara et al, 2016 Aim: to investigate whether sarcopenia is a risk factor for cardiovascular events experienced by patients with CLI. Study design: Retrospective cohort study.	114 CLI patients with CT scan imaging.	• Transverse CT image at L3 to determine the cross-sectional areas of the skeletal muscles in the region using standard protocol. • Sarcopenia defined as skeletal muscle area of <114cm2 in men and <89.8cm2 in women	• CV event-free survival • <2-year death • Causes of death	**Prevalence** of sarcopenia: 53/114 (46.5%). CVD mortality sarcopenic vs non-sarcopenic: 15 vs 4 (p<0.01). **3-year survival sarcopenia vs non-sarcopenic**: 43.1% vs 91.2% (p<0.01) **Association between sarcopenia and CVD event-free survival**: HR, 4.81; 95%CI 2.58-9.43; p<0.01 (univariate) HR, 3.07; 95% CI, 1.56-6.29; P< .01 (multivariate)	Increased CVD-mortality rates in sarcopenic CLI patients and fewer survived to 3 years. There was a significant association between sarcopenia and poorer outcomes in terms of CVD event-free survival.
Sugai et al, 2018 Aim: to determine whether skeletal muscle mass and intramuscular fat deposition evaluated on CT can predict major	327 consecutive patients with PAD. Mean±SD age was 73.5±8.8 and 259 (79.2%) were male. Mean BMI 22.1±3.5kgm2.	• Psoas muscle area obtained via single slice CT imaging at the L3 level. • Patients were stratified into tertiles based on mean psoas muscle CT value.	• Associations between psoas muscle and incidence of poor outcomes over 2500 days follow-up.	MACLE, major CVD events and amputations all increased with decreasing mean psoas muscle CT value over the follow-up period (p=0.0082, 0.021, 0.0236 respectively). **Mean psoas muscle CT value as a predictor of MACLE (Univariate analysis**): HR 0.525 95%CI 0.428-0.657; p<0.001	Lower mean psoas muscle CT value is associated with more negative outcomes over time and is also an independent predictor of MACLE.

adverse cardiovascular and limb events (MACLE) in patients with PAD. **Study Design: Prospective cohort study.**			• (MACLE: CVD death, rehospitalisation due to stroke, ACS, heart failure or amputation) •	(multivariate analysis – 2 models) HR 0.784 95%CI 0.617-0.955; p=0.045 HR 0.699 95%CI 0.548-0.889; p=0.003	
Diabetic Foot Disease					
Study (author, year) Aim, study design.	**Participants**	**Method of diagnosing sarcopenia/reduced muscle mass**	**Relevant outcome measure**	**Results**	**Conclusion**
Cheng et al, 2017 Aim: to investigate the association of sarcopenia and diabetic foot disease (DFD) in a cross-sectional study. Study Design: Cross-sectional study.	1105 T2DM patients, (120 with newly diagnosed DFD). Mean age of DFD 66.84±11.18yrs.	• Body composition assessed using dual-energy x-ray absorptiometry scans. • Skeletal muscle index was calculated, and sarcopenia was defined as SMI <7kg/m2 in men or 5.4kgm2 in women.	• % of sarcopenia in DFD and non-DFD groups. • Skeletal muscle Index (SMI). • Associations between sarcopenia and complications/ outcomes.	**SMI (DFD vs non-DFD):** 6.79 ± 1.20 vs. 7.21 ± 1.05 kg/m2, *P* < 0.001. **% of sarcopenia in DFD vs non-DFD:** 35.3% vs. 16.4%, *P* < 0.001. **Multivariable logistic regression analysis**: sarcopenia was independently associated with DFD (OR 2.06[95% CI 1.08,3.95], *P* = 0.029. **Median ulcer size** (Sarcopenic vs non-sarcopenic DFD) 6.5cm^2 (2.1, 12.0) vs 3.0cm^2 (1.2,6.0) p=0.007)]. **Ulceration:** Were more likely to have multiple ulcers (p=0.022) and of worsening severity (p=0.003). **Amputation rate** (Sarcopenic vs non-sarcopenic DFD) 21.4% vs 7.8%, p=0.044	Sarcopenia is independently associated with DFD. Worse prognosis is seen in patients with DFD accompanied by sarcopenia compared to DFD without sarcopenia.
Kim et al, 2018 Aim: to determine whether sarcopenia affects the mortality	167 patients (112 males, mean age 61.9years, range 29-80yrs) who	• Sarcopenia was defined by using sex-specific cut-off points for skeletal muscle index (SMI) at the	• Prevalence of sarcopenia.	**Prevalence** of sarcopenia: 112/167 (67.1%). **5-year mortality**	Statistically significant difference in survival between

rate of patients undergoing diabetic foot amputation. Study Design: Retrospective cohort study.	underwent LEA due to diabetic complications and had an abdominal CT scan within 1 year before amputation. Participants were separated into major and minor LEA groups according to amputation level.	level of the third lumbar vertebra (L3). • The L3 SMI was calculated as the total area of the L3 skeletal muscle area (cm2) divided by the height squared (m2). • Cut-offs of 52.4 cm2 /m2 for men and 38.5 cm2 /m2 for women were used to determine sarcopenia.	• Overall 5-year mortality rate. (Kaplan-Meier) Associations between factors and survival rate (Cox regression)	sarcopenic vs non-sarcopenic (whole sample): 60.7% vs 36.4%; p=0.006 sarcopenic vs non-sarcopenic (minor LEA): 57.7% vs 37.0%, p=0.007. sarcopenic vs non-sarcopenic (major LEA): 67.6% vs 33.3%, p=0.061 **Sarcopenia as a prognostic factor for mortality** (HR, [95%CI]): Univariate: 2.252 [1.161-4.369] p=0.016 Multivariate: 1.747 [1.008-3.027] p=0.047	sarcopenic and non-sarcopenic on univariate and multivariate analyses. Limitations: retrospective, selection bias, presence of PVD and infection not collected.
Mixed vascular patients					
Study (author, year) Aim, study design.	**Participants**	**Method of diagnosing sarcopenia/reduced muscle mass**	**Relevant outcome measure**	**Results**	**Conclusion**
Heard et al, 2018 Aim: to investigate the prevalence of sarcopenia in a vascular patient group. Study Design: Retrospective cohort study.	314 patients admitted to a vascular unit. 62.4% male mean age 70.8yrs. Occlusive disease in 73.3% (n=230) of patients, 22.3% aneurysmal patients. Data collected retrospectively.	• Transverse computed tomography (CT) slice at the level of the third lumbar vertebral body (L3) analysed to derive a skeletal muscle area (SMA) in cm^2. • SMA was normalised for height to derive skeletal muscle index (SMI). • Sarcopenia was defined as SMI of <41cm2/m2 in females and non-obese males and <53cm2/m2 in obese males	• Hospital length of stay (LOS). • Procedures during admission. • Discharge destination and mortality at 3 years.	**Prevalence** of sarcopenia: 129/314 (41.1%). No significant difference in operations/procedures undergone by sarcopenic and non-sarcopenic participants (p=0.28). No statistically significant difference in likelihood to have a non-home discharge. (p=0.10). **Median LOS of sarcopenic vs non-sarcopenic**: 9 (5,19) vs 8 (4, 16) p value not reported. **Mortality**: Sarcopenia not significantly predictive of death on Kaplan-Meier analysis (p=0.22). **Sarcopenia and predictive of time to death**: HR 0.887 95%CI 0.595, 1.321. p=0.55	There was a high prevalence of sarcopenia is patients however it did not impact on admission outcomes or mortality at 3 years. There was a median 1-day difference in LOS however p value wasn't reported to determine significance.

				Sarcopenia and predicting discharge to nursing home/death in hospital vs discharge to home: OR: 1.352 CI: 0.720, 2.541. p=0.35	

2.2.2 Are individuals with vascular disease at risk of poor micronutrient status?

The literature review across the five databases (search strategy displayed in appendix 1) yielded 2377 articles for consideration. Following the removal of duplicates (n=142) and screening by title and abstract, 246 remained. Full text screening resulted in 14 articles, with hand-searching of reference lists yielding an additional 11. Therefore 25 articles were included in the review (appendix 2 displays the screening process). There were three studies in aneurysmal disease (158-160), seven studies in diabetic foot disease (161-167), six in venous disease (90, 168-172) and nine in occlusive disease (85, 87, 88, 91, 113, 116, 173-175). A summary of the studies is presented in table 5.

Overall, the majority of studies were of level IV evidence according to the 'aetiology' arm of the NHMRC hierarchy of evidence (132). Four studies were level II evidence (90, 91, 166, 167) and one was level III-2 (85). One study (161) was rated as positive quality, seven studies were neutral (85, 88, 91, 113, 165-167) and seventeen were negative quality (87, 90, 116, 158-160, 162-164, 168, 169, 171-175). Key limitations were high risk of selection bias and lack of blinding of outcome assessment. Other limitations varied and are discussed in the sections to follow (appendix 3).

Aneurysmal Disease

Three studies were located that investigated micronutrient status in individuals with aneurysmal disease and are summarised in Table 5 (158-160). One study investigated vitamin E status (159) whereas the two remaining studies investigated B group vitamin status (158, 160). All three were prospective case control studies with healthy controls, the vitamin E study (159) also included a third group, atherosclerotic patients referred for coronary bypass surgery (CABG).

All three studies are of level IV evidence according to the NHMRC evidence hierarchy (132) and all were of negative quality due to high likelihood of bias in subject selection, and inadequate consideration of study limitations and bias in the conclusions. One study also had inadequate description of outcome measures (159) and another study inadequately described statistical methods (160).

Sakalihasan (159) explored vitamin E status in nineteen AA patients undergoing elective repair, compared to coronary artery bypass graft (CABG) patients (n=18) and healthy volunteers (n=13). Plasma vitamin E and the vitamin E/total lipid ratio were measured in all three groups, with significantly lower levels ($p<0.001$) of both parameters observed in the AA group compared to both the CABG and healthy control groups. It was hypothesized that there is an increased rate of oxidative stress and lipid peroxidation in the AA group and subsequent increased utilisation of vitamin E resulting in lower plasma levels of the antioxidant. Another important aspect to note is the significant age difference between the groups with the healthy volunteers and CABG patients being much younger (mean age 35.2±16.3 years and 61.2±7.4 years respectively) than the AA participants (mean age 72.5±6.6 years) which may affect results as lower plasma Vitamin E levels have been observed in older adults, particularly those with frailty (176).

Both studies investigating B group vitamins observed lower levels in the AA group compared to controls. Lindqvist et al compared the serum levels of folate, vitamin B12 and B6 of infrarenal AA patients (n=119) classified in three groups, (1) small non-ruptured (2) large non-ruptured and (3) ruptured, to a group of healthy controls (n=36) (158). All blood samples were collected pre-operatively and before the administration of any blood products. The authors explored the difference in levels between the AA who had ruptured

versus controls and found significantly lower folate ($p<0.01$) and vitamin B6 levels in the ruptured AA group ($p<0.001$). Vitamin B12 was also lower in the ruptured verses controls ($p<0.01$) but was higher in the small non-ruptured AA compared to controls ($p<0.01$). When ruptured versus non-ruptured AA groups were compared, levels of all three vitamins were significantly lower in the ruptured group indicating that there may be worsening B Vitamin status as severity of disease increases.

Warsi et al compared thirty-eight AA patients to 36 controls for vitamin B12 and folate status. The authors observed a lower B12 level in the AA group compared to the controls ($p<0.004$) and while mean folic acid level was lower in the AA group, it didn't reach statistical significance (8.02ng/mL (SE±0.71) vs 9.8ng/mL (SE±0.69) $p>0.05$) (160).

No further studies were located that explored micronutrient status in aneurysmal disease, hence drawing conclusions from only three studies that are of negative quality and level IV evidence should be done with caution. Results indicate that aneurysmal patients tend to have lower levels of some micronutrients compared to controls and that there may be an association with disease severity, however there is a strong possibility of selection and assessment bias across the studies.

Diabetic Foot Disease/Ulcers

Seven studies were located that investigated micronutrient status in individuals with DFD or DFUs (table 5) (161-167). Five explored vitamin D (161, 163-165, 167), one examined iron status (166) and the remaining one explored a range of micronutrients (162).

Two studies (166, 167) were classified as level II evidence according to the NHMRC hierarchy of evidence (132) and the remaining five studies were level IV. Of the seven studies, one was of positive quality (161), 3 were neutral (165-167) and 3 were negative quality (162-

164). The key quality issues were lack of blinding at outcome measures, and high risk of subject selection bias. Inadequate considerations of study limitations and biases was also an issue across the negative and neutral studies. Three studies were lacking in appropriate comparable study groups or did not adjust for differences in their analyses (162-164), two studies had issues with unclear or inadequate descriptions of outcome measures (163, 164) and four studies did not have robust descriptions of statistical methods (163-165, 167).

All five studies investigating vitamin D levels, compared individuals with DFUs to individuals with diabetes and no ulceration. Two studies also included a healthy control group free from diabetes (161, 164). Study samples ranged from 30 -162 DFU participants and all five studies examined the 25(OH)D form of vitamin D.

Caglar et al compared the mean vitamin D level between 58 DFU and 47 newly diagnosed type 2 diabetes patients, the majority of which were male (163). Lower mean vitamin D level was observed in the DFU group (7.9±6.3 vs 11.6±6.5 $p<0.001$) compared to the non-DFU group, with the mean level of the DFU group being at a level consistent with significant deficiency (<10ng/ml). Whilst the non-DFU group had a higher mean vitamin D level, it was still within the level consistent with 'deficiency' so while DFU patients have a lower vitamin D status, individuals with newly diagnosed type 2 diabetes also had poor status. Similar results were also observed in a study which compared vitamin D status in DFU participants to T2DM participants without ulceration and also to healthy controls (164). Significantly lower levels (ng/ml) were observed in the DFU participants compared to the T2DM group (11.8±11.3 vs 19.0±14.4, $p<0.01$) and the healthy controls (11.8±11.3 vs 27.3±12.3, $p<0.01$) and also in the T2DM group compared to the controls (19.0±14.4 vs 27.3±12.3, $p<0.01$), again indicating that individuals with T2DM have poorer vitamin D status compared to

healthy individuals and that it worsens in those with DFU. This study found that >55% of DFU participants had a vitamin D level <10ng/ml (severely deficient) and that there was a significant negative correlation ($r=-0.241$, $p<0.01$) between ulcer wound classification and vitamin D level. This is further evidence that poorer vitamin D status occurs with increased disease severity. Proposed mechanisms for poor vitamin D status in DFU patients is likely multi-factorial. Firstly, reduced mobility due to wounds could impact on a patient's ability to mobilise outdoors and hence exposure to sunlight required for conversion of vitamin D into its active form may be reduced. Secondly, vitamin D is a non-specific regulator of the immune system, playing a role in the induction of antimicrobial peptide production in keratinocytes of DFU's (164), and lowering pro-inflammatory cytokines while increasing the anti-inflammatory response such as through the induction of Interleuking-10 (161). Hence utilisation of vitamin D may be increased in DFU patients during inflammation.

Tiwari et al (165) investigated 125 DFU participants and 164 individuals with diabetes but free from foot disease to study the prevalence of vitamin D inadequacy at 3 levels of deficiency (suboptimal, deficient or severe deficiency). They also examined the risk of vitamin D inadequacy in DFU cases and the control group. Mean serum vitamin D levels (nmol/L) were lower in the DFU group (40.25±38.5 vs 50.75±33.0, $p = 0.012$) and consistent with being in the deficient category. Controls had a higher level but were still in the suboptimal category. The prevalence of severe deficiency appeared higher in the DFU group (45.6% vs 17.3%) however the p value was not reported. When risk of vitamin D inadequacy was examined, there was a higher risk (OR(95%CI)) of severe deficiency in DFU participants which held true when adjusted for other factors such as age (OR 4.3 (2.5,7.5)), HbA1c level (OR 3.7 (2.1, 6.4)) and duration of diabetes (OR 3.8, (2.0,7.0)) ($p <0.0001$ for all).

Similar results were observed by Zubair et al (167) in younger DFU patients in India with lower median (IQR) vitamin D levels compared to patients with diabetes and no ulceration (8.4 (7.1-9.2) ng/ml vs 29.8 (15.6-44.2) ng/ml, p<0.005). The median vitamin D level for DFU participants was again in the severely deficient category with the non-DFU being in the deficient category. This study also explored vitamin D as a predictor for DFU development via multiple linear regression and forward stepwise regression and found that serum vitamin D level independently predicted DFU development (R^2 Coefficient 0.0046, p<0.001).

One study was located that contradicted the findings of the other studies. Afarideh et al (161) investigated vitamin D levels in 30 DFU, 30 patients with type 2 diabetes but no ulcer and 28 controls and found increasing levels (median, (IQR)) of vitamin D from a disease-free state (controls) to those with ulcers of 8 (7.9) ng/ml, 16.0 (14.1)ng/ml and 16.8 (24.6)ng/ml (p=0.002) although the increase in levels between non-ulcerative diabetes and those with ulcers didn't reach significance (p=0.478). Further to this, a positive correlation of circulating vitamin D with DFU was observed in an adjusted logistic regression model (OR 2.194; 95% CI 1.003, 4.415) with higher levels of vitamin D leading to increased risk of DFU. Interestingly, while higher levels were observed with increasing disease severity, the mean vitamin D level in the DFU patients was 26.5ng/ml which is still classified as deficient.

Out of the seven studies located, six found micronutrient deficits, particularly vitamin D, in individuals with DFU compared to controls with diabetes and/or healthy controls highlighting nutritional vulnerability. The cause of the deficits cannot be determined from the studies due to nature of their design, however potential reasons include increased utilisation of micronutrients due to inflammatory state, reduced intake of nutrients, and in the case of vitamin D there could be reduced exposure to sunlight due to the physical

impact of DFU. The associations found between DFU presence and serum vitamin D levels by some studies lend support to the notion that nutrient deficits require attention to ameliorate disease progression in this group. When interpreting these results, it is important to consider the quality of the evidence as there is a high potential for selection and assessment bias across most of the studies.

Venous disease/Ulcers

Six studies (table 5) were located that examined micronutrient status in individuals with VLUs (90, 168-172). Study sample sizes ranged from 7-50, with four studies examining venous ulcers only (90, 170-172) and two studies including a heterogenous group of participants that included venous ulcers (168, 169). Two studies examined vitamin D only (90, 170), whereas the other four examined a range of micronutrients.

One study was classified as level II (90) and the remainder as level IV according to the NHMRC levels of evidence (132). All studies were rated as negative quality with the key issues being a lack of blinding of outcome assessment, and high risk of subject selection bias along with inadequate consideration of study limitations when making conclusions. Four studies did not have a clearly stated research question (168-170, 172), and four studies did not have adequate description of or robust statistical methods (90, 168-170). Three studies did not clearly indicate the presence or absence of funding or conflicts of interest which could be a source of bias (168, 169, 171).

Burkievcz et al and Krejner et al both studied the prevalence of vitamin D deficiency in 27 and 19 individuals with VLUs respectively (90, 170). Burkievcz compared the 27 chronic VLU outpatients with 58 controls recruited from rheumatology clinics (170). Vitamin D levels were separated into 4 categories ranging from severe deficiency (<8ng/dl) through to

normal (>30ng/dl) and the proportion of individuals in each category were determined and compared between the two groups. A higher proportion of VLU participants were found to have insufficient vitamin D status (8-20ng/dl) compared to controls and a higher proportion of controls were in the normal status category (p=0.04). Based on how the data were figuratively presented, it wasn't possible to determine the proportions in the remaining categories accurately. Another issue noted with this study is that the vitamin D cut-offs appear to have utilised the incorrect units (ng/dl) when the reference used indicated units of mg/dl or ng/ml. However, this could be an error in the manuscript rather than a methodological error based on the study results.

Krejner et al made no comparisons to a reference group in their pilot study (90). In this study, normal vitamin D status was classified as >30ng/ml with none of the 19 participants attaining normal status. Mean vitamin D level was 18.2±7.1ng/ml (Range 4-29ng/ml) which is in the "insufficient" category and while a negative correlation was found between vitamin D level and wound healing rates, it did not reach statistical significance (R= -0.34, non-significant (p not reported)).

Multiple micronutrients were studied in the remaining four studies. Agren et al compared serum selenium, iron, copper and zinc levels in 24 elderly women with leg ulcers (12 venous, 12 arterial) to 40 elderly adults (21 women) with dementia but with no history of leg ulcers and the differences in micronutrient levels in those with poor and good ulcer healing (168). The mean (±SD) age of both groups appeared similar at 81±6 years (leg ulcer group) and 80±5 years (control group) but no statistical comparisons were reported. Sub analysis by age and gender reported no correlation between these variables and levels of trace elements, however no data were presented to support this. Mean serum iron, zinc and

selenium levels were lower in the ulcer group ($p<0.05$, <0.001 and <0.05 respectively) with no difference in copper levels (p value not reported). Nineteen participants were in the "good healing" group and five were in the "poor healing" group. Comparisons found that serum copper and the copper: zinc ratio were higher in the poor healing group ($P<0.02$ and <0.01 respectively). The authors concluded that this difference was linked to the proposed relationship between copper levels and a more pronounced inflammatory state.

Balaji and Mosley examined the proportion of participants with deficiencies in vitamin C, zinc, folate and iron in 50 individuals with large (average area 169cm^2, range 110-250cm^2) non-healing leg ulcers (169). The ulcers were of mixed origin with 17 arterial, 25 venous and 8 "others". Participants were analysed as a total group and by subgroup. Overall, 60% (n=30) had vitamin C deficiency and approximately 20% were deficient in the other nutrients. Of the venous participants, 72% (18/25) were vitamin C deficient and in the "other" group seven out of eight participants were vitamin C deficient. No information was provided regarding the "other" group and no rationale was provided for the cut-offs used to determine deficiency, so results need to be interpreted with some caution.

The remaining two studies were very small samples of seven (172) and eight (171) participants with VLUs. Tobon et al examined vitamins A and C and zinc in overweight or obese participants and the correlation to wound healing using the Leg Ulcer Measurement Tool (LUMT) (171). The LUMT evaluates wounds using 14 clinician-rated domains that includes type and amount of necrotic tissue, granulation tissue, edges, peri-ulcer skin viability, type and location of leg oedema and assessment of bioburden. Three patient-related domains related to the ulcer are also included, the amount and frequency of pain and quality of life. Scores range from 0-68 with higher scores indicative of greater wound

severity (171). Of the eight participants, three had a vitamin C level below the range, one had a low zinc level and no participants were low in vitamin A. Despite the small sample size, a significant negative correlation (r^2 -0.83, p=0.01) was observed between vitamin A level and LUMT score meaning that lower vitamin A is associated with poorer healing (higher LUMT score). Surprisingly, the reverse was found for vitamin C, a positive correlation (r2 = 0.74, p=0.04) was observed between LUMT score and vitamin C, indicating that higher vitamin C levels are associated with poorer healing (higher LUMT score). The authors surmised that this unusual result could have been due to confounding factors that were unknown.

In the study by Wipke-Tevis & Stotts, none of the seven participants with VLUs had a low vitamin C level and three had a low zinc level (172). The mean serum levels of both micronutrients were in the normal ranges. The result for vitamin C in both of these small studies is very different to that observed by Balaji and Mosley where a high proportion of participants were classified as vitamin C deficient (169). An important difference apart from sample size is the severity of the ulcers in the study. Balaji and Mosely had an average ulcer area of 169cm^2 compared to a mean of 6.1cm^2 (172) and a median of 9.5cm^2 (171) in the other two studies which indicates that ulcer severity/extent could impact on vitamin C status via increases in utilisation as ulcer severity increases.

While there are some conflicting results in the studies examining VLUs and other leg ulcers, a number indicate that suboptimal micronutrient status is a potential issue and that status may vary due to disease severity/ulcer size. Comparisons between studies is however made more challenging by the variations in reference ranges employed to determine normal or

deficient micronutrient status. The quality of the studies is poor with a high risk of selection and assessment bias and hence results need to be interpreted with caution.

Occlusive Disease

Nine studies were located that examine micronutrient status in occlusive disease and are summarised in table 5 (85, 87, 88, 91, 113, 116, 173-175). One study examined vitamin C (87), two studies investigated B group vitamins (113, 173), one looked at multiple nutrients (175), four studied vitamin D (85, 88, 91, 174) and 1 study looked at iron status, which also included B group vitamins (116). Study sample sizes varied from 35 to 1435 patients. Four studies were prospective (87, 173-175) and five were retrospective audits or sub-analyses of a larger cohort study (85, 88, 91, 113, 116).

Of the nine studies, 7 were classified as level IV evidence (87, 88, 113, 116, 173-175), 1 was level III-2 (85) and 1 was level II (91). Four studies were rated as neutral quality (85, 88, 91, 113), with the remaining five being of negative quality (87, 116, 173-175). Key potential sources of bias across the studies were in subject selection and in the lack of blinding of outcomes. Three studies did not have a clearly articulated research question (113, 173, 175). Four studies did not adequately consider study limitations in their conclusions (116, 173-175) and three did not declare the absence of presence of conflicts of interest and/or funding sources (113, 174, 175).

The single study examining vitamin C investigated vitamin C levels in 85 patients with Fontaine stage 2 PAD (78% male, Mean age 68±10years), 106 hypertensives without PAD (42% male, Mean age 62±14 years), and 113 healthy subjects (45% male, Mean age 61±12 years) (87). Serum vitamin C concentrations were found to be lower among PAD patients (median (IQR) 27.8 (15.8-42.5) umol/L, $p<0.0001$) compared to the other two groups with

subclinical vitamin C deficiency observed in 14% of the PAD patients but not in the other groups. Vitamin C level was negatively correlated (r=-0.742, P<0.0001) with serum C-reactive protein (CRP) concentrations which was significantly higher in PAD patients (P<0.0001). This indicates that the presence of inflammation impacts negatively on plasma vitamin C levels. The relative risk of vitamin C deficiency in PAD patients with a CRP>4.8mg/l (the median level in this study) was 1.68 (95% CI, 1.27-2.21). A significant positive correlation was observed between absolute claudication distance (ACD) and vitamin C level, (r=0.552, p<0.0001) indicating those with higher vitamin C levels could walk further without encountering claudication pain. The association between vitamin C and inflammatory markers indicates increased utilisation or increased requirements for vitamin C in inflammation.

B group vitamins were solely examined in two studies and included in a third study examining iron status. Zsori et al reported plasma vitamin B12 and folate levels as part of their retrospective study investigating B group vitamins, MTHFR-C677T polymorphism and risk of PAD (113). Two-hundred and ninety-three patients with PAD (186 males, mean age 66 ± 0.7 years) and 293 matched controls (mean age 62 ±0.8 years) were examined. There was no difference in mean folate levels between PAD patients and controls (15.5 ± 0.4nmol/L vs 16.0±0.5 nmol/L, p=0.745), however PAD patients had a significantly lower B12 compared to controls (222 ±6.3pmol/L vs 296±9.3pmol/L, p<0.005). A significantly higher proportion of PAD patients had a lower level of B12, with 43% of PAD patients, compared with 25% of controls having a B12 in the lowest quartile (<188pmol/L).

Bunout et al compared serum folate, and vitamin B12 levels of 32 patients with PAD (aged 69.6 +/- 11 y) to those of 24 age- and sex-matched healthy individuals (173). They found the

reverse of Zsori et al (113) with lower folate levels in the PAD patients compared to the controls (4.48 +/- 2.42 and 7.14 +/- 4.04 ng/mL, p<0.02) and no differences in vitamin B12 levels between vascular patients and control subjects. An important consideration is the difference in sample size between this study and Zsori et al (113) which may in part account for the difference in outcomes. There were also differences in the robustness of the study methodology and reporting which may account for differences in results due to increased bias in the study by Bunout et al (173) compared to that of Zsori et al (113). Bunout et al (173) did not include blinding of assessment outcomes and PAD patients with diabetes and renal disease were excluded. The severity of PAD in the participants of Bunout et al (173) is unclear and hence there may be differences in the type and severity of PAD which also may have led to differences in results as disease severity has been associated with micronutrient status.

Similar to other measures of nutritional status, there is evidence that vitamin B12 and folate deficits worsen with disease progression. Vega de Ceniga et al assessed the prevalence of vitamin B12 and folate deficits in 624 patients suffering from IC (n=420, 67.3%) and critical CLI (n=204, 32.7%) (116). Overall prevalence of B12 and folate deficit (<179pg/mL and <2.4ng/mL respectively) was low in both IC and CLI patients, however the differences between the IC and CLI were significant, with higher prevalence of deficit in the CLI or patients with more progressive disease (6.7% vs 15.7%, p=0.002 and 2.9% vs 6.4%, p=0.018 for B12 and folate respectively). This study also examined iron and haemoglobin deficit and similarly to the other nutrients, found a higher prevalence of deficit in the CLI group compared to the IC participants demonstrating worsening iron status in more severe disease.

A study by Mansoor et al involving 65 patients with PAD (35 males) and 65 matched controls investigated the relationships between plasma trace element and vitamin levels and PAD and was the only study located that examined multiple micronutrients in occlusive disease participants (175). Of the four trace elements (selenium, zinc, copper and iron) no significant differences ($p>0.05$) were observed between the PAD group and controls. With selenium, no significant difference in selenium level was found when the PAD patients as a whole group were compared to controls however subgroup analysis showed that patients with supra-inguinal disease had a significantly lower selenium level compared to controls ($p=0.01$). Vitamin E, A and beta-carotene levels were also studied with higher vitamin E levels in the PAD patients (mean (95%CI): 35.4umol/L (28.3-42.6) vs 30.3umol/L (27.3-33.3). $p<0.05$). No difference was found in vitamin A levels, however, the beta-carotene level was lower in the PAD group which may indicate a higher rate of conversion of beta-carotene into vitamin A to maintain vitamin A levels in PVD patients.

Four studies were located that examined vitamin D in occlusive participants. Two studies were conducted by the same research team utilising data from a large cohort study to firstly examine vitamin D status in 402 PVD patients (305 non-PAD comparator group) and to test for associations with functional performance (88) and in the follow-up study (91), mortality and decline in function were explored in 395 PVD patients and compared to 263 non-PAD controls . In both studies, baseline vitamin D levels were defined according to four categories and functional outcomes were measured including a range of walking and balance tests and the Short Physical Performance Battery (SPPB) (refer to summary table 5). In the second study functional decline was examined over a mean follow-up of 39.3±16.4 months and mortality, including deaths from coronary heart disease (CHD), stroke, PAD and other CVD were examined over a mean follow-up of 47.5±16.3months (91). In the first

study (88), no significant difference was found in mean vitamin D levels between PAD and Non-PAD participants (53.7±24.9nmol/L vs 54.6±23.7nmol/L, p=0.63) and while a significant proportion of both groups had some level of vitamin D insufficiency, there was again no difference between groups. Associations were examined between vitamin D level and functional performance outcomes and while there were significant differences in a range of variables (poorer outcomes at lower vitamin D levels), statistical significance was lost when all potential confounders were included in the analysis. In the second study (91), PAD patients with vitamin D levels in the lowest category had a faster decline in the 6-minute walk test, and SPPB scores (p = 0.04 and 0.028 respectively). There was also a significant association between lower vitamin D levels and faster decline in 6-minute walk test when adjusted for all confounders (p=0.012). Similarly, there was also an association between vitamin D and function in non-PAD participants with a significantly faster decline in fast paced 4-metre walking velocity (4MWV) between the lowest and highest category of vitamin D status (p=0.0164) and a significant association between vitamin D and faster decline in fast-paced 4MWV when adjusted for confounders (p = 0.003). No associations were observed between vitamin D and mortality in either the PAD or non-PAD groups. From these studies, it appears that vitamin D insufficiency is common in both PAD and non-PAD participants that doesn't affect function/performance at baseline, but when examined over time, poorer vitamin D status leads to a faster decline in function/performance across both groups.

A large retrospective study (85), investigated the associations between vitamin D level and risk of amputation in 1435 patients (mean age 70.8±10.5 years) with PAD. Vitamin D deficiency was classified as <20ng/ml which was a lower cut-off than that used in the studies by McDermott et al (88, 91), with 40.8% of participants being classified as vitamin D

deficient. When those who underwent amputations were compared to those who did not have an amputation, prevalence of deficiency didn't reach statistical significance with 52% deficiency compared to 40% in the no amputation group (p=0.063). When amputation rate was compared, the rate was higher in participants who were vitamin D deficient (6.7% vs 4.2%, p=0.029), however during logistic regression analysis where confounders were included, there was no statistical association between vitamin D level/status and amputation. The link between the prevalence of vitamin D deficiency and amputation is likely multifactorial and probably not dissimilar to that proposed for DFU patients. Amputation implies more progressive PAD and hence reduced mobility due to pain and wounds could impact on a patient's ability to mobilise outdoors and hence exposure to sunlight required for conversion of vitamin D into its active form may be reduced. Secondly, vitamin D is a non-specific regulator of the immune system, lowering pro-inflammatory cytokines while increasing the anti-inflammatory response such as through the induction of Interleuking-10 (161). Given PAD has an inflammatory component, utilisation of vitamin D may be increased in during inflammation.

Subjective feeling of disability was investigated by Fahrleitner et al (174) in relation to vitamin D status in a retrospective study of 161 (97 males) PAD outpatients. The PAD participants were separated into two groups, group A (PAD stage 2, n=84) and group B (PAD stage 4, n=77) to enable comparisons across disease severity and to 45 age and gender-matched controls. Serum 25(OH)D3 was measured with deficiency set at <9ng/ml. Level of disability was assessed via a scored questionnaire and classified as mildly, moderately or severely handicapped in daily life due to disease. No details were provided on the questionnaire or how the classification of patients into the 3 groups was conducted and is a major limitation of this study. Mean vitamin D3 levels were significantly lower in group B

compared to controls (p=0.0001) and compared to group A (p=0.0001). There was no difference between controls and group A. A high proportion (71.4%) of group B had vitamin D3 deficiency with 31% showing levels that placed them at risk of osteomalacia. Prevalence wasn't reported in the other 2 groups. When vitamin D3 level was examined according to self-assessed level of disability, individuals with severe disability had a significantly lower vitamin D3 level compared to both mild and moderate disability groups (p = 0.0001 for both). Those with moderate disability had a lower mean vitamin D3 level compared to the mild group which approached statistical significance (p=0.05). The results remained true when stratified for severity of disease.

Whilst in general, the quality of the studies in PAD are of lower quality and level of evidence, the results indicate that vitamin D deficits are common in PAD patients but the association between vitamin D and outcomes varies depending on the outcome studied. It also appears that while vitamin D is an issue in PAD patients, the effects are also observed in non-PAD individuals.

Conclusion

In conclusion, micronutrients have crucial roles to play in the health of vascular disease patients due to their roles in scavenging of free radicals, skin and tissue integrity, immunity and wound healing. Research has investigated micronutrient status in vascular disease patients; however, the extent of this research is variable across the micronutrients and the disease types. Twenty-four studies were located that examined micronutrient status in vascular disease patients. Research highlights that micronutrient deficits are prevalent in patients with vascular disease, particularly in vitamin D and B group vitamins and in some studies, vitamin C, zinc and iron. Results indicate that disease severity has an impact on

level/prevalence of deficiency which may be related to increasing levels of inflammation with disease progression. The impact of micronutrient deficiencies varies depending on the outcome studied but it is apparent that individuals with deficiencies are potentially at risk of poorer outcomes. The impact on outcomes isn't isolated to patients with vascular disease as these results were also observed in control groups in some studies. The potential causes or mechanisms for micronutrient deficiencies in this group are likely multifactorial, including suboptimal diet (177, 178), potential drug-nutrient interactions (179) and altered utilisation/metabolism of micronutrients in vascular patients (162). What is apparent is that identifying and addressing micronutrient deficits is important in this patient group to optimise nutritional health and outcomes and that nutrition and dietary guidelines for the management of vascular patients must include recommendations for the assessment or micronutrient status and management strategies.

When interpreting these studies, it is important to consider that the methodological design and/or the quality of reporting was neutral at best, except for one positive study (161) and that subject selection bias was highly likely across the studies. Assessment bias is also a key potential bias with a lack of blinding of outcome assessment a key issue across most studies. Future studies should address these issues to strengthen the body of evidence in this area of research

Table 5: Summary of articles examining micronutrient status in vascular disease patients

<table>
<tr><th>Study
(author, year)
Aim. Study design.</th><th>Participants</th><th>Relevant outcome measure</th><th>Results</th><th>Conclusion</th></tr>
<tr><td colspan="5">Aneurysmal Disease</td></tr>
<tr><td>Lindqvist et al, 2012.
Aim: Secondary aim to investigate whether AAA are associated with decreased levels of Vitamins B6, B12 and/or folate.
Study design: case control study.</td><td>119 infrarenal AAA patients (n=78 non-ruptured, n=41 ruptured) and 36 controls.

Median age ≥70 years and >75% male across the groups.</td><td>• Serum levels of B12, Folate, B6 between controls, non-ruptured AAA (small vs large) and ruptured AAA participants</td><td><table><tr><th></th><th>Control</th><th>Small non-rupture</th><th>Large non-rupture</th><th>Rupture</th><th>P value rupture vs no rupture</th></tr><tr><td>B12 (pmol/L)</td><td>264 (194-321)</td><td>365 (247-459)*</td><td>246 (220-333)</td><td>197 (147-265)*</td><td><0.001</td></tr><tr><td>Folate (nmol/L)</td><td>12.5 (10.5-15.5)</td><td>11.5 (8.9-14.2)</td><td>12.0 (9.0-15.6)</td><td>10.4 (8.2-12.6)*</td><td>0.022</td></tr><tr><td>B6 (ug/L)</td><td>4.7 (3.5-6.4)</td><td>3.69 (3.0-6.5)</td><td>3.6 (2.7-5.8)</td><td>2.7 (2.0-3.6)**</td><td><0.001</td></tr></table>Median (IQR) presented.
*p<0.01 **p<0.001 compared to the control group</td><td>Significantly lower median folate and B6 levels in ruptured AAA vs controls. Median B12 level lower in ruptured AAA vs controls but higher in small AAA compared to controls.</td></tr>
<tr><td>Sakalihasan et al, 1996.
Aim: investigated the plasma vitamin E (a-tocopherol) concentration in patients with AAA.
Study Design: Cross-sectional study.</td><td>Grp 1: Patients undergoing elective AAA repair (n=19, mean age 72.5±6.6yrs).
Grp 2: atherosclerotic patients referred for coronary bypass surgery (n=18, mean age 61.2±7.4yrs).
Grp 3: Healthy volunteers (n=13, mean age 35.2±16.3yrs)</td><td>• Plasma vitamin E levels and Vitamin E/Total lipid ratio and differences in levels between the AAA group and other groups combined (combined control group).</td><td><table><tr><th></th><th>Volunteers</th><th>CABG</th><th>AAA</th></tr><tr><td>Vitamin E</td><td>10.9±3.12</td><td>11.0±4.79</td><td>1.63±2.44*</td></tr><tr><td>Vit E/Total lipids ratio</td><td>2.01±0.47</td><td>2.51±1.6</td><td>0.26±0.37*</td></tr></table>* p<0.001 vs CABG & volunteers</td><td>Plasma Vitamin E level and the vitamin E/total lipid ratio in AAA patients are significantly lower than in healthy volunteers and CABG patients. Proposed reason is an increase in lipid peroxidation in AAA</td></tr>
</table>

				patients due to oxidant stress.
Warsi et al, 2004 Aim: To study the relationship between plasma homocysteine, serum B12 and folic acid levels, and AAA. Study design: cross-sectional study	**Group 1**: AAA group (n=38, mean age 70 years, range 53-79) **Group 2**: Control group free from AAA and PVD (n=36, mean age 66, range 48-79)	• Serum B12 and Folic acid levels	**Mean B12 in AAA vs Control**: 332.11pg/mL (SE±16.44) vs 414.33pg/mL (SE±19.72), p<0.004. **Mean Folic acid in AAA vs Control**: 8.02ng/mL (SE±0.71) vs 9.8ng/mL (SE±0.69) p>0.05	AAA patients have lower B12 levels than control participants but no difference in folate levels.
Diabetic Foot Disease				
Study (author, year) Aim, study design.	**Participants**	**Relevant outcome measure**	**Results**	**Conclusion**
Afarideh et al, 2016 Aim: (i) to compare the serum concentrations of selected cytokines of the inflammatory system and 25(OH)D across the three groups, patients with chronic active DFU, control patients with type 2 diabetes and without DFU, and healthy controls; (ii) to assess the impact of serum 25(OH)D on the level of selected pro-inflammatory cytokines and their correlation with DFU. **Study Design: Cross-sectional study.**	30 DFU patients (Median age 59 years, IQR 18.2. 22 male) 30 T2DM controls with no history of ulcers. (Median age 54.5 years, IQR 18.5. 13 males) 28 healthy controls (Median age 38.0 years, IQR 10.5. 15 males.) No significant difference in age between the two diabetes groups (p=0.155) however healthy controls were significantly younger (p<0.001). No difference in gender balance between	• Serum 25(OH)D (ng/ml). • Association between serum 25(OH)D and presence of DFU.	**Median (IQR) serum 25(OH)D levels (Healthy vs T2DM vs DFU):** 8 (7.9) ng/ml vs 16 (14.1) ng/ml vs 16.8 (24.6) ng/ml (p=0.002). **Logistic regression (fully adjusted) for associations between 25(OH)D and DFU**: OR 2·104; 95% CI 1·003, 4·415	Increasing serum vitamin D levels from a disease-free state which was significant between healthy controls and those with disease however the increase from those with diabetes to those with DFU didn't reach significance. A positive association was also observed between Vitamin D and DFU indicating higher levels are associated with DFU.

<table>
<tr><td></td><td>diabetes groups (p=0.058), however higher proportion of males in the DFU group compared to controls (p=0.018).</td><td></td><td></td><td></td></tr>
<tr><td>Bolajoko et al 2017.
Aim: To investigate the levels of some vitamins and minerals in association with oxidative stress markers in diabetic foot ulcer (DFU) patients in Ibadan, Oyo State, Nigeria.
Study design: cross-sectional study.</td><td>70 Nigerian DFU patients, 50 healthy volunteers.
DFU Wagner’s Grade 2 were included (ulcer involving ligament, tendon, joint capsule, or fascia but no abscess or osteomyelitis).

Mean age of DFU 51.63±1.07yrs, Mean BMI 26.08±0.3kgm2. no difference between controls for age but controls had a lower mean BMI 22.93±0.24 kg/m2, p<0.001</td><td>• Difference in serum Vitamin C, Vitamin E, copper, selenium, and zinc between DFU and control participants.</td><td><table><tr><th>Nutrient</th><th>DFU</th><th>Control</th><th>p- value</th></tr><tr><td>Vitamin C</td><td>3.76±0.43</td><td>5.57±0.43</td><td>0.003</td></tr><tr><td>Vitamin E</td><td>19.57±1.01</td><td>25.57±0.27</td><td><0.001</td></tr><tr><td>Selenium</td><td>0.48±0.01</td><td>0.81±0.04</td><td><0.001</td></tr><tr><td>Zinc</td><td>15.4±0.24</td><td>15.97±0.20</td><td>0.072</td></tr><tr><td>Copper</td><td>14.59±0.31</td><td>15.19±0.35</td><td>0.203</td></tr></table>*all in umol/L</td><td>Mean Vitamin C, E and Selenium were lower in DFU patients. NO difference in Zinc or Copper.</td></tr>
<tr><td>Caglar et al, 2018
Aim: to compare the levels of osteoprotegerin (OPG) and 25-hydroxy vitamin D (25(OH)D) in patients with diabetic foot and patients with newly diagnosed type 2 diabetes mellitus (DM) and to investigate the prevalence and severity of 25(OH)D insufficiency in patients with diabetic foot.
Study design: Cross-sectional study.</td><td>58 DFU patients (42 males, mean age 63.6 years, range 31-90 years).

47 newly diagnosed type 2 DM patients (27 males, mean age 51.4 years, range 29-85 year) (control group).

DFU patients significantly older (p<0.05) than control group.</td><td>• Serum 25(OH)D levels in both groups.</td><td>Mean (±SD) 25(OH)D levels DFU vs control (ng/ml)
7.9±6.3 vs 11.6±6.5 p<0.001.</td><td>Mean level was in the significant deficiency level for the DFU group and deficient level for the controls indicating that while DFU participants had worse status, both groups had suboptimal levels of vit D.</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Feldkamp et al, 2018.
Aim: measure the Vitamin D level in DFU patients and compare to healthy controls and type 2 DM patients without DFU.
Study design: Cross-sectional study.</td>
<td>99 Healthy controls mean age 69.6±9.7 years.

104 (64 males) DFU patients mean age 70.2±12.2 years. 63 were inpatients.

103 T2DM patients mean age 69.4±10.3 years.

No statistical difference in age between groups.</td>
<td>• Serum 25(OH)D levels in all three groups</td>
<td>Mean Serum Vit D levels (ng/ml):
Controls: 27.3±12.3*^.
T2DM: 19.0±14.4#^
DFU: 11.8±11.3*# (*^*# p<0.01)

55.8% DFU (n=58) had 25(OH)D <10ng/ml

Armstrong wound classification & 25(OH)D level:
r=-0.241, p<0.01</td>
<td>Mean Vitamin D levels were lower in DFU compared to T2DM which were lower than healthy controls. (p<0.01)
DFU patients had a lower vitamin D level than healthy controls. (p<0.01)
There was a slight negative correlation between wound severity and vitamin D status indicating lower vitamin D status in those with more severe wounds.
55.8% of DFU had severe vitamin D deficiency.</td>
</tr>
<tr>
<td>Tiwari et al, 2013
Aim: to study the prevalence and severity of vitamin D deficiency in patients with diabetic foot infection.
Study design: cross-sectional study.</td>
<td>Cases: Diabetic patients with foot infection (n=125, mean age 53.6±10.7).

Controls: Diabetic patients without foot infection (n=164, mean age 51.0±10.8, p=0.039)</td>
<td>• Mean serum 25(OH)D levels.

• Prevalence of Vitamin D inadequacy at 3 cut-offs of <75, (suboptimal) <50 (deficient) and <25nmol/L (severe deficiency).</td>
<td>Mean Serum 25(OH)D cases vs controls:
40.25±38.5 vs 50.75±33.0, p = 0.012.

Prevalence of inadequacy Cases vs controls:
87.4%, 70% and 45.6% vs 82.6%, 56.2% and 17.3% (p value not reported)

Risk of Vit D Inadequacy in cases vs controls: (OR (95%CI))
<table>
<tr><th></th><th>Unadjusted</th><th>Age adjusted</th><th>HbA1c adjusted</th><th>DM duration adjusted</th></tr>
</table>
</td>
<td>Mean serum vit D levels were lower in DFU patients and the prevalence of severe deficiency appears higher in DFU compared to controls however p value wasn’t reported.</td>
</tr>
</table>

		• Risk of Vit D inadequacy.	<table><tr><td><25</td><td>4.0** (2.4, 6.9)</td><td>4.3** (2.5,7.5)</td><td>3.7** (2.1,6.4)</td><td>3.8** (2.0,7.0)</td></tr><tr><td><50</td><td>1.8* (1.1,3.0)</td><td>1.9* (1.2,3.2)</td><td>1.8* (1.0,3.0)</td><td>1.5 (0.9,2.6)</td></tr><tr><td><75</td><td>1.5 (0.8,3.0)</td><td>1.7 (0.8,3.5)</td><td>1.6 (0.8,3.4)</td><td>1.9 (0.9,4.0)</td></tr></table> *P<0.05, **P<0.0001	Risk of severe Vitamin D deficiency was higher in cases which held true when adjusted for other factors.
Wright et al, 2015 Aim: to assess the incidence of anaemia and further classify the iron deficiency seen in a high-risk DFU patient group. Study design: prospective cohort study.	All patients with severe DFU attending clinic over 4 months. N=27, 22 (81.5%) make, median (range) age 67 (27-86) years.	• Anaemia: Hb <12g/dL • Severe anaemia: <10g/dL • Absolute/Functional Iron Deficiency: (AID – total body iron depletion FID – normal iron stores with inability to mobile iron from reticuloendothelial system.)	**Prevalence of anaemia:** 14 (51.9%) anaemic, 2 (7.4%) severe anaemia. **Prevalence of AID**: n=1 **Prevalence of FID**: n=7 (non-anaemic patients). 21 (77.8%) participants were classified has abnormal when definitions for anaemia and iron deficiency were combined.	High prevalence of anaemia and iron deficiency in patients with DFU
Zubair et al, 2013 Aim: to evaluate plasma levels of 25(OH)D in subjects with diabetic foot in comparison with subjects without foot complications. Study design: Prospective cohort study.	Group A: 162 Diabetic patients with DFU (mean age 46.29± 13.19 years, 63.5% male) Group B: 162 diabetic patients without ulceration (matched for age, gender, BMI and BP). Mean age 47.1±12.13yrs, 62.9% male. Conducted in India	• Difference in median Serum Vitamin D levels between groups. • Vitamin D as a predictor for DFU.	**Median (IQR) serum vitamin D**: group A vs group B 8.4 (7.1-9.2) ng/ml vs 29.8 (15.6-44.2) ng/ml, p<0.005 **Serum 25(OH)D as an independent predictor of foot ulcer**: Multiple linear regression: R^2 Coefficient 0.0046, p<0.001 Forward stepwise regression: p value <0.001 One-way ANOVA: p value<0.05	DFU patients have lower serum vitamin D levels compared to non-ulcer DM patients. Serum vitamin D is correlated with foot ulcer development.

Venous disease /leg ulcer

<table>
<tr><th>Study
(author, year)
Aim, study design.</th><th>Participants</th><th>Relevant outcome measure</th><th>Results</th><th>Conclusion</th></tr>
<tr>
<td>Agren et al, 1986
Aim: to determine serum concentrations of selenium, zinc, iron and copper in geriatric patients with and without leg ulcers.
Study design: prospective observational study.</td>
<td>24 (16 women) participants aged 81±6 years with mean ulcer size 5.1±5.0cm2.
12 arterial and 12 venous aetiology. Mixed aetiology was excluded.

40 participants (21 women) aged 80±5years with dementia and no ulcers/history of leg ulcers served as controls.</td>
<td>• Serum selenium, iron, copper and zinc levels.

• Healing: good (visible granulation, 25% reduction in size for arterial and 50% for venous PLUS ulcer free from slough for 8 weeks) vs poor (enlargement of ulcer area, antibiotics were required, or “good” criteria not met).</td>
<td>
<table>
<tr><th>Variable (umol/L)</th><th>Ulcer patients N=24</th><th>Controls N=40</th><th>P value</th></tr>
<tr><td>Fe</td><td>19.7±7.2</td><td>26.9±16.1</td><td><0.05</td></tr>
<tr><td>Cu</td><td>22.0±3.1</td><td>23.6±6.3</td><td>NS</td></tr>
<tr><td>Zn</td><td>11.0±1.2</td><td>16.8±7.6</td><td><0.001</td></tr>
<tr><td>Se</td><td>1.01±0.51</td><td>1.27±0.51</td><td><0.05</td></tr>
</table>
Healing:
Good n=19, Poor n=5.
Serum Copper: higher in the poor healing group (p<0.02)
Serum copper: zinc ration higher in poor healing group (p<0.01)
</td>
<td>Mean serum iron, Zinc and selenium levels were lower in the ulcer group compared to the controls but no difference in copper levels.

When poor and good healing were compared, serum copper was higher in the poor healers as well as the copper: zinc ratio. May be due to the proposed relationship between serum copper levels and a more pronounced chronic inflammatory state. Not possible to determine if low levels depict deficiency or a redistribution of trace elements within the body</td>
</tr>
</table>

<table>
<tr>
<td>Balaji &Mosley, 1995
Aim: to assess the contribution of nutritional status, arterial insufficiency and venous problems in the causation of large leg ulcers.
Study design: cross-sectional study.</td>
<td>50 participants with non-healing leg ulcers (mixed aetiology, 17 arterial, 25 venous, 8 others).

Mean age 76 years (range 62-90yrs), 30 (60%) female.

Ulcer size: average area 169cm^2, range 110-250cm^2</td>
<td>• Plasma Zinc, folate and iron deficiency.
• Vitamin C depletion (saturation test)</td>
<td>
<table>
<tr><th></th><th>Arterial (n=17)</th><th>Venous (n=25)</th><th>Others (n=8)</th><th>Total (n=50)</th></tr>
<tr><td>Vitamin C Deficiency</td><td>5</td><td>18</td><td>7</td><td>30</td></tr>
<tr><td>Zinc <10umol/l</td><td>0</td><td>3</td><td>6</td><td>9</td></tr>
<tr><td>Folate <150ug/l</td><td>3</td><td>2</td><td>4</td><td>9</td></tr>
<tr><td>Iron <10umol/l</td><td>3</td><td>2</td><td>5</td><td>10</td></tr>
</table>
</td>
<td>60% of patients had vitamin C deficiency with approximately 20% having deficiencies in the other nutrients studied.

No rationale provided for the cut-offs used for deficiency.</td>
</tr>
<tr>
<td>Burkievcz et al 2012
Aim: To study if the prevalence of vitamin D deficiency in patients with venous leg ulcer is higher than in the control population.
Study design: Cross-sectional study.</td>
<td>85 participants in total. Mean age 59.35±9.55, 71 (83.5%) female.

27 VLU outpatients (recruited from a vascular outpatient clinic in Brazil) with mean age of 57.41±2.11years

58 controls (recruited from rheumatology clinics) with a mean age of 60.26±11.22 years (p=0.21)</td>
<td>• Serum 25(OH)D levels
• Vitamin D levels were separated into ranges:
• <8ng/dl (severe deficiency); 8-20ng/dl; (insufficiency) 21-30ng/dl (deficiency) and >30ng/dl (normal)

Cut-offs appear to be in the incorrect units as the reference indicates units of mg/dl or ng/ml. This may be a reporting error in the manuscript rather than actual use of incorrect units based on results.</td>
<td>46.1% of patients with ulcers were in the 8-20ng/dl group (p value not reported)

43% of controls were in the >30ng/dl (p=0.04).</td>
<td>A higher proportion of ulcer patients have insufficient vitamin D levels compared to controls.
Remainder of results for the Vitamin D ranges were represented in a figure that was difficult to extract information from so unable to determine proportions accurately in the other vitamin D ranges.</td>
</tr>
</table>

Krejner et al, 2017 Aim: the aim of our proof of concept study was to verify the possible relationship between serum concentrations of vitamin D, human cathelicidin LL-37, and the healing of chronic venous leg ulcers. Study Design: Prospective observational study.	19 patients (12 females, mean age 68.6±13.8 years) with chronic VLUs for at least 8 weeks and <2 years.	• Mean serum levels of 25(OH)D. • Normal status defined as >30ng/ml	**Mean vitamin D level**: 18.2±7.1ng/ml. Range 4-29ng/ml. No participants were classified has having normal vitamin D status **Correlation between 25(OH)D level and wound healing rates**: R= -0.34, non-significant (p not reported).	Suboptimal vitamin D levels are prevalent in ulcer patients however there was no correlation between vitamin D status and wound healing rates.
Tobon et al, 2008 Aim: purpose of this pilot study was to describe the nutritional status and its relationship to the severity of nonhealing VLUs in adults who are overweight or obese. **Study Design: Cross-sectional study**	Convenience sample of 8 outpatients with VLU and BMI>25kgm2. Six men, 2 women aged 53-79 years.	• Serum vitamins A and C and Zinc. • LUMT: a tool to evaluate each wound using 14 clinician-related domains and 3 patient-related domains. Scores range from 0-68 with higher scores indicating greater wound severity. • Correlation between nutrient levels and LUMT score	**Vitamin A**: 0/8 had levels below the reference range. **Vitamin C**: 3/8 had levels below the reference range **Zinc**: 1/8 had levels below the reference range. **Vitamin C and LUMT Score**: r2 = 0.74, p=0.04 **Vitamin A and LUMT score**: r2 -0.83, p=0.01 No Significant correlation between Zinc and LUMT score (statistics not reported)	Lower vitamin A levels are correlated with higher LUMT scores and hence greater wound severity. The reverse was found for vitamin C which is surprising. Authors reported that the results could have been confounded by unknown factors.

Wipke-Tevis & Stotts,1996 Aim: The purpose of this pilot study was to explore the nutritional risk, status and intake of seven patients with venous ulcers. Study design: Cross-sectional study.	Convenience sample of 7 patients with one or more VLUs. Three men, 4 women aged 47-84.	• Serum Zinc and vitamin C levels	**Mean (SD) Vitamin C** = 1.1 (0.5) mg/dl (normal range 0.2-2) **Mean (SD) Zinc** = 59.6 (5.0)mcg/dl (normal range 55-150) **Vitamin C**: 0/7 patients had low levels **Zinc**: 3/7 had low levels.	Prevalence of poor vitamin C status was zero in this very small sample of VLU participants. 3 out of 7 had suboptimal Zinc status.
Occlusive disease				
Study (author, year) Aim, study design.	**Participants**	**Relevant outcome measure**	**Results**	**Conclusion**
Bunout et al, 2000 Aim: to compare serum homocysteine, folate, and vitamin B12 levels of patients with coronary and peripheral vascular disease with those of age- and sex-matched healthy individuals. Study Design: Cross-sectional study.	32 patients with peripheral vascular disease (10 female), aged 69.6 +/- 11 y. PVD included those with IC and significant arterial occlusion per angiography or those with more than 25% stenosis of the common carotid artery. 24 (10 female) age- and sex-matched control subjects	• Serum folic acid (ng/ml) and Vitamins B12 (pg/ml) and E (mg/l).	**Folate levels PVD vs controls** (mean ±SD): 4.48±2.42 and 7.14±4.04 ng/mL (P < 0.02). **Vitamin B12 levels PVD vs controls** (mean ±SD): 318±142.8 vs 342.1±180.7 (NS) **Vitamin E levels PVD vs controls** (mean ±SD): 8.0±4.0 vs 7.2±5.9 (NS)	Folate levels were significantly lower in the PVD participants compared with controls. No differences in vitamin B(12) or tocopherol levels were observed between patients and control subjects.
Fahrleitner et al, 2002 Aim: To investigate via the vitamin D status whether patients with PAD tend to develop vitamin D deficiency that in turn influences their clinical symptoms.	161 (97 men) with PAD visiting angiology outpatients. **Group A**: PAD stage 2 (n=84, 55 males. Median age 69±2 years **Group B:** PAD stage 4 (n=77, 42 males) with local ulcers	• Serum 25(OH)D3. • Deficiency was based on levels <9ng/ml (22nmol/L) • Comparison of Vitamin D level based	**Mean Vitamin D levels** (Group A vs Group B vs Control) 23.4±1.4ng/ml vs 9.4±1ng/ml*# vs 20.5±1.2ng/ml. *p=0.0001 vs group A. # p=0.0001 vs control Group B: 55 (71.4%) had vitamin D level <9ng/ml. **Level of disability**:	Stage 4 PAD patients had significantly lower vit D levels compared to stage 2 PAD and controls. A high proportion (>71%) of stage 4 participants were

<table>
<tr>
<td>Study design: Cross-sectional study,</td>
<td>current or past. Median age 66±1year
Control: 45 age and gender matched controls. Median age 66±1year.

Participants also categorized into 3 groups: mild, moderate or severely handicapped in daily life due to pain/claudication caused by disease. (stratified for disease severity)</td>
<td>on subjective feeling of disability</td>
<td>
<table>
<tr><th></th><th>Mild restriction (A)</th><th>Moderate restriction (B)</th><th>Severe restriction (C)</th><th>P value</th></tr>
<tr><td>Vit D*</td><td>23±1.9</td><td>17.7±1.7</td><td>8.7±0.8</td><td></td></tr>
<tr><td>C vs B</td><td></td><td></td><td></td><td>0.0001</td></tr>
<tr><td>C vs A</td><td></td><td></td><td></td><td>0.0001</td></tr>
<tr><td>B vs A</td><td></td><td></td><td></td><td>0.05</td></tr>
</table>
*reference range of 9-45ng/ml
</td>
<td>deficient in vitamin D.
When compared according to level of handicap/restriction, vitamin D status was lower in the severe group compared to moderate and mild groups. The moderate group also had lower vitamin D level when compared to the mild group.</td>
</tr>
<tr>
<td>Gaddipati et al, 2011
Hypothesis: vitamin D status is associated with cardiovascular risk factors and that vitamin D deficiency (25(OH)D <20 ng/mL) enhances the risk of amputation.
Study design: retrospective cohort study.</td>
<td>Retrospective audit of 1435 patients with PAD and available data on 25(OH)D. Mean age 70.8±10.5years. 75 (5.2%) had amputations performed.</td>
<td>• Vitamin D level. Deficiency classified as 25(OH)D <20ng/ml</td>
<td>Mean Vitamin D level: 24.1±11.8ng/ml.
Proportion with vitamin D <20ng/ml = 40.8%

Amputations vs no amputations:
Mean Vit D: 22.1ng/ml vs 24.2ng/ml
% deficient: 52% vs 40% (p=0.063)

Vitamin D deficient participants: Amputation rate 6.7% vs 4.2% (p=0.029).

Logistic regression: no significant association between vitamin D level and deficiency status and amputation.</td>
<td>A high prevalence of vitamin D deficiency amongst PAD patients at 40.8%.

Amputation rate was higher in those who were vitamin D deficient.

When other covariates (BMI, blood lipids, HT and DM) were accounted for there was no statistical relationship between vitamin D and amputation.</td>
</tr>
</table>

<table>
<tr>
<td>Langlois et al, 2001
Aim: to assess whether inflammation is associated with antioxidant status in patients with intermittent claudication.
Study design: Prospective cohort study.</td>
<td>85 (78% male) PAD participants with Fontaine stage 2. Mean age 68±10year

106 (42% male) with hypertension but no PAD. Mean age 62±14 years

113 (45% male) healthy volunteers. Mean age 61±12 years.

PAD with revascularisation interventions and/or taking vitamin supplements were excluded.

No significant difference in age but higher % of males in the PAD group. Vitamin C intake was estimated via diet history and no significant differences between the groups.</td>
<td>• Serum vitamin C
• C-reactive protein level.
• Absolute claudication distance (ACD) via treadmill test.</td>
<td>Vitamin C and inflammatory markers (median and IQR)
<table><tr><td></td><td>Healthy (n=113)</td><td>HT (n=106)</td><td>PAD (n=85)</td><td>P value*</td></tr><tr><td>Vitamin C (umol/L)</td><td>51.7 (42.8-63.5)</td><td>49.6 (38.1-62.5)</td><td>27.8 (15.8-42.5)</td><td><0.0001</td></tr><tr><td>CRP (mg/L)</td><td>2.51 (0.78-4.16)</td><td>2.32 (1.28-3.58)</td><td>4.80 (2.00-9.55)</td><td><0.0001</td></tr><tr><td>Fibrinogen (g/l)</td><td>3.12 (2.35-3.86)</td><td>3.64 (2.99-4.84)</td><td>4.95 (2.00-9.55_</td><td>0.002</td></tr></table>PAD patients:
52% had vitamin C <28.4umol/L and 14% <11.4umol/L
Correlation between Vitamin C and CRP: r=-0.742, p<0.0001
Correlation between vitamin C and fibrinogen: r=-0.387, p<0.0001
Relative risk of vitamin C deficiency (controlled for smoking and aspirin intake) = 1.68 (95% CI, 1.27-2.21) in PAD patients with a CRP >4.8mg/L (median).

Effect of vitamin C level on median (IQR) ACD (n=70):
Vitamin C <28.4umol/L = 325m (175-400) m
≥28.4umol/L = 488m (375-600) (p<0.0001)
Correlation r=0.552, p<0.0001</td>
<td>Vitamin C levels were lower in PAD patients compared with both healthy controls and the HT group.
52% had suboptimal vitamin C status and 14% were deficient.
Inflammatory markers were higher in the PAD group compared with other groups.
There were significant negative correlations between vitamin C levels and inflammatory markers.

ACD was shorter in those with suboptimal Vitamin C level and there was a positive and significant correlation between vitamin C level and ACD.
Overall vitamin C levels are lower in PAD patients and are associated with</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>inflammation and functional state.</td></tr>
<tr><td>Mansoor et al, 2000
Relevant aim: to determine the concentrations of trace elements, antioxidants and B vitamins in PVD patients.
Study design: Case control study.</td><td>65 patients with PVD. (35 males, mean ages of 3 subgroups 45.8±6.9, 50.7±5.4 and 50.7±5.2 years)

65 age and gender-matched controls (34 males, mean age 48.8±6.4 years)</td><td>• Concentrations of trace elements: Selenium, Zinc, copper, Iron in patient's vs controls.

• Concentrations of folate, Vitamin B12, vitamin E, Vitamin A, B carotene in patients vs controls.</td><td>Plasma concentrations of patients with PVD and healthy controls. (Mean, 95%CI)

<table><tr><td>Variable</td><td>PVD patients</td><td>Controls</td><td>P value</td></tr><tr><td>Selenium*</td><td>1.4 (1.3-1.6)</td><td>1.4 (1.3-1.5)</td><td>NS</td></tr><tr><td>Zinc*</td><td>12.0 (10.2-13.7)</td><td>11.8 (9.3-14.3)</td><td>NS</td></tr><tr><td>Copper *</td><td>20.3 (18.7-22.0)</td><td>18.8 (17.7-20.0)</td><td>NS</td></tr><tr><td>Iron*</td><td>25.2 (21.6-28.9)</td><td>24.3 (21.2-27.3)</td><td>NS</td></tr><tr><td>Folate^</td><td>12.7 (10.3-15.1)</td><td>13.2 (11.7-14.7)</td><td>NS</td></tr><tr><td>Vit B12$</td><td>353 (309-397)</td><td>362 (325-399)</td><td>NS</td></tr><tr><td>Vitamin E#</td><td>35.4 (28.3-42.6)</td><td>30.3 (27.3-33.3)</td><td>0.05</td></tr><tr><td>Vitamin A#</td><td>1.3 (1.2-1.4)</td><td>1.2 (1.1-1.3)</td><td>NS</td></tr><tr><td>B carotene#</td><td>0.4 (0.3-0.6)</td><td>0.6 (0.4-0.8)</td><td>0.0006</td></tr></table>*ug/g, ^nmol/L, $pmol/L, #umol/L</td><td>No significant differences in trace element and vitamin levels between PVD patients and controls except for Vitamin E and B-carotene.

Authors also report that B6 concentration was lower in PVD group however these data were not presented. Lower B carotene may be indicative of a higher rate of conversion of B carotene into vitamin A to maintain vitamin A levels in PVD patients.</td></tr>
<tr><td>McDermott et al, 2012
Aim: hypothesized that lower levels of 25-hydroxyvitamin D would be associated with poorer functional performance, more</td><td>402 PAD patients.
305 non-PAD patients.

Participants were part of the WLACS II cohort study who had baseline vitamin D levels collected.</td><td>• 6-minute walk test (6MWT)
• Repeated chair raises (RCR)
• Standing balance (SB)
• 4-meter walking velocity (4MWV)</td><td>PAD patient's vitamin D status:
20.4% had 25(OH)D <30nmol/L.
48.8% had levels <50nmol/L.
Non-PAD patients:
15.4% <30nmol/L and 46.9% <50nmol/L

Mean Vit D levels (PAD vs non-PAD): 53.7±24.9nmol/L vs 54.6±23.7nmol/L (p=0.63).</td><td>A significant proportion of both the PVD and non-PVD participants had suboptimal vitamin D levels with no significant differences between</td></tr>
</table>

adverse calf muscle characteristics, and poorer peripheral nerve function in people with PAD. Study Design: Secondary analysis of prospective cohort study.		• Short physical performance battery (SPPB.) • Vitamin D level defined as the following four categories: vitamin D < 30 nmol/L (deficient), vitamin D 30 to < 50 nmol/L (insufficient), vitamin D 50 to < 75 nmol/L, and vitamin D 75–125 nmol/L.	**Associations between lower vitamin D and functional outcomes** (adjusted for age, gender, race): Poorer 6MWT (p trend 0.002), slower usual pace 4MWV (p trend 0.0303), slower fast-paced 4MWV (p trend 0.043) and lower SPPB scores (p trend 0.031). All lost significance when BMI, smoking, comorbidities, physical activity and WALCS cohort were added into the model. Similar outcomes were observed in just the PAD participants.	groups. There was no association between vitamin D level and functional outcomes when other covariates were included into the model.
McDermott et al, 2014 Aim: to study associations of baseline vitamin D levels with subsequent functional decline and mortality among individuals with and without PAD. Study Design: Secondary analysis of prospective cohort study.	395 individuals with PAD and 263 non-PAD individuals from the WALCS II cohort study with baseline blood samples and follow-up data on function and mortality. Mean follow-up of 39.3±16.4 months for functional outcomes and 47.5±16.3months for mortality.	• 6-minute walk test (6MWT) • Repeated chair raises (RCR) • Standing balance (SB) • 4-meter walking velocity (4MWV) • Short physical performance battery (SPPB.) • Death, including deaths from CHD, stroke, PAD and other CVD. • Vitamin D level defined as the following four categories: vitamin	**Mean vitamin D with and without PVD**: 53.9±25 vs 55.7±23.7nmol/L (p=0.362). 20% of PAD and 14% of non-PAD had Vitamin D <30nmol/L. **PAD patients and decline in functional outcomes**: Lower Vitamin D levels associated with faster decline in 6MWT (p=0.012, fully adjusted model). PAD with vitamin D <30nmol/L faster decline in 6MWT compared to those with vitamin D 50-75nmol/L (p=0.04) and faster decline in SPPB scores compared to vitamin D levels of 30-50 (p=0.028) and those with vitamin D level of 50-75nmol/L (p=0.034) **Non-PAD patients and decline in functional outcomes**: Lower Vitamin D levels associated with faster decline in fast-paced 4MWV (p trend 0.003, fully adjusted). Non-PAD with vitamin D of <30nmol/L had faster decline in fast paced 4MWV compared to those with vitamin D of 75-120nmol/L (p=0.0164).	Lower vitamin D levels are associated with more rapid decline in some functional outcome measures in patients with PAD. Functional decline in also observed in non-PAD with lower vitamin D levels. No associations were found between vitamin D and mortality.

<table>
<tr>
<td></td>
<td></td>
<td>D < 30 nmol/L (deficient), vitamin D 30 to < 50 nmol/L (insufficient), vitamin D 50 to < 75 nmol/L, and vitamin D 75–125 nmol/L.</td>
<td>PAD patients and mortality:
93 (24%) mortality during follow-up.
No association between vitamin D and mortality.

Non-PAD patients and mortality:
31 (12.9%) mortality during follow-up.
NO association between vitamin D and mortality.</td>
<td></td>
</tr>
<tr>
<td>Vega De Ceniga et al, 2011
Aim: to assess basal prevalence of anaemia, iron, B12-vitamin and folic acid deficits in our patients suffering from ischemic claudication (IC) and critical limb ischaemia (CLI).
Study Design:
Retrospective study.</td>
<td>624 patients with PAD

420 with IC (mean age 66±10.3years, 89% male) and 204 with CLI (mean age 72±11.2 years, 76.5% male). P <0.0001 for both age and gender differences.</td>
<td>• Decreased circulating concentrations of iron (<58 mcg/dl), vitamin B12 (<179 pg/ml), folic acid (<2.4 ng/ml) and haemoglobin (<12.9 g/dl in men and <11.9 g/dl in women).</td>
<td>Prevalence of anaemia, iron and vitamin deficits:

<table>
<tr><th></th><th>IC
n=420</th><th>CLI
N=204</th><th>P value</th></tr>
<tr><td>Hb deficit</td><td>41 (9.8%)</td><td>101 (49.5%)</td><td><0.0001</td></tr>
<tr><td>Iron deficit</td><td>28 (6.7%)</td><td>65 (31.9%)</td><td><0.0001</td></tr>
<tr><td>B12 deficit</td><td>28 (6.7%)</td><td>32 (15.7%)</td><td>0.002</td></tr>
<tr><td>Folic acid deficit</td><td>12 (2.9%)</td><td>13 (6.4%)</td><td>0.018</td></tr>
</table>
</td>
<td>Anaemia, and iron and vitamin deficits were prevalent in both the IC and CLI groups however they were significantly more common in the CLI group indicating that status may worsen as disease progresses.</td>
</tr>
<tr>
<td>Zsori et al, 2013
Aim: to examine whether plasma vitamin B12 and folate levels and MTHFR-C677T polymorphism are associated with the risk of PAD.
Study design:
Retrospective study</td>
<td>293 symptomatic PAD patients (186 males, mean age of 66.3 ±SEM0.7 years, 180 with Fontaine stage IIa, 103 with Fontaine stage IIb, and ten cases with Fontaine stage III).

293 gender-matched controls with mean age of 62.1 ± SEM0.8</td>
<td>• Vitamin B12 and folate levels.</td>
<td>Mean±SEM Vitamin B12 in patients vs controls:
222±6.3 vs 296±9.3pmol/L p<0.005

Mean±SEM folate in patients vs controls:
15.5±0.4 vs 16.0±0.5nmol/L p=0.745

Comparison of mean (95%CI) vitamin levels in PAD and control participants adjusted for age, DM, smoking, BMI, hypertension, hyperlipidaemia, hs-CRP and creatinine
<table>
<tr><th></th><th>PAD</th><th>Controls</th><th>P value</th></tr>
<tr><td>Vit B12 (pmol/L)</td><td>199 (187-212)</td><td>241 (22-260)</td><td><0.001</td></tr>
<tr><td>Folate (nmol/L)</td><td>13.9 (13.2-14.7)</td><td>13.5 (12.6-14.4)</td><td>0.499</td></tr>
</table>
</td>
<td>PAD patients had a significantly lower vitamin B12 level than controls but no difference in folate levels.</td>
</tr>
</table>

2.2.3 What malnutrition screening tools are valid and/or reliable for use in surgical patients?

The identification and management of malnutrition in vascular surgery patients is critical due to its association with poorer clinical outcomes (80, 86, 180). Past studies have observed rates of malnutrition as high as 60-90% in vascular disease patients (82-84). Despite the consequences of malnutrition and the prevalence observed, malnutrition remains under-recognised across patient groups in the clinical setting (122, 123, 127, 181).

The literature search was conducted across the five databases (search strategy displayed in appendix 1). Key search terms were a combination (using OR) of synonyms for malnutrition screening tools such as "screening" or "assessment" combined. Medical Subject Headings (MeSH) were broadened to include all surgery patients following a preliminary review indicated that there were no studies conducted in vascular surgery patients specifically, such as "surg*" and "operati*" and "perioperati*" combined (using OR). The search yielded 995 articles for consideration. Following the removal of duplicates (n=138) and screening by title and abstract, 107 remained. The articles were grouped into two groups, studies examining (1) diagnostic concordance or agreement and (2) predictive validity. Full text screening and hand-searching of reference lists resulted in 2 studies (182, 183) that were conducted exploring predictive validity of malnutrition screening tools in vascular surgery patients. No articles were found in vascular surgery patients that examined diagnostic concordance or agreement, hence articles that examined malnutrition screening tools in other surgical groups were included, resulting in 7 articles (184-190) for review (appendix 2). The surgical groups included gastrointestinal surgery, cardiac surgery and mixed surgical patients. A summary of the 9 studies is displayed in table 6.

Diagnostic Concordance/Agreement

Seven studies were located that examined diagnostic concordance/agreement of nutrition screening tools at identifying malnutrition (184-190). Sample sizes ranged from 45 to 634 and examined a range of screening tools with the most common ones being the Nutrition Risk Screen-2002 (NRS-2002) in six studies (184-189) and the Malnutrition Universal Screening tool (MUST) in four studies (184, 187, 189, 190). Other screening tools were included in one study each. A range of reference standards were used as an assessment of nutritional status, however the most common one was the Subjective Global Assessment (SGA) which was used in five studies (184-187, 189). Three studies were conducted in a mixed sample of surgical patients (184, 187, 188), two were conducted in patients undergoing gastrointestinal surgery (185, 186) and two in cardiothoracic surgery patients (189, 190). In studies where sensitivity analysis was conducted, the a-priori values of 80% for sensitivity and 60% for specificity were employed as the cut-off for a valid screening tool (191).

Using the NHMRC evidence hierarchy (132) based on the 'diagnostic' classification, four studies (184-187) were classified as level III-2 evidence and three were of level II evidence (188-190). All studies were of neutral quality (131). The consistent areas of reduced quality and increased risk of bias was due to unclear or poor reporting of methods and details of administering the screening tools and nutrition assessment, inadequate or no accounting for differences between groups and lack of blinding of outcome assessment (appendix 3).

Table 6: Summary of the validity of screening tool articles within surgical patients

<table>
<tr><th>Study (author, year)
Aim, study design</th><th>Participants</th><th>Screening Instruments and protocol.</th><th>Relevant outcome measure</th><th>Results</th><th>Comments</th></tr>
<tr><td colspan="6">Diagnostic Concordance/Agreement</td></tr>
<tr><td>Almeida et al, 2012
Aim: to test the capacity in identifying patients at nutritional risk, by comparing BMI, recent %weight loss, and three malnutrition screening tools with Subjective Global Assessment (SGA), considered the standard.
Study design: cross-sectional study.</td><td>300 (132 males) adult surgical patients with a predicted length of stay ≥4 days.

Mean age 60±17years (45% ≥ 65 years).
163 (54%) elective surgery. 76% GI surgery participants.

30% were obese/overweight, 6% underweight.</td><td>All data collected prior to surgery and within 3 days of admission by dietitian.

• BMI classified using WHO criteria
• % weight loss over 6 months, ≥5% significant
• SGA, classified as A, B or C.
• NRS-2002
• MUST
• NRI (n=237)

Screening tool and SGA results were dichotomised to enable comparisons as well-nourished and moderately/severely malnourished (SGA) and low risk or medium/high risk for MUST and NRI</td><td>• Agreement using Kappa and Spearman correlation.
• Sensitivity (Sn)
• Specificity (Sp)
• Predictive values (positive and negative, PPV and NPV)</td><td>Classification of Nutritional Status:
SGA: 64% malnourished
NRS-2002: 66% at risk
MUST: 66% at risk
NRI: 87% at risk

Agreement of screening tools vs SGA
<table><tr><td>Tool</td><td>Kappa</td><td>P value</td></tr><tr><td>NRS-2002</td><td>0.853</td><td><0.001</td></tr><tr><td>MUST</td><td>0.912</td><td><0.001</td></tr><tr><td>NRI</td><td>0.336</td><td><0.05</td></tr></table>
Screening tools vs SGA
<table><tr><td>Tool</td><td>Sn*</td><td>Sp*</td><td>PPV</td><td>NPV</td></tr><tr><td>NRS-2002</td><td>0.8 (0.76-0.84</td><td>0.89 (0.84-0.92)</td><td>87%</td><td>100%</td></tr><tr><td>MUST</td><td>0.85 (0.79-0.87)</td><td>0.93 (0.87-0.95)</td><td>89%</td><td>99%</td></tr><tr><td>NRI</td><td>0.29 (0.26-0.33)</td><td>0.27 (0.23-0.29)</td><td>24%</td><td>27%</td></tr></table>*percentage (95%CI)</td><td>Excellent agreement between both NRS-2002 and MUST with SGA but low agreement between NRI and SGA.

MUST and NRS-2002 performed strongly again SGA with good Sn, Sp and predictive values. NRI performed poorly and wouldn't be recommended for use in this population. NRI incorporates albumin which is a broad risk predictor rather than nutrition in acute patients.</td></tr>
</table>

<table>
<tr>
<td>Badia-Tahull et al, 2014.
Aim: To evaluate the nutritional status of non-critically ill digestive surgery patients at the moment of parenteral nutrition initiation using three different nutritional test tools and to study their correlation.
Study design: cross-sectional study.</td>
<td>45 patients ≥ 18years admitted for digestive surgery and began PN.
73.3% male, median (range) age 65 (18-85) years.</td>
<td>Data collected with 72hr of PN initiation.
BMI
Weight loss over 6 months
SGA (3 categories)
PG-SGA Score (≤8 normal, 9-14 moderate malnutrition, ≥15 severe malnutrition)
NRS-2002 (≤2 normal, 3-4 moderate risk, 5-7 severe risk)
Hospital LOS
In-hospital mortality</td>
<td>Classification of nutritional status and risk.
Agreement using Kappa.
SGA vs NRS-2002
PG-SGA vs NRS-2002</td>
<td>Classification according to tools (%).
<table><tr><th></th><th>Well nourished</th><th>Moderate risk/ malnutrition</th><th>Severe risk/ malnutrition</th></tr><tr><td>SGA</td><td>48.9</td><td>35.6</td><td>15.6</td></tr><tr><td>PG-SGA</td><td>47.7</td><td>31.8</td><td>20.5</td></tr><tr><td>NRS-2002</td><td>42.2</td><td>44.4</td><td>13.3</td></tr></table>Agreement
SGA vs NRS-2002: k 0.53, p<0.0001
PG-SGA vs NRS-2002: k0.31, p=0.004</td>
<td>High prevalence of nutritional risk/malnutrition in the group however no statistics reported to determine differences between the tools.

Moderate agreement between NRS-2002 when SGA used as the reference, only fair agreement between PG-SGA and NRS-2002.

There was no further testing of the validity of the NRS-2002 against nutritional assessment. Other analyses were conducted exploring individual variables such as albumin and NRS-2002.</td>
</tr>
<tr>
<td>Chi et al, 2017.
Aim: to describe the nutritional status of Chinese patients with gastrointestinal cancer undergoing surgery and to compare the ease of use, diversity, and concordance of the Nutritional Risk Screening 2002 with the Subjective Global Assessment in the same patients.
Study design: cross-sectional study.</td>
<td>280 patients ≥ 18years with gastrointestinal cancer undergoing elective surgery. 116 were male, mean age was 62.9±11.9years with 34.1% being aged >70 years.
Mean BMI 23.6±3.5kgm^2.</td>
<td>All data collected by trained nursing staff within 48hr of admission.
SGA – dichotomised into well-nourished (A) and malnourished (B+C).
NRS-2002</td>
<td>Diagnostic concordance between NRS-2002 and SGA using Kappa and
Paired Chi-square test</td>
<td>Classification of nutritional risk by NRS-2002:
46.8% “normal”, 53.2% “at risk” of malnutrition.
Classification of nutritional status by SGA:
66.1% as “well nourished”, 33.9% “malnourished”
NRS-2002 rated more as “at risk” compared to SGA. (p<0.001)

Diversity and Concordance:
NRS-2002 vs SGA (whole group): k 0.54, p<0.001. McNemar’s test p<0.001.

<70years: k 0.81, p <0.001. McNemar’s test p=0.14.
>70 years: k 0.085, p=0.096. McNemar’s test p<0.001</td>
<td>Based on kappa reference levels used in this study, there was fair-good agreement between NRS-2002 and SGA across the whole group which increased to “excellent” agreement in the <70 years group. Agreement in the older age group was poor which may be due to the inclusion of age (1 point for age 70 or over) in the screening tool leading to over-identification of nutritional risk in the older group.
NRS-2002 identified significantly more people “at risk” which is likely due to the</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>over-identification in the older group.</td></tr>
<tr><td>Karateke et al 2013
Aim: To investigate the reliability of nutritional risk screening (NRS-2002) and Subjective Global Assessment (SGA) tools to predict the length of hospital stay, complications and mortality, and to compare these tools in predicting outcomes of surgical patients.
Study design: prospective observational study.</td><td>588 (45.9% male) surgical patients.
Median age 45 years, range 18-85.

Divided into 3 groups:
1 – major surgery for GI malignancy
2- moderate surgery
3- Minor surgery</td><td>NRS-2002 (≥3)
SGA: A- minor, B- moderate, C - major risk

Screening was conducted pre-operatively</td><td>• Nutritional risk on NRS-2002 and SGA.</td><td>Nutritional risk:
SGA-A: 84.7%, B: 12.6%, C: 2.7%
NRS-2002: ≥3: 16.4%
Correlation between SGA and NRS-2002 scores:
r 0.874, p<0.001</td><td>A strong positive correlation was found between SGA and NRS-2002 scores indicating higher scores are associated with poorer nutritional status</td></tr>
<tr><td>Lomivorotov et al 2013
Aim: to detect the most sensitive nutritional screening tool
and to assess its prognostic value with regards to an adverse clinical course in patients with heart valve disease undergoing cardiopulmonary bypass (CPB).
Study Design: prospective observational study.</td><td>441 patients scheduled for cardiothoracic surgery with CPB.
Median (IQR) age 58 years (51-64), 54% female.</td><td>Pre-operative screening by trained anaesthesiologists within 48hr of admission using
• SNAQ
• MUST
• NRS-2002
• MNA (MNA-SF)
Nutritional status assessed by SGA. SGA-A: well nourished, SGA-B&C – malnourished.</td><td>• Sn, Sp, PPV and NPV of all tools for detecting malnutrition and predicting outcomes.
• (2 levels of risk on each tool)</td><td>Prevalence of malnutrition risk:
SNAQ: 25.2%, MUST: 25%, NRS-2002: 9.7%, MNA: 27.7%.
Prevalence of malnutrition according to SGA: 8.8%

Ability of tools to detect malnutrition by SGA
<table><tr><td></td><td>Sn</td><td>Sp</td><td>PPV</td><td>NPV</td></tr><tr><td>SNAQ</td><td>92.3</td><td>81.3</td><td>32.4</td><td>99.1</td></tr><tr><td>MUST</td><td>100</td><td>82.3</td><td>35.5</td><td>100</td></tr><tr><td>NRS2002</td><td>43.6</td><td>93.5</td><td>39.5</td><td>94.5</td></tr><tr><td>MNA</td><td>84.6</td><td>77.9</td><td>27.1</td><td>98.1</td></tr></table></td><td>Low PPV in all tools shows high rate of false positives and is unable to detect those with malnutrition appropriately.</td></tr>
<tr><td>Mourao et al, 2004
Aim: the goal of this cross-sectional study in surgical patients was to test a comprehensive set of</td><td>100 general surgery patients (51 women) with mean age 55.0±18.9 years.</td><td>Assessment of risk:

• NRS-2002 (labelled NRA in this study)</td><td>• % deemed at risk by screening tools
• Concordance according to</td><td>% at risk or malnourished:
ANST: 75% at risk
NRS2002: 53% at risk
MUST: 53% at risk
NSI: 57% at risk</td><td>High prevalence of malnutrition according to SGA with similar level of risk identified by the screening tools.</td></tr>
</table>

<table>
<tr>
<td>nutritional risk and status parameters, in order to assess their utility by exploring their interrelationships, and to propose thereafter a feasible and sensitive method to assess nutritional risk and status in hospital routine practice.
Study design: cross-sectional study.</td>
<td></td>
<td>• MUST (labelled MST in this study)
• NSI
• ANST

Assessment of status:
• SGA
• Anthropometry according to McWhirter and Pennington Criteria

Assessment of nutritional risk and nutritional status was performed within 3 days of admission by 2 trained and supervised medical students.</td>
<td>kappa between risk assessment tools and status assessment methods.</td>
<td>SGA: 56% malnourished (16% severe)
McWhirter: 41% obese/overweight, 50% well nourished, 9% malnourished.

Concordance of screening tools to assessment methods (kappa)
<table>
<tr><td></td><td>McWhirter</td><td>SGA</td></tr>
<tr><td>NRS2002</td><td>0.29</td><td>0.39</td></tr>
<tr><td>MUST</td><td>0.72*</td><td>0.90^</td></tr>
<tr><td>NSI</td><td>0.66*</td><td>0.70*</td></tr>
<tr><td>ANST</td><td>0.30</td><td>0.55</td></tr>
</table>
*p≤0.05 ^p<0.0001

Sn, Sp of tools vs SGA
<table>
<tr><td>Tool</td><td>Sn (%)</td><td>Sp (%)</td></tr>
<tr><td>NRS2002</td><td>96</td><td>30</td></tr>
<tr><td>MUST</td><td>54</td><td>25</td></tr>
<tr><td>NSI</td><td>60</td><td>10</td></tr>
<tr><td>ANST</td><td>96</td><td>7</td></tr>
</table></td>
<td>Excellent and significant concordance between SGA and MUST and NSI. Concordance between screening tools and McWhirter criteria was not as good likely due to the use of anthropometry only to determine nutritional status whereas SGA incorporates nutrition symptoms, medical history.
NRS2002 and ANST had the best sensitivity but at the detriment of specificity so they over classified individuals as at risk. While it is preferable to have higher sensitivity than specificity, there are significant resource implications, particularly when specificity was so low.
No involvement of Nutrition professionals in the assessment or screening.</td>
</tr>
<tr>
<td>Van Venrooij et al 2011
Aim: compare the Short Nutritional Assessment Questionnaire and Malnutrition Universal Screening Tool, in patients undergoing cardiac surgery with respect to their accuracy in detecting undernutrition measured by a low-fat free mass index (FFMI; calculated as kg/m^2), and secondly, to assess their association with</td>
<td>325 patients undergoing coronary artery bypass graft and/or heart valve surgery with extracorporeal circulation. Mean age 65.7±10.1 years, 57.2% aged 65 years or more, 27.7% female.
39.1% deemed high operation risk and</td>
<td>All collected on admission to the ward pre-operatively.
• SNAQ (≥2)
• MUST (≥1)
• Weight history
• FFMI by BIS (≤14.6kgm2 in women, ≤16.7kgm2 in men)</td>
<td>• Accuracy of the tools by PPV, NPV, AUC.
•</td>
<td>Classification of Nutritional status/risk
Prevalence of malnutrition on FFMI: 8.3%
MUST: 20.9% at risk
SNAQ: 7.5% at risk.

Ability of tools to detect low FFMI:
MUST: Sn 59.3%, Sp 82.7%, PPV 23.9%, NPV 95.7%, AUC 0.71 (0.6-0.82)
SNAQ: Sn 18.5%, Sp 93.6%, PPV 20.8%, NPV 92.6%, AUC 0.56 (0.44-0.68)</td>
<td>Prevalence of malnutrition was low according to FFMI in this patient group. MUST identified higher % of ‘at risk’ patients likely due to its inclusion of other relevant factors that wouldn’t be considered in FFMI.

Both tools had low Sn and PPV and hence were unable to identify patients with low FFMI adequately.</td>
</tr>
</table>

postoperative adverse outcomes. **Study Design: Prospective observational study.**	33.5% medium risk on EuroScore.				
Predictive Validity					
Study (author, year) Aim, study design.	**Participants**	**Screening Instruments and protocol.**	**Relevant outcome measures/ analyses**	**Results**	**Comments**
Shiraki et al 2016 Aim: to explore whether nutritional status assessed by the GNRI at admission influences overall and limb prognosis of CLI patients following EVT. Study Design: Retrospective cohort study.	Retrospective analysis of 473 consecutive CLI patients undergoing EVT for de novo infrainguinal lesions. Mean age 74±10yrs with 59% males. Patients were divided into 2 groups based on median GNRI: Higher group GNRI≥91.2 and lower group GNRI <91.2. Higher group were more likely to have poorer functional status, tissue loss and bilateral CLI as well as hypertension, dyslipidaemia and CHF.	• GNRI calculated on admission Ideal body weight was calculated at BMI= 22kgm^2. GNRI is a continuous scale and unlike other screening tools does not have a designated cut-point to determine nutritional risk.	• Mortality • Major amputations • Cox proportional hazard model used to determine association between GNRI and outcomes. • Case-matched sensitivity analysis for overall mortality and limb salvage. Cases matched based on propensity score (derived from functional status and comorbidities) resulting in 171 pairs.	**3yr survival**: 74% vs 48%, p<0.001 (higher vs lower GNRI). **3yr limb salvage**: 92% vs 84%, p<0.001 (higher vs lower GNRI). **Matched pair analysis**: Lower overall **survival** in low GNRI group (p<0.001) and lower **limb salvage** rate (p=0.005). **GNRI as a predictor of mortality**: Multivariate (per decrement of 10) HR 1.35 (95%CI, 1.12-1.63) p value not reported. **GNRI as a predictor of major amputation:** Multivariate (per decrement of 10) HR 1.49 (95%CI, 1.13-1.97) p value not reported.	Rates of survival and limb salvage at 3 years follow-up were lower in the participants in the lower GNRI group. GNRI Score was also an independent predictor of mortality and major amputation with a 35% increase risk of mortality and 49% increase risk of amputation per 10- point reduction in GNRI. Limitations of the study: retrospective design and all participants Japanese so generalisability or results is reduced. Past smoking history could not be determined and hence not accounted for in analyses (current smoking was included). Authors use the term nutritional status when discussing GNRI when it

					should be nutritional risk or risk of malnutrition.
Xie et al, 2017 Aim: to determine the predictive relationship between GNRI and prognosis among DFU patients undergoing LEA. **Study design: retrospective cohort study**	271 patients with DFU. Minor amputation: distal to the ankle joint. Major amputation: above the ankle joint. Mean age was 66.9 ± 11.1 years; 59.8% male	GNRI ≥92 = low/no risk GNRI<92 = mod/severe risk. Data were retrospectively collected to allow calculation of the GNRI. Follow-up data via medical records or telephone interview. Follow-up period not clearly described but appears to be ~70 months on survival curves.	• Mortality during follow-up • Survival analysis using Kaplan-Meier. • Cox proportional hazard model for association between GNRI and mortality.	**51% deemed 'at risk' on GNRI** **GNRI as predictor of all-cause mortality (multivariate)** HR 0.945 (0.921-0.971) p<0.001 **Survival** **Mean-survival time (low GNRI vs high GNRI):** 45.8±2.6 (40.8-50.8) months vs 60.1±2.2 (55.9-64.3) months. Log-rank p<0.001) **GNRI as a predictor of mortality in those with minor amputations (multivariate)** HR 0.936 (95% CI 0.908–0.965 p < 0.001),	Overall, lower GNRI scores before surgery is significantly associated with mortality. This was also true in those with minor amputations. GNRI includes albumin level which is a known predictor of mortality and hence this in-part explains the ability of the GNRI to predict mortality which may not be related to nutritional status given the effects of inflammation (in DFU) on albumin level. There was no assessment of whether GNRI was reflective of nutritional status in this patient group

Abbreviations: AUC (Area under the curve), BMI (body mass index), CONUT (controlling nutritional status index), FFMI (Fat free mass index), GNRI (Geriatric nutritional risk index), LOS (length of stay), MNA-SF (Mini Nutritional Assessment – Short Form), MUST (Malnutrition Universal Screening Tool), NPV (negative predictive value) NRI (Nutrition Risk Index), NRS-2002 (Nutritional Risk Screening-2002), PG-SGA (Scored Patient-Generated Subjective Global Assessment), PNI (prognostic nutritional index), PPV (positive predictive value) SGA (Subjective Global Assessment), Sn (sensitivity), Sp (Specificity)

Cardiothoracic Surgery Patients

Lomivorotov et al and Van Venrooij et al, examined a range of screening tools to determine the prevalence of nutritional risk, the agreement of the tools with an assessment of nutritional status and the associations with clinical outcomes (to be discussed in the relevant section) in cardiothoracic patients (189, 190). Both studies had a good sample size (441 and 325 participants) and exploration of the MUST and SNAQ were common to both studies. Lomivorotov et al also examined the NRS-2002 and Mini-Nutritional Assessment -Short Form (MNA-SF) (189). Different reference assessment methods were used in the two studies, with Lomivorotov using the SGA, whilst Van Venrooij used low fat free mass index (FFMI ≤14.6kgm2 in females, ≤16.7kgm2 in males) determined by bioelectrical impedance spectroscopy (BIS) (189, 190).

Prevalence of malnutrition according to SGA in the study by Lomivorotov et al was 8.8% with the four screening tools classifying between 9.7% and 27.7% as 'at risk'. Van Venrooij found a similar prevalence of malnutrition (8.3%) despite using a different method of assessment (fat free mass, FFM) and a wide variation in the proportion classified as 'at risk' on screening (7.5% and 20.9%). Sensitivity (Sn) was high in all screening tools except the NRS-2002, and specificity (Sp) met a-priori levels in all but the MNA-SF in the Lomivorotov study, however the positive predictive value (PPV) was low across all tools showing a high rate of false positives and over classification of malnutrition risk (189). Sensitivity results in the second study were lower (59.3%, 18.5%) and again PPV (23.9%, 20.8%) was low for both tools (190). The results of these two studies indicate that despite the method used as the reference standard, the screening tools examined did not perform well in this group of patients and that they tend to overclassify nutritional risk. It is important to consider that both studies were of neutral quality according to the ADA quality appraisal (131) due to subject selection bias and lack of blinding of outcomes when interpreting the results. Also, given there are only two studies in this patient group definitive conclusions

cannot be made, however these studies indicate that the MUST, SNAQ, NRS-2002 and MNA-SF do not perform well at identifying 'at risk' patients.

Gastrointestinal Surgery Patients

The two studies conducted in gastrointestinal surgery examined the classification of nutritional risk according to the NRS-2002 and the agreement with the SGA and/or Patient-Generated Subjective Global Assessment (PG-SGA Score) (185, 186). Both studies had very different sample sizes of 280 (186) and 45 (185).

Prevalence of malnutrition according to the SGA/PG-SGA varied across the two studies with Chi et al classifying 33.9% as malnourished on the SGA, and Badia-Tahull et al (185) finding approximately 52% malnourished on both the SGA and PG-SGA, however classification of 'at risk' on the NRS-2002 were similar at 53.3% (186) and 57.7% (185). Agreement between the SGA and NRS-2002 was similar across both studies and rated as moderate (k 0.54, $p<0.001$ (186) and k 0.53, $p<0.0001$ (185)). Chi et al also examined agreement in those above and below 70 years (186). Agreement was found to be excellent in the younger age group (k 0.81, $p<0.001$) and very poor in the older age group likely as a result of the inclusion of scores for age >70 years in the NRS-2002 leading to over-inflation of nutritional risk. The inclusion of age in the screening tool also goes part-way to explaining the over classification of risk across the whole sample (53.3% 'at risk' vs 33.9% malnourished, $p<0.001$).

A difference between the two studies is the number of categories of risk. Badia-Tahull et al (185) considered three categories of risk/status for comparison compared to two levels in the other study (moderate and severe risk groups combined) (186). Agreement may have been improved if 2 levels of risk were considered and given full nutrition assessment would be warranted in patients who are mildly malnourished or at medium risk as well as those in the severe categories, consideration of two levels of risk seems appropriate as was the case in the other study (186).

Both of these studies were of level III-2 evidence and of neutral quality due to unclear reporting of blinding of assessment outcomes and comparisons between instruments, which reduces the ability for conclusions to be drawn, in addition to the small number of studies (n=2) in this patient group. The results of these studies indicate that there is moderate agreement between the NRS-2002 and the SGA in gastro-intestinal surgery patients, however there is the potential for over-classification of nutritional risk, particularly in older patients.

Mixed Surgery Patients

The three studies of mixed surgery samples ranged in size from 100 - 588 patients and the screening tools examined were the NRS-2002, MUST, NSI, NRI and ANST (184, 187, 188). Across all three studies, SGA was used as the reference with malnutrition being diagnosed in 64% (184), 56% (187) and 15.3% (188) of participants.

The NRS-2002 was examined in all three studies against the SGA with Karatake et al finding a strong correlation between the two instruments ($r=0.874$, $p<0.001$) with 16.4% being classified as 'at risk' versus 15.3% diagnosed on SGA (188). Classification of 'at risk' was similar to the proportion diagnosed as malnourished in the study by Muorao et al (55% vs 56%) (187) and Almeida et al (66% vs 64%) (184) however agreement determined by kappa varied with high agreement ($k=0.853$, $p<0.001$) in Almeida et al (184) but low and non-significant agreement in the other study ($k=0.29$, $p>0.05$) (187). Sensitivity and Sp was also examined in two of the studies, with values exceeding the a-priori levels for Sn, Sp, PPV and negative predictive value (NPV) appropriate screening tool (191) in the study which reached high agreement (184). In the other study, specificity was poor (187).

The MUST was examined in two studies against the SGA with both studies finding fair ($k=0.72$, $p<0.05$) (187) to high agreement ($k=0.912$ $p<0.001$) (184) between the instruments. When Sn and Sp was again explored by Mourao et al, the MUST performed poorly with values of 54% and 25% respectively (187).

The remaining three screening tools were each examined in a single study. The NRI was found to have poor Sn, Sp, NPV and PPV (29%. 27%, 24% and 27% respectively) against the SGA in the study by Almeida et al (184). Agreement, while statistically significant, was low between the NRI and SGA and hence the NRI was deemed to not be appropriate in this patient group. This is likely due to the inclusion of albumin which in the clinical setting is a broader predictor of risk rather than a nutritional risk indicator, hence leading to over-classification of patients as 'at risk'.

The NSI and ANST were both included in the study by Mourao et al (187) and similar to the results observed with the NRS-2002 and MUST, both tools had low Sp (10% and 7% respectively) and hence were not able to identify the well-nourished patients adequately leading to over-classification of risk. Agreement was good ($k=0.7$, $p<0.005$) for the NSI but not statistically significant for the ANST ($k=0.55$, $p>0.05$). The over-classification of risk by the ANST (75%) and poor agreement could be attributed to the classification of risk based solely on a medical diagnosis. On the ANST, patients are classified as 'at risk' if they have one or more of a list of diagnoses which includes items such as diabetes and multiple fractures which are not routinely incorporated as a marker of malnutrition.

Overall results within the mixed-surgery patient group were positive for the NRS-2002 with the exception of the study by Mourao et al (187) which yielded poor results across all of the tools examined and could in part be attributed to the smaller sample size. All three studies were of neutral quality with main quality issues being lack of blinding of measurements and inadequate description of how the tools were administered. The screening and assessments in the Mourao et al (187) study were conducted by medical students, whereas they were conducted by a dietitian in the Almeida et al study (184). It was unclear in the Karatake et al (188) study who conducted the screening and assessments.

Across all surgical patients, concordance and agreement is variable. The NRS-2002 appears to have fair to good agreement compared with the SGA across studies, particularly in the older population, however there is a tendency to over-classify risk which has implications for nutrition and dietetic resource utilisation to provide full assessments to patients who are incorrectly classified.

Predictive Validity

Two studies were located that examined the predictive ability of malnutrition screening tools in vascular surgery patients and are summarised in table 6. Sample sizes were 271 (183) and 473 (182) and both were retrospective cohort studies.

Using the NHMRC evidence hierarchy based on the 'Prognosis' classification (132), both studies were level III-3 (182, 183), with one being of neutral quality (183) and the other study (182) classified as negative quality (131). The consistent areas of poor quality and risk bias was due to unclear or poor reporting of the research aims and questions, unclear subject selection or representation of the relevant population, lack of blinding of outcome assessment. Xie et al was also unclear in their acknowledgement of conflicts of interest and funding as well as unclear reporting of outcome measures (183).

Both studies examined the GNRI, with one examining the ability of the GNRI to predict mortality and lower limb salvage post EVT in Japanese participants with CLI (182), whereas the second study explored mortality post amputation in DFU patients (183). Both studies were conducted in Asian populations hence their generalisability to other populations is unclear.

The first study (182) divided 473 participants into those with lower (<91.2) and higher (≥91.2) GNRI scores ('at risk' and 'no risk' respectively). The authors found that survival and limb salvage at 3-year follow-up was poorer in the lower score group (74% vs 48%, $p<0.001$ and 92% vs 84%, $p<0.001$ respectively) which remained true when matched pair analysis was conducted. GNRI

score was found to independently predict mortality and major limb amputation (HR 1.35 (95%CI, 1.12-1.63) and HR 1.49 (95%CI, 1.13-1.97) respectively. (p values not reported) with a 35% increase risk of mortality and 49% increase risk of amputation per 10- point reduction in GNRI score. The second study (183) found that the GNRI was predictive of mortality in DFU patients. A similar cut-off of GNRI (Score of 92) was used with 51% of participants being deemed 'at risk'. Mean survival time was significantly lower in the 'at risk' group ((Mean ± SD) 45.8±2.6 (40.8-50.8) months vs 60.1±2.2 (55.9-64.3) months, p<0.001) and multivariate analyses showed that GNRI independently predicted all-cause mortality across all participants (HR 0.945 (0.921-0.971) p<0.001) and in those with minor amputations (HR 0.936 (95% CI 0.908–0.965 $p < 0.001$).

It is relevant to consider that the GNRI is a risk assessment tool that encompasses albumin level which is a known predictor of poor outcomes and not necessarily a parameter of nutritional status in the clinical setting and given the presence of infection and/or inflammation in both CLI and DFU patients, albumin is likely to be affected and hence score will be affected regardless of actual nutritional status. Unlike other screening tools such as the MNA-SF and the MUST, the GNRI is a continuous scoring index based on equation modelling and doesn't have a designated cut-point to determine nutritional risk however a score of 92 appears to be consistently used. Despite these factors, these studies demonstrate that a measure of nutritional risk can predict outcomes in vascular surgery patients.

Conclusion

In conclusion, there were variable results in terms of validity and predictive ability of screening tools across surgical patients. The NRS-2002 and MUST were the most studied across the 7 studies examining diagnostic agreement/concordance with some variation in results depending on the patient population studied which highlights further the importance of using a tool that is valid in the patient group. The quality of the studies varied, with the key issues for those of lower quality

being inadequate description of the screening protocol and blinding and unclear subject selection/representativeness.

Two studies were included that examined the predictive ability of the GNRI in vascular surgery patients, however no studies were located that examined the validity of screening tools at identifying nutritional risk in these patients. Hence there is a crucial gap in the literature regarding the appropriateness of malnutrition screening tools in this patient group.

2.3 Summary and implications for this thesis

From the literature studied, it is apparent that vascular disease patients are a nutritionally vulnerable group. The prevalence of undernutrition, including micronutrient deficits is high with evidence to show that this is linked to poorer clinical outcomes. Micronutrient deficits have been observed in patients classified as overweight and obese, hence undernutrition may be difficult to recognise using traditional methods of nutrition screening and assessment. While there are numerous malnutrition screening tools available that have been studied in surgery patients, none have been developed or validated in the vascular surgery setting and so it is not known whether currently adopted malnutrition screening tools are able to correctly recognise those patients who are at risk of undernutrition/malnutrition to enable appropriate nutrition/dietetic intervention. Hence, this thesis will address the following research questions which are informed by the comprehensive literature review and the gaps identified during the review. Ensuring a high quality, original contribution that has relevance to the clinical management of a growing patient group that incurs significant economic burden.

2.4 Research Questions

1. What is the prevalence of malnutrition and sarcopenia in a heterogenous sample of acute care inpatients admitted to a vascular surgery unit?

2. How do four commonly used nutrition screening tools perform (validity) in a heterogenous sample of acute care inpatients admitted to a vascular surgery unit?
3. In the absence of an adequate/appropriate screening tool for use in this population, can a valid screening tool be developed that performs better than tools that are currently available?
4. What are the clinical outcomes and health care costs for vascular surgery patients over 12-months of follow-up and can they be predicted by a malnutrition screening tool developed for use in vascular surgery patients?

Chapter 3: Study Methods

3.1 Study Design

This study was a prospective, observational study. Ethical approval was granted by the Southern Adelaide Health Research Ethics Committee (SAHREC) (approval number 258.14) and governance approval from the Flinders Medical Centre, Bedford Park South Australia. Data collected within this study were utilised for the analyses described in chapters 4-7 of this thesis.

3.2 Recruitment

Participants for this study were recruited consecutively from the Southern Adelaide Local Health Network (SALHN) vascular surgery unit, Adelaide Australia. Appendix 4 depicts the flow of participants through the study. All new admissions to the vascular surgery unit were obtained twice daily Monday-Friday each week via the South Australian Health Oacis (Open Architecture Clinical Information System) system, first thing in the morning and again early in the afternoon and screened for eligibility by a research team member. Screening was conducted within 24 hours for patients admitted from Sunday to Friday. Patients admitted from Friday evening to Sunday evening were screened in the morning on Monday (48 hours). All admissions were assigned an identification number and recorded in a log-book along with the following information; Name, medical record number (MRN), date of birth, age, gender, reason for admission, vascular disease type, admission and discharge date, whether eligible for inclusion or not, whether consent was obtained and the day of admission on which they consented to participate where relevant. Vascular disease types were classified as aneurysmal, PAD (encompassing aorto-iliac and infra-inguinal disease), occlusive other (encompassing carotid and upper limb ischaemia), venous disease, diabetic foot infection and 'other' based on the admitting vascular surgeon's diagnosis. Those classified as other included renal access, surgical management of thoracic outlet syndrome, trauma, ulcers of mixed or

unknown aetiology, admission for post-operative complications and lower limb infection not attributed to occlusive disease or diabetes. The PAD participants were further classified into the Rutherford's stages of PAD which is shown in Table 1 (5).

Assessment of eligibility was completed by a research team member using details available via Oacis and medical records against the inclusion and exclusion criteria.

Inclusion criteria: Patients were included if they were aged 18 years or above and informed written consent was able to be obtained from the patient or by their legal representative or next of kin (NOK).

Exclusion criteria: Patients were ineligible if they met either of the following criteria; (1) admitted for elective day procedures only as these patients are not admitted to the vascular surgery ward (2) Emergency presentation without admission to the vascular surgery ward or subsequent transfer to a private hospital, (3) previously consented or declined to participate during a prior admission, (4) unable to be recruited within 48-72 hours of admission, e.g. ICU admission, (5) Patients in a terminal phase of illness who were for comfort care only. If patients declined to participate but indicated that they were agreeable to being re-approached in subsequent admissions, this was recorded and not used to exclude that patient during subsequent admissions.

Following the screening for eligibility, eligible patients were approached within 2 days of admission (3 days for those admitted on a Friday evening) by a research team member. The study was explained verbally to the patient (or legal representative/next of kin) outlining the purpose of the study and what was required of the patient if they agreed to participate. It was also explained that they were free to withdraw from participating at any time with no implications for their medical care/treatment. Details of the study were also provided via a written Patient Information Sheet (Appendix 5). Signed, written consent was obtained from the patient or legal representative/NOK either at the time or on a return visit by the team member

if the patient wished to consider their involvement further. Upon consent, participants were provided with a copy of their signed consent form (see appendix 5) and a second copy was filed in the participants medical records.

The calculation of sample size was based on determining the precision of the expected sensitivity and specificity of the proposed screening tools.(192, 193) A prevalence of malnutrition of 61% was determined from a prospective, observational, audit of vascular surgery patients in an elective setting.(82) A total sample size of 322 participants would need to be recruited to obtain 197 participants with malnutrition (prevalence of the malnutrition is 61%). The sample size calculation allows a point estimate of 85% sensitivity and specificity to be measured with a precision of +/- 5% with 95% confidence. The sample size calculation was also based on investigating the effect of nutritional status on complications and health care outcomes. Although several outcomes have been addressed, patient's mortality was chosen to justify the power and sample size calculation. Using a hierarchical cox regression model on a 3 year follow-up study of vascular patients with lower limb ulcers, Miller et al(194) demonstrated that those patients with BMI <30 kg/m^2 were 4.6 times more likely to die than those with BMI ≥ 30 kg/m^2 (95% confidence interval [CI]: 1.04-20.4; *P* 0.04). As the confidence interval was so wide, we used a risk of death at the lower end of the confidence interval to detect a large sample size. A two-sided log rank test with an overall sample size of 266 subjects (133 in the BMI < 30 kg/m2 group and 133 in the BMI ≥ 30 kg/m2 group) achieves 90.0% power at a 0.05 significance level to detect a hazard ratio of 1.50. The Power Analysis & Sample Size Software (PASS) was used to calculate the sample size.(195)

3.3 Data Collection & Management

Data for this study was collected between October 2014 and August 2016 and involved research Accredited Practising Dietitians (APDs), research assistants and the vascular surgery unit nursing staff. The APDs (including the PhD candidate) were not members of the clinical team responsible for the care of the participants during their admission and hence there was no conflict of interest. Appendix 4 depicts the movement of participants through the data collection process and the associated data collection forms that were used for each participant. All hard copy data collection forms were stored in a locked filing cabinet within the Nutrition and Dietetics discipline of Flinders University, where the research was conducted. All data were de-identified for entry into a password protected database that was saved on the Flinders University main server. Both the hard copy data and database were only accessible by the research team members involved in data entry and data analysis for this study.

3.4 Assessment of Participants

3.4.1 Baseline assessments

Within 2-3 days of admission, demographic data were collected from the participant's medical records by the research dietitian. Demographic data included age, gender, living situation, past medical history and current medications, reason for admission and type of vascular disease. All data collection was performed by the research dietitian or appropriately trained personnel as described in the following sections. Data collection forms used for baseline assessment can be viewed at appendix 6. All baseline nutrition assessments conducted as part of this study were not part of standard clinical care within the vascular surgery service. If participants were identified to have nutritional issues as part of the baseline assessments, and not under the care of the clinical dietitian within the service, the participant was referred on to vascular dietitian by the research dietitian for further assessment and intervention where necessary. Participant consent for referral to the vascular dietitian was sort prior to referrals being made.

Malnutrition screening

The malnutrition screening was completed by the vascular surgery unit nursing staff. Training regarding the completion of the screening was provided to the unit nursing staff via a series of in-service education sessions by the APDs. During these sessions, feedback was also obtained regarding the layout and organisation of the form so to make it more user-friendly. Following the training sessions and throughout the data collection period, the research dietitians were available to provide support and advice regarding the screening form. In instances where the screening could not be completed by nursing staff in the allotted time period, it was completed by a research team member who was not involved with the nutrition assessment of that participant to maintain blinding for the purpose of validity testing. A review of the literature (Chapter 2) regarding the validity and predictive validity of screening tools showed that a variety had been examined across groups of surgical patients, with 2 studies examining predictive validity in vascular disease patients. The commonly examined screening tools were the NRS-2002 (196), the MNA-SF (197) and the MUST (198). A tool also commonly used in Australia is the MST (192) and hence these four screening tools were chosen for examination as part of this thesis.

Each of these malnutrition screening tools have been determined to have acceptable levels of validity and reliability. However these data come from studies of mixed populations, or specific disease groups including oncology (199, 200), respiratory disease (201) or even specific settings such as residential aged care (202), inpatient and outpatient settings (203). It is well recognised that malnutrition screening tools need to be validated for the population in which they are to be administered to expedite nutrition interventions where indicated and allow resources to be used efficiently (204). The MST, a tool with two questions relating to unintentional weight loss and poor appetite, was originally developed for use in acute care adult inpatients across medical and surgical specialties (192) but has since been validated in additional populations including oncology

(191, 199), residential aged care (202) and geriatric rehabilitation (205). Validation has been demonstrated with values of Sn and Sp between 78-100% and 92-96%, respectively (206). The MUST comprises three clinical parameters: BMI, weight loss and presence of acute disease and has been validated for use in hospital inpatients of mixed aetiology and outpatients (207) with levels of Sn and Sp between 67-97% and 49-93% respectively (206, 208). NRS-2002 was developed by the European Society for Parenteral and Enteral Nutrition (ESPEN) and has three domains: (1) nutritional parameters including weight loss, BMI or reduced food intake; (2) severity of disease; and (3) age. Validity studies for the have occurred in adult surgical patients, general adult inpatients and elderly patients with varying levels of Sn (62-92%) and Sp (83-93%) (184, 206, 209).

The MNA-SF was developed for use in older adults and has six questions encompassing BMI (or calf-circumference) and unintentional weight loss and parameters know to impact on nutritional status including mobility, psychological stress and depression. It has been validated in the acute care residential care and community settings achieving Sn and Spy levels of 85-100% and 41-88% respectively (206, 210, 211).

As this study aimed to investigate the validity of four commonly used screening tools, a screening questionnaire was developed using questions from the four screening tools to reduce repetition and the burden and bias for study participants and nursing staff that would be associated with administering four tools separately. Questions from all four screening tools were pooled and duplicates were removed. The remaining questions were utilised in the screening questionnaire. The pooled nutrition screening form which can be viewed at appendix 7 addresses the areas of anthropometric data (weight, ulnar length (used to estimate height), recent unintentional weight loss), mobility (able to go out through to bed/chair bound), recent changes in food intake and appetite and the presence and severity of disease/illness (including psychological stresses, acute disease). The data collected from the screening process was subsequently used to populate each

of the four individual screening tools by a research team member who was not involved in the nutritional assessment to minimise assessment bias and maintain blinding for the purpose of validity testing .

Nutrition Assessment

Patient-General Subjective Global Assessment (PG-SGA)

Assessment of nutritional status was completed by a research APD trained in conducting the PG-SGA which can be viewed at appendix 8 (212). Subjective global assessment (SGA) is a validated method of nutritional assessment that incorporates a medical history (weight change, dietary intake change, gastrointestinal symptoms that have persisted for more than 2 weeks, changes in functional capacity) and physical examination (loss of subcutaneous fat, muscle wasting, ankle/sacral oedema and ascites) (213). It has been utilised as a method of assessing nutritional status and predicting complications in a number of different patient groups (214-216) and has been correlated with a number of objective parameters (anthropometric, biochemical and immunological), measures of morbidity (incidence of infection, use of antibiotics, LOS), and QoL (192, 213, 217). A recent review of the evidence for the use of the SGA in patients with PAD concluded that it appeared to be the best instrument for assessing nutrition status of hospitalised PAD patients when compared to other known methods such as anthropometry and biochemical parameters (218). However, SGA lacks the sensitivity to detect improvements in nutritional status observed over a short period of time which led to an adaptation of the SGA. The patient-generated-subjective global assessment (PG-SGA) was initially developed specifically for patients with cancer (214) but has since been validated in a number of clinical conditions including stroke, geriatric rehabilitation and acute abdominal surgery (219-221). However, it is yet to be validated in the vascular surgery population and will be examined as part of this thesis. The PG-SGA includes additional questions regarding the

presence of nutritional symptoms and short-term weight loss and was designed so that the components of the medical history can be completed by the patient themselves. The remainder of the medical history and the physical examination is then performed by a health professional, e.g. dietitian, physician or nurse. The scored PG-SGA is a further development of the PG-SGA that incorporates a numerical score as well as providing a global rating of well-nourished, moderately or suspected of being malnourished or severely malnourished. For each component of the scored PG-SGA, points (0-4) are awarded depending on the impact of the symptom on nutritional status. A total score is then summed and provides a guideline as to the level of nutrition intervention required, as well as facilitating quantitative outcome data collection (212). The higher the score the greater the risk for malnutrition. A score ≥9 indicates a critical need for nutrition intervention. On completion of the scored PG-SGA, each participant was awarded a PG-SGA score and a PG-SGA global rating of A (well nourished), B (suspected or moderately malnourished) or C (severely malnourished). Patients identified as being malnourished or at risk of becoming malnourished were referred to the vascular surgery unit dietitian by the research dietitian for dietetic input and monitoring.

Micronutrient Assessment

Fasting blood samples were collected by a trained phlebotomist and analysed by the hospital or state pathology service depending on the analytical test. Where possible, blood samples for research purposes were collected concurrently with routine blood samples to reduce the burden to participants. Blood samples were analysed for albumin, C-reactive protein (CRP), Iron studies, lipid studies, vitamin B12 and folate, vitamin A, C, E and D and the trace elements zinc and selenium.

Micronutrient status was determined as suboptimal, normal or high according to reference ranges (shown in parentheses) provided by the analysing laboratory, for vitamin B-12 (>260 ng/L) and folate (6.5-45 ug/L), vitamin A (1-3.1 umol/L), vitamin C (26-85 umol/L), vitamin E (12-46 umol/L) vitamin

D (60-160 nmol/L) and the trace elements zinc (9-21 umol/L), iron (8-30 umol/L), and selenium (0.8-1.64 umol/L).

Comprehensive Dietitian's Assessment

In addition to the PG-SGA, a comprehensive dietitian's assessment of nutritional status was conducted to enable additional parameters of nutritional status to be assessed that aren't included in the PG-SGA or other nutrition assessment instruments. The additional items included BMI, the presence of a low serum albumin in the presence of normal CRP, iron-deficiency anaemia and micronutrient deficiencies. This was conducted to enable the research team to investigate the nutritional status of the participants further, and to explore the validity of the four nutrition screening tools against alternative measures of nutritional status such as micronutrient status.

Following the data collection period, a research APD retrospectively audited all nutrition-related data collected during the baseline data collection to assess participants for nutritional status. The parameters audited are shown in table 7, along with the cut-offs used to classify nutritional status. A participant was determined as 'undernourished' and coded as "yes" requiring full comprehensive nutrition assessment and/or intervention if they displayed any of the characteristics shown Table 7.

Table 7: Nutrition-related parameters and the associated cut-offs used to determine nutritional status during the comprehensive dietitian's assessment.

Nutrition-related Parameter	Cut-off for Nutritional vulnerability	Source
Low BMI for age	BMI < 22kgm^2 if aged 65 years and over BMI < 18.5/20kgm^2 if aged under 65 years	Landi et al(222) WHO(223)
PG-SGA score	≥9	Ottery F. (212)
PG-SGA Global Rating	B (moderately or suspected malnourished) C (severely malnourished)	Ottery, F (214)
Low Albumin in the presence of a normal CRP	Albumin < 34 with CRP > 8	Merck Sharp & Co. (224)
Iron-deficiency Anaemia	Ferritin<15g/L plus Haemoglobin <130g/l for males or <120g/L for females	Pasricha S-RS, et al (225)
Vitamin A deficiency	<1umol/l	Merck Sharp & Co.(224)
Vitamin C deficiency	<0.29mg/dl	Goebel L. (226)
Vitamin D deficiency	<60nmol/l	Merck Sharp & Co.(224)
Vitamin B12 deficiency	200pg/ml	Johnson L. (227)
Folate deficiency	<3ug/l	Merck Sharp & Co(224)
Zinc deficiency	<9.0umol/l	Merck Sharp & Co. (224)
Selenium deficiency	<0.7umol/l	Poitou Bernert C, Ciangura C, Coupaye M, et al. (228)

Anthropometry

Body Weight and Height

Participants' body weight was measured by nursing staff or research team members using calibrated seated weighing scales (HVL-CS Hospital Chair Scale, A&D Mercury Pty Ltd) to the nearest 0.1kg in light clothing and no shoes.

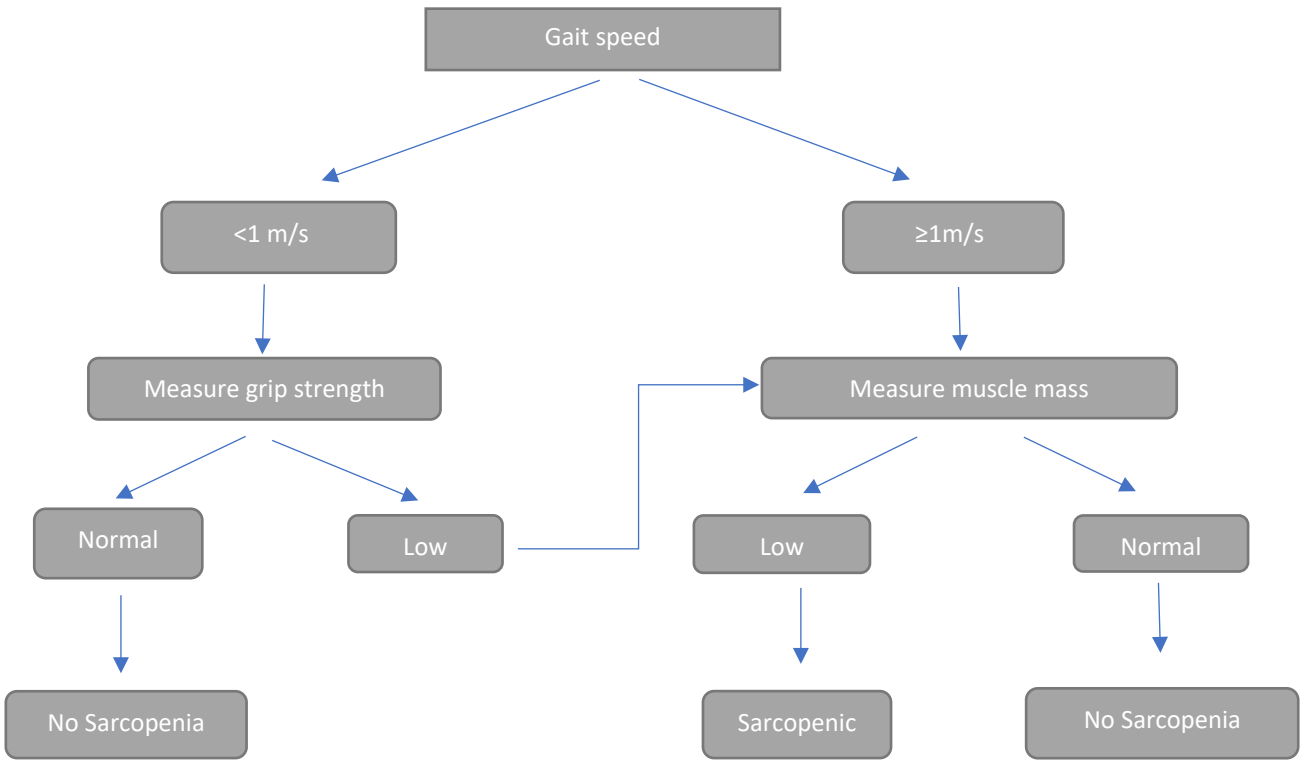
Ulna length was measured in a seated or standing position, from the olecranon process to the midpoint of the styloid process on the left arm using a flexible non-stretch steel measurement tape to the nearest 0.5cm according to standard protocol (198) by nursing staff or research team members. Ulna length was converted to estimated height using the MUST conversion

table to the nearest 1cm (198). BMI was calculated as weight (kg) divided by the square of height (m^2) estimated from ulna length. Age-appropriate BMI cut-offs were used to classify participants as underweight, normal weight or overweight/obese for those over 65 years (<22kgm^2, 22-27kgm^2, >27kgm^2 respectively) (222) and under 65 years (<18.5kgm^2, 18.5-24.9kgm^2, >25kgm^2 respectively) (223).

Determination of Sarcopenia

The parameters used to define sarcopenia are the amount of muscle and its function measured via muscle mass, strength and physical performance (92). The EWGSOP outlined that DEXA, handgrip strength and gait speed can be used to diagnose sarcopenia (92). To enable the determination of sarcopenia in the present study, measurements for each parameter were converted into the relevant low/normal cut-offs and then incorporated into the EWGSOP algorithm for diagnosing sarcopenia which is shown in figure 1.

Figure 1: EWGSOP Algorithm for the diagnosis of sarcopenia in adults aged 65 years or older.



Skeletal Muscle Mass: Dual-energy x-ray absorptiometry (DEXA)

DEXA is a globally accepted method for measuring fat mass (FM) and fat-free mass (FFM). In this study, skeletal muscle mass was determined using the Lunar Prodigy Pro dual-energy x-ray absorptiometer in conjunction with Encore software version 7.5. All scans were completed by trained researchers. Before the scan, a checklist was conducted to clarify potential pregnancy, medication usage, including calcium and iron supplementation in the past 24 hours, history of recent scans and X-rays, past history of fractures or other conditions that would affect hips, forearm or spine. Participants were asked to remove all metal accessories and to declare the presence of metal implants (e.g. hip prosthesis) as these can then be confirmed and removed post-procedure using the Encore software before analysis. Participants were in light clothing and positioned in the supine position, feet in neutral position with hands flat by their sides for approximately 10 minutes to allow for the attenuation of a photon beam. The scanner uses a fan beam and multiple detectors to collect data and therefore only a single pass along the length of the scan was required. An x- ray source emits two different photon energy peaks which allows for tissues to be differentiated from other body matter due to differing absorption of the two photon energy peaks. Material of low density allows more photons to pass through and high-density materials such as bone will transmit fewer photons. The image produced allows researchers to determine FM and FFM of participants. Appendicular lean soft tissue (ALST) mass was calculated as the sum of the lean soft tissue in both upper and lower limbs which was then converted to skeletal muscle mass (SMM) (kg) according to the equation of Kim et al (229) which is shown below.

$$\textit{Total-body SM} = (1.13\ \textit{ALST}) - (0.02\ \textit{age}) + (0.61\ \textit{sex}) + 0.97$$

Where sex is 0 = female and 1 = male

SMM (kg) from DEXA was adjusted for height to produce the SMI (kg/m^2) according to the equation by Baumgartner et al (230). Sarcopenia was defined as SMI being less than two standard deviations below the mean of a young reference group of 229 non-Hispanics as suggested by Baumgartner et al (230) resulting in a cut-off of <6.4kgm^2 for males and <5.5kgm^2 for females.

Muscle strength: Handgrip Strength

Handgrip strength has been shown to be correlated with lower extremity muscle power, with low handgrip strength being a clinical marker of poor mobility and a reliable surrogate measure for more complicated measures of muscle strength in the lower arms or legs (92). In the present study, grip strength was measured using an Advanced Hand Dynamometer (Mentone Educational, Australia) with the participant standing facing forward with legs straight and feet approximately 15cm apart. If unable to stand, grip strength was collected with the participant in a seated position. Murugan et al (231) found no difference in hand grip strength between sitting and standing postures with mean of force production almost equal hence it was chosen as an appropriate alternative in participants unable to stand appropriately. Grip strength was collected from the dominant hand unless affected by disease or disability in which case the non-affected hand was used. Participants were instructed to hold the dynamometer so that it did not touch the thigh and to squeeze with maximum force, without swinging the arm, for three seconds. The measurement was performed in triplicate and the mean value was used in analysis.

For handgrip strength, gender specific cut-offs for low muscle strength were established using data from the North West Adelaide Health Study at two standard deviations below the mean of young adults resulting in cut-offs of <28kg and <16kg for males and females respectively (232).

Physical Performance: Gait Speed

Several tests are available for assessing physical performance. One such test, gait speed, has been shown to be predictive of adverse health events and disability and has been listed by the EWGSOP as a test that can be used in clinical and research settings (92). In the present study, gait speed in metres per second (m/s) was determined via a 6-metre timed walk test carried out by a research team member. Six meters was chosen based on the space available and has been shown to be valid and reliable in assessing walking ability when compared to the standard 10 metre timed walk test (233). Participants were asked to stand with their toes positioned behind the start line at 0m, in non-slip footwear or bare feet depending on participant preference and medical instructions regarding footwear. Timing began with an electronic stopwatch as toes crossed the start line and ceased when toes crossed the 6m line. Participants were asked to walk at their usual pace and a handrail was available for the full 6m for safety. The walk was measured in triplicate and an average (recorded to the nearest 0.1 sec) was used for analysis.

A gait speed cut-off point of <1m/s was used to identify suboptimal physical function and risk of sarcopenia as per the EWGSOP (92). Participants who were unable to complete the gait speed test were classified as being "unable" and hence were included in the group of participants with a gait speed of <1.0m/s to signify suboptimal physical performance for further analyses.

Health-related Quality of Life.

Health-related quality of life was assessed using the well-validated EQ-5D-5L which can be viewed at appendix 9 (234). The EQ-5D-5L includes five questions related to mobility, self-care, usual activities, pain/discomfort and anxiety/depression with five levels of impairment recognised in each domain: no, slight, moderate, severe and extreme problems in the relevant dimension of health. Using these responses, the EQ-5D-5L can distinguish between 3,125 states of health. Each EQ-5D health state can be converted into a utility value using a valuation algorithm (235). EQ-5D-

5L utility value typically has a range of 0 to 1: the maximum score of 1 representing perfect health, a score of 0 representing death while scores less than 0 represent health states that are worse than death (236-238). In this thesis, the UK valuation set was utilised to calculate the utility scores as an Australian valuation set was not available at the time of analyses.

The generic nature of the EQ-5D-5L allows it to be used across several patient populations. During the bed-side interview, the research dietitian administered the EQ-5D-5L questionnaire (234) asking each question individually and ending with the EuroQol Visual Analogue Scale (VAS) of perceived health on the day of interview. Participants were asked to rate their overall health from zero (worst health imaginable) to 100 (best health imaginable) and to record it on the VAS.

3.4.2 Discharge assessment

On the day of discharge, the research dietitian conducted a discharge interview to repeat the PG-SGA (212), EQ-5D-5L (234) and measure body weight. Admission events and discharge details were collected from the medical records. Data included date of discharge, length of stay and discharge destination, medical complications and events during the admission, particularly those associated with vascular and arterial disease and malnutrition and details regarding any dietetic involvement. Appendix 10 shows the discharge data collection form.

3.4.3 Follow-up Assessment

Follow-up assessment was conducted at 12 months post-discharge by a research dietitian via Oacis and a telephone call to participants. Prior to contacting the participant, Oacis was used to check for mortality and to access information regarding all hospital admissions, procedures/surgeries, and vascular surgery follow-up during the follow-up period. Vascular surgery reports were viewed for diagnoses including the development or deterioration of lower limb ulcers/wounds, vascular stenosis and for details of any procedures or surgeries performed. During the telephone call, information gathered from Oacis was clarified and

information regarding hospital admissions to facilities outside of the South Australian public health system was collected. Dates and reasons for admissions were collected along with details regarding any medical procedures and/or surgeries that had occurred. Information was also collected regarding peripheral and cardiovascular health, particularly the development or deterioration of lower limb ulcers/wounds, whether they had been diagnosed with vascular stenosis by medical professionals and any cardiovascular events such as a myocardial infarction or cerebrovascular accident (CVA). In addition to the medical/health related information, the EQ-5D-5L (234) was conducted, including the EQVAS which was asked verbally by the research dietitian. The follow-up data collection form can be viewed at appendix 10.

3.5 Statistical Analysis.

All statistical analyses were conducted using SPSS for Windows version 25 (SPSS Inc, Chicago, IL) and Stata version 15.0 (StataCorp LLC, College Station, TX). Significance was set at the $p<0.05$ level (239). Continuous variables were assessed for normality using the Shapiro-Wilk test and reported as mean (standard deviation, SD) or median (interquartile range, IQR). Descriptive statistics were expressed as frequencies (n, %) with Chi-square analysis or Fishers Exact Test used to determine differences between groups for categorical variables. Continuous variables were compared using Independent–samples t-test/Mann-Whitney U test or One-way ANOVA/Kruskal-Wallis Test. Inferential statistics relevant or specific to each research question will be presented in each relevant chapter.

Chapter 4: What is the prevalence of malnutrition and sarcopenia in a heterogenous sample of acute care inpatients admitted to a vascular surgery unit and does nutritional status affect short-term clinical outcomes? (Research Question 1)

The prevalence of malnutrition and sarcopenia component of this study has been published in the *Asia Pacific Journal of Clinical Nutrition* , a quartile two journal in medicine according to 2018 Scimago Journal Rankings. This chapter was used to prepare the publication, hence there is a direct overlap in content and phrasing. Please see Appendix 11 for the accepted pre-print version (included with permission).

4.1 Introduction

Vascular disease is an increasing health problem in the developed world with an ageing population and growing prevalence of chronic disease (240, 241).

As discussed in Chapter 2, it is well established that malnutrition (undernutrition) is present in patients with vascular disease and is strongly associated with poorer clinical outcomes. In brief, rates of malnutrition vary from 60 – 90% in the literature depending on the type and severity of vascular disease studied (82-84). Malnutrition has been associated with poorer outcomes, such as increased rate of septic complications (83), higher rates of infection (180), longer hospital LOS and discharge to a care facility (86) and increased likelihood of limb amputation in patients with limb-threatening diabetic foot ulcers (80).

Sarcopenia, along with malnutrition, contributes to and overlaps with frailty which is further associated with poor health outcomes such as falls, hospitalisation and mortality (92). Patients with vascular disease resulting from a range of pathologies are at risk of SMM loss as

demonstrated in chapter 2. It is known that individuals with PAD have functional impairment and faster deterioration in function compared to individuals without PAD (105) with reports that patients with severe intermittent claudication (IC) are physically impaired by up to 75% compared to the functional ability of healthy controls (242). Reduced activity and immobility contributes to a reduction in muscle mass (92) which is also accelerated by age-related changes in body composition, including increased fat mass and reduced muscle mass (243). These factors place patients with PAD at risk of reduced muscle mass and sarcopenia and that this could be masked by the high prevalence of overweight and obesity in this group is cause for concern. Recent work conducted by the supervisory panel of this thesis showed that changes in muscle mass are not confined to PAD patients as an association between larger aortic abdominal aneurysms (AAA) and a reduction in muscle mass was observed (244). Due to the importance of muscle mass and strength in the performance of activities of daily living and other physiological processes (93) and in the management of vascular disease via exercise (6), sarcopenia in this population warrants further investigation.

The investigation of malnutrition also involves consideration of micronutrient status. The underlying mechanism for the development of atherosclerosis and progression of vascular disease is pro-oxidative and pro-inflammatory in nature (245) hence micronutrients with anti-oxidative properties are important, along with micronutrients that are important in the prevention and management of other vascular disease manifestations such as wounds and ulcers. Several studies have investigated micronutrient status in patients with vascular disease which have been

discussed previously in chapter 2. The impact of micronutrient deficiencies can be significant. A study of 1435 American veterans with PAD observed a significantly higher rate of amputations in those with low vitamin D levels and that vitamin D levels were significantly and inversely correlated with BMI providing support to the notion that deficiencies are present in individuals who are of a higher BMI (85). Other micronutrients such as vitamin C, vitamin A and zinc are involved in wound healing and epithelial integrity, along with immune function, hence deficiency prolongs wound healing time and contributes to reduced resistance to infection (106). The potential causes or mechanisms for micronutrient deficiencies in this group are likely multifactorial, including suboptimal diet (177, 178, 246), potential drug-nutrient interactions (179) and altered utilisation/metabolism of micronutrients (247).

Given some or all of the important deficits in nutritional status may be masked by a high BMI in patients with vascular disease, it is important to highlight areas of concern and how these may differ across the various vascular disease types such that clinicians can be informed and ideally identify patients who may be of concern despite weight status.

The first aim of this study was to investigate the nutritional status of a heterogeneous sample of patients admitted to a vascular surgery unit as assessed by a comprehensive dietitians assessment and a commonly used nutrition assessment tool (PG-SGA) (212) and to determine the prevalence of malnutrition (including nutrient deficiencies) and sarcopenia in this group. The second aim was to investigate the relationship between nutritional status on admission and clinical outcomes

collected on discharge. These aims are to address research question 1 of this thesis shown in 2.4 Research Questions.

4.2 Methods

4.2.1 Study Sample

Participants were recruited consecutively from the SAHLN Vascular Surgery Unit according to inclusion and exclusion criteria outlined in 3.2 Recruitment. The study received ethical approval from the Southern Adelaide Health Research and Ethics Committee (approval number 258.14) and governance approval from the Flinders Medical Centre.

4.2.2 Data collection

Data collection occurred between October 2014 and August 2016 and has been described in 3.3 Data Collection. In brief, data included demographic data and vascular disease type according to surgeon diagnosis.

Assessment of Micronutrient Status

Fasting blood samples were collected and analysed as described in section 3.4.1 Nutrition Assessment. Participants with levels below the reference range were deemed to have suboptimal micronutrient status in that nutrient.

Assessment of Nutritional Status

Patient-Generated Subjective Global Assessment

The PG-SGA was conducted by an Accredited Practicing Dietitian (APD) during an in-person consultation, with each participant awarded a PG-SGA score and a global rating of A (well nourished), B (suspected or moderately malnourished) or C (severely malnourished) (212). A detailed description of the PG-SGA is available in 3.4.1 Baseline assessments and can be viewed in appendix 8.

Comprehensive dietitians Assessment

The comprehensive dietitian's assessment was conducted retrospectively using all data collected during the baseline data collection as described in 3.4.1 Nutrition Assessment.

Determination of Sarcopenia

The presence of sarcopenia was determined using the EWGSOP algorithm for diagnosing sarcopenia (Figure 1) (92). A detailed description of the methodology used is available in 3.4.1 Determination of Sarcopenia

Discharge data collection

Admission events and discharge details were collected from the medical records. Data included date of discharge, length of stay and discharge destination, medical complications and events during the admission, the occurrence of unplanned procedures/surgery, infections (including pneumonia), wound/ulcer development or deterioration, vascular restenosis/acute occlusion, CVD events, acute renal impairment and death.

4.2.3 Statistical analysis

The approach used for describing the data using descriptive statistics is provided in 3.5 Statistical Analysis.. Chi-square analyses was used to determine differences between types of vascular participants for the categorical variables gender, age categories and whether participants lived in their own home, whereas Fishers Exact test was employed for the variables BMI categories, living in aged care and living in supported care.

One-way ANOVA with Tukey post hoc test or Kruskal-Wallis test was used for determining differences in continuous variables including age, median BMI, hospital LOS, and variables relating to proportions of participants classified as malnourished. To explore clinical outcomes on discharge, all admission complications were aggregated into one variable 'in-hospital complications' to provide an adequate sample size for further analyses. Chi-square analysis or

Fishers Exact test were employed to determine differences in discharge destination and in-hospital complications according to malnutrition status (comprehensive dietitians assessment and micronutrients individually). Mann-Whitney U test was used to explore LOS. Spearman's Rho was used to determine the correlation between LOS and number of micronutrient deficiencies with Kruskal-Wallis test to determine differences in LOS according to the number of micronutrient deficiencies.

4.3 Results

A total of 2229 patients were admitted to the vascular surgery ward during the study period. All were screened for study eligibility. Of these, 1327 (59.5%) were ineligible (admitted for less than 48hrs, previous participant), 568 (25.5%) declined to participate, and 12 (0.5%) participants withdrew before data collection resulting in 322 participants (consent rate = 35.7%) available for data collection.

Table 8 displays the participant demographics. Most study participants were male (69.3%) and over 65 years old (61.6%). Sixty-four per cent of study participants were overweight or obese according to BMI. Nearly all (95.7%) lived independently, either alone or with another person/s and the most prevalent comorbidities across all participants were hypertension (66.9%), type 2 diabetes (51.1%) and hyperlipidaemia (45.5%). The most common types of vascular disease were PAD (29.2%) and DFD (28.6%).

Subgroup analysis showed that there were some differences amongst the types of vascular disease including a significant difference in age across the groups with post-hoc analyses finding the participants in the aneurysmal group being significantly older ($p<0.001$) than the diabetic foot participants. Significant differences were also observed in median BMI across the disease types with the DM foot disease group having a higher median BMI compared to the PAD and aneurysmal group ($p<0.001$), BMI category ($p<0.001$), and median LOS ($p=0.003$), with the aneurysmal having

a longer LOS compared to the venous group and in the prevalence of all comorbidities except for smoking status.

Table 9 shows the results of the participants for a range of parameters measuring nutritional status. According to the PG-SGA, 15.8% of participants were assessed as either moderately/suspected malnourished (PG-SGA-B) or severely malnourished (PG-SGA-C). Across the vascular disease types, between 3.6 and 20% were assessed as PG-SGA-B. Only 1 participant was assessed as a PG-SGA-C. Analyses showed no statistical difference in PG-SGA ratings across the vascular types ($p=0.607$). Similarly, with the dietitian's assessment, there were no differences across vascular types ($p=0.442$), however the proportion classified as malnourished was much higher than that from the PG-SGA at 67.9 – 83% across the vascular types and 75.5% overall.

Table 8: Participant Characteristics of 322 patients admitted to a vascular surgery unit.

	Aneurysmal (n=35, 10.9%)	**PAD** (n=94, 29.2%)	**Occlusive other** (n=28, 8.7%)	**Venous** (n=20, 6.2%)	**DM foot Disease** (n=92, 28.6%)	**Other** (n=53, 16.5%)	**Total** (n=322)	**P-value**
Male (n, %)	28 (80)	63 (67.0)	17 (60.7)	13 (65)	67 (72.8)	35 (64.3)	223 (69.3)	0.549
Age (median, IQR)	75.0 (60, 90)	72.5 (52.5, 92.5)	70.0 (11.86)	69.5 (49.5, 89.5)	63.0 (45,81)	68.0 (48, 88)	68.0 (48, 88)	<0.001
Age Categories (n,%)								<0.001
<65 years	2 (5.7)	31 (33.0)	11 (39.3)	7 (35)	52 (56.5)	20 (37.7)	123 (38.2)	
65 and above	33 (94.3)	63 (67.0)	17(60.7)	13 (65)	40 (43.5)	33 (62.3)	199 (61.8)	
BMI (median, IQR) (n=320)	26.4 (24.1,29.7)	26.4 (23.4, 28.9)	27.9 (26.2,30.9)	30.6 (24.4,35.3)	31.5 (27.4, 37.1)	28.9 (25.6,34.0)	28.2 (20.3, 35.2)	<0.001
BMI Category								
(n, %) (n=320)								<0.001
Underweight	2 (5.7)	15 (15.8)	1 (3.6)	3 (15.8)	0 (0)	7 (13.2)	28 (8.8)	
Normal	16 (45.7)	36 (37.9)	8 (28.6)	3 (15.8)	11 (12.0)	12 (22.6)	86 (26.9)	
Overweight/Obese	17 (48.6)	44 (46.3)	19 (67.9)	13 (68.4)	81 (88)	32 (60.4)	206 (64.4)	
Living situation								
(n, %)								
Lives alone	11 (31.4)	32 (33.7)	11 (39.3)	6 (30)	28 (30.4)	17 (32.1)	105 (32.6)	0.97
Lives with another person/s	24 (68.6)	54 (57.4)	17 (60.7)	12 (60)	62 (67.4)	34 (64.2)	203 (63.0)	0.78
SCF	0	0	0	1 (5)	1 (1.1)	0	2 (0.6)	0.16
RACF	0	8 (8.5)	0	1 (5)	1 (1.1)	2 (3.8)	12 (3.7)	0.07
Comorbidities								
(n,%)								
Hyperlipidaemia	17 (48.6)	47 (50.0)	13 (46.4)	5 (25)	48 (52.2)	18 (32.1)	146 (45.3)	0.048
Hypertension	27 (77.1)	61 (64.9)	23 (82.1)	9 (45)	67 (72.8)	30 (53.6)	215 (66.8)	0.009
Diabetes	10 (28.6)	39 (41.5)	5 (17.9)	5 (25)	92 (100)	14 (25)	164 (50.9)	<0.001
IHD	13 (37.1)	27 (28.7)	5 (17.9)	1 (5)	15 (16.3)	11 (19.6)	71 (22)	0.027
Current smoker	6 (17.1)	18 (18.9)	4 (14.3)	3 (15)	10 (10.9)	8 (14.3)	49 (15.2)	0.777
LOS (Median, IQR)	10 (6, 16)	8 (5, 14)	6 (4,11)	4 (3, 8.75)	8.5 (6, 13)	7 (3.5, 10)	8 (5, 12)	0.003

Abbreviations: SCF – Supported Care Facility, RCF = residential care facility, LOS – Length of stay

Table 9: Proportion (n,%) of participants identified as malnourished according to the Comprehensive dietitians Assessment, PG-SGA, nutritional biochemistry or sarcopenic.

	Aneurysmal (n=35, 10.9%)	**PAD** (n=94, 29.2%)	**Occlusive other** (n=28, 8.7%)	**Venous** (n=20, 6.2%)	**DM foot Disease** (n=92, 28.6%)	**Other** (n=53, 16.5%)	**Total** (n=322)	**P-value**
Dietitians Assessment	25 (71.4)	78 (83)	19 (67.9)	14 (70)	69 (75)	38 (71.7)	244 (75.5)	0.442
PG-SGA Rating								0.607
A	28 (80)	75 (79.8)	27 (96.4)	16 (80)	81 (88)	4 (83)	271 (84.2)	
B	7 (20)	18 (19.1)	1 (3.6)	4 (20)	11 (12)	9 (17)	50 (15.5)	
C	0	1 (1.1)	0	0	0	0	1 (0.3)	
Micronutrients								
Vitamin A (n=241)	10 (37)	12 (16.7)	1 (5.3)	2 (14.3)	15 (19.7)	5 (14.7)	45 (18.7)	0.169
Vitamin C (n=243)	21 (77.8)	57 (78.1)	18 (94.7)	10 (71.4)	59 (77.6)	27 (77.1)	191 (78.6)	0.323
Vitamin D (n=243)	12 (44.4)	43 (58.1)	10 (55.6)	8 (57.1)	49 (64.5)	14 (40)	135 (55.6)	0.389
Vitamin E (n=240)	0	0	0	0	1 (1.3)	0	1 (0.4)	0.826
Zinc (n=244)	14 (51.9)	37 (50)	7 (36.8)	7 (50)	29 (38.2)	14 (40)	107 (43.9)	0.569
Selenium (n=244)	6 (22.2)	17 (23)	0	2 (14.3)	10 (13.2)	10 (28.6)	45 (18.4)	0.229
Iron (n=270)	17 (58.6)	40 (50.6)	12 (52.2)	3 (17.6)	31 (38.3)	22 (51.2)	124 (45.9)	0.065
Vitamin B12 (n=258)	10 (35.7)	35 (45.5)	11 (50)	8 (50)	30 (39)	18 (45)	111 (43)	0.833
Folate (n=254)	0	0	0	0	1 (1.3)	0	1 (0.4)	0.951
Sarcopenia* (n, %)	1 (3.8)	6 (10.3)	0	1 (7.1)	2 (3.4)	0	10 (5)	0.386

*only calculated for those aged 65 years and over (n=199; aneurysmal, n=33; PAD, n=63; occlusive other, n=17; venous, n=13; DM foot infection, n=40; other, n=33)

The number and proportion of participants that had altered micronutrient status is also displayed in Table 9. Vitamin and trace element status varied however the majority of participants (78.6%) had vitamin C levels below the reference range and over half (55.6%) had low vitamin D levels. Further analysis showed that 57.2% of participants were deficient in vitamin C (vitamin C ≤ 0.29mg/dl) (226). Other nutrients of note were zinc, iron and vitamin B12 with over 40% of participants having suboptimal levels. Suboptimal levels of Folate and Vitamin E were only observed in one participant. Subgroup analysis found no significant differences between the vascular disease types for any of the nutrients or nutrition related biochemistry.

One hundred and ninety-nine participants were assessed for sarcopenia (those aged 65 years and older) using appropriate cut-offs and algorithm (92). Only 5% (n=10) of the participants were found to be sarcopenic with no significant difference observed between the vascular types (p=0.386). The prevalence of sarcopenic obesity was also investigated within the 10 participants by investigating their BMI status. All sarcopenic participants were either of low (n=6) or normal BMI (n=4) hence no participants were classified has having sarcopenic obesity.

At discharge, sixty-nine participants (21.5%) had experienced at least one in-hospital complication. Fifty-seven (18%, n=317) were discharged to another institution with 260 (82%) being discharged to their previous place of residence. Median (IQR) LOS for the whole sample was 8 (5, 12) days. Two participants (0.6%) died during admission. Due to the small number of deaths during admission, this outcome was not explored in further analyses.

Table 10 displays the results of the exploration of the associations between clinical outcomes at discharge and malnutrition according to the dietitian's comprehensive assessment and according to micronutrient status. Vitamin E and folate were not included in this analysis due to only one participant having a deficiency in each of these micronutrients. Malnutrition according to the dietitian's comprehensive assessment was significantly associated with all three clinical outcomes

(LOS, in-hospital complications and discharge to a place other than prior residence). Participants who were malnourished had a median LOS that was 1 day longer (p=0.012), were more likely to be discharged to an institution (p=0.002) and have complications during admission (p=0.005). When micronutrients were examined, the results were mixed. Participants who were deficient in iron and/or vitamin A had a longer median LOS by 2 and 1.5 days respectively (p=0.027 and 0.012). Participants with a deficiency in either vitamin C, iron or vitamin D were all more likely to suffer complications during admission (p=0.039, 0.026 and 0.023 respectively). Iron was also significantly associated with being discharged to an institution (p=0.028). There were no significant associations between other micronutrients and clinical outcomes a discharge. Further exploration of the relationship between micronutrients and hospital LOS showed a significant positive correlation observed between LOS and the number of micronutrient deficiencies (r=0.243, p<0.001) meaning the more deficiencies a participant had, the longer the LOS (Table 11).

Table 10: Clinical Outcomes of 322 vascular surgery patients according to whether participants were malnourished across a variety of nutritional parameters

Discharge Outcome	Nutritional Parameter															
	Dietitians Assessment		Vitamin A		Vitamin B12		Vitamin C		Vitamin D		Iron		Zinc		Selenium	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Length of Stay (Median (IQR))	8 (5, 13)	7 (4,10)	9.5 (8,13.8)	8 (4,13)	8 (5,11.5)	8 (5,12.8)	10 (6, 14)	8 (5,11.5)	8 (6, 14)	7.5 (5,12.8)	9 (6,14)	7 (5,11)	9 (5,13)	8 (5,12.8)	10 (6.5,14)	8 (5,13)
Test (p value)	Z=-2.508 (0.012)		Z=-2.506 (0.012)		Z=-0.063 (0.950)		Z=-1.468 (0.142)		Z=-1.305 (0.192)		Z=-2.217 (0.027)		Z=-1.218 (0.223)		Z=-0.996 (0.319)	
In-hospital Complications (n=321)	61/243	8/78	13/44	42/196	10/49	50/208	31/105	25/137	39/134	18/108	36/123	26/146	30/107	27/136	5/21	52/222
p value	0.005		0.247		0.589		0.039		0.023		0.026		0.135		0.968	
Discharge to an institution (n=317)	52/239	5/78	9/44	36/193	12/48	38/206	22/103	15/85	28/133	18/106	31/122	21/143	23/105	23/134	1/20	45/220
p value	0.002		0.783		0.304		0.524		0.428		0.028		0.356		0.136^	

^Fishers Exact Test.

Abbreviations: Y: undernourished/deficit present, N: well-nourished/no deficit present.

Table 11: Median hospital length of stay according to the number of micronutrient deficiencies.

	Number of micronutrients deficits							
	0	1	2	3	4	5	6	P value
Median (IQR) Length of stay	6 (4, 10)	6.5 (3.75, 9.25)	7.5 (4, 16)	9 (7, 14)	9 (5.5, 15)	10 (7.25, 11)	11.5 (7, 21.25)	0.024

4.4 Discussion

This is the first study to conduct a comprehensive exploration of nutritional status in a large heterogenous sample of vascular surgery inpatients and to investigate how nutritional status affects clinical outcomes on discharge.

4.4.1 Prevalence of malnutrition

This study found that assessment of nutritional status using the PG-SGA resulted in approximately 16% of participants being identified as malnourished, however when micronutrient status was explored, over half of participants displayed suboptimal status in several micronutrients, increasing to almost 79% with low vitamin C serum levels. The comprehensive dietitian's assessment which incorporated a wide range of parameters encompassing micronutrient status and other measures of malnutrition found that three-quarters of participants had nutritional deficits that could warrant intervention. Only a small proportion of the participants displayed sarcopenia. The majority of participants were overweight or obese lending support to the notion that weight status is masking nutritional deficiencies in this group and that the PG-SGA may not be appropriate in this patient group for identifying malnutrition and will be explored further in this thesis. While there were some differences across the types of vascular disease with respect to participant characteristics, there were no differences in the proportions of participants classified as undernourished according to the dietitian's assessment, the PG-SGA or in the proportion with micronutrient deficits.

The prevalence of malnutrition according to the dietitian's comprehensive assessment was 75% which is within the range observed in previous studies of 61-90% (82-84) despite differences in the method of assessment. De Waele et al (82) found 61% of their 23 patients

were malnourished according to the NRS-2002, laboratory measures and a physical exam however insufficient details were provided to determine what the physical exam encompassed. It is important to note that the NRS-2002 is a screening tool and not an assessment tool, hence it isn't appropriate for the diagnosis of malnutrition, rather it indicates risk of malnutrition. Durkin et al (83) assessed 71 patients using a number of validated parameters including mid-arm muscle circumference, weight change and BMI and serum albumin, however insufficient details were available to determine how these parameters were used to determine nutritional status. Neither of these studies included measurements of micronutrient status hence it is difficult to determine whether the similarities in rates of malnutrition are valid. Eneroth et al (84) found the highest rate of malnutrition at 90% in 32 participants all undergoing trans-tibial amputation. These participants had more progressive disease which may explain the higher rate of malnutrition in this group so again it makes comparisons difficult. Neither of these studies were conducted in Australia which also impacts on the ability to make comparisons.

The prevalence of malnutrition according to the PG-SGA was 15.8% overall, varying from 12-20% across the groups, with the majority being PG-SGA –B, moderately or suspected malnourished. These results are much lower than other studies mentioned and the rates of the current study when a dietitian's comprehensive assessment was used to determine nutritional status. In the current study the difference can be attributed to the inclusion of micronutrient status in the dietitian's assessment which is absent from the PG-SGA and a prevalent issue in this patient group.

In terms of comparing this result with other studies, it is difficult to draw conclusions due to several factors. A key difference between the current study and other studies in vascular

disease patients is the heterogeneity of our sample and the types of pathologies included compared to much of the previous work being conducted in a single vascular disease type. One vascular type that has been well studied is PAD which was included as a subgroup in the current study. The PAD participants in the current study had a median BMI in the overweight category, similar to previous studies (248, 249) and almost half were either overweight or obese. Overall prevalence of malnutrition in the PAD group was 83% according to the dietitian's comprehensive assessment, which is within the rates observed by two studies that assessed malnutrition solely in PAD patients. The study by Durkin et al (83) had a similar sample size of 71 participants (compared to 94 in the current study) attending a pre-admission clinic, with a median age of 65 years (range 26-85) compared to 72.5 years (IQR 52.5, 92.5) and found that 73% of participants were malnourished. The study by Eneroth et al (84) had a smaller sample size (32 participants) that were admitted for trans-tibial amputations and hence at the severe end of the spectrum of PAD. The participants were also elderly (median age 80 years, range 54-88 years) which may account for the slightly higher prevalence of malnutrition at 88%. Based on these studies, it appears that the PAD patients in the current study are not dissimilar in the prevalence of malnutrition despite differences in the methods of diagnosing malnutrition.

4.4.2 Micronutrient Deficits

In terms of the micronutrient status of PAD patients in the study, there are similarities to previous literature. Fifty-eight percent of PAD participants in the current study had suboptimal vitamin D which is slightly higher than the 49% observed in McDermott et al (88) and 41% in Gaddipati et al (85) but in line with the findings of a meta-analysis conducted by Nsengiyumva et al (250). Similarly, the prevalence of suboptimal vitamin B12 and folate in

the present study (45.5% and 0% respectively) is similar to that of Zsori et al (43% and 0%) which had a large sample of 293 PAD patients (113). An important factor to consider when comparing the current results to previous research are the parameters used to determine low or deficient micronutrient status. In the current study, 51% of PAD participants had suboptimal iron levels which is higher than that found by Vega De Ceniga (116) at 32% in 204 participants with intermittent claudication (IC). The cut-offs used to determine low iron were also different, with the current study using <8umol/L as opposed to the equivalent of <10.4umol/L, so if the current study had used the same cut-off the prevalence of low iron would have been even higher than currently stated. Suboptimal vitamin C level was the most prevalent of the micronutrient deficits in the PAD participants in the current study at 78% with suboptimal levels (<26umol/L) and 57.2% having levels classified as deficient (<0.29mg/dL which equates to <16.5umol/L). In the study by Langlois et al (87) which studied vitamin C status in 85 PAD patients, deficiency was observed in only 14% of participants however, a different cut-off was used at <11.4umol/L, lower than the current study and hence a contributing factor to the disparity in results with the current study. Despite the difference in cut-off the prevalence in the current study is still a great deal higher than Langlois et al (87).

What is key from this study is that nutritional status requires a broader assessment by including micronutrient status. This study observed alarming rates of nutrient deficits in participants particularly for vitamin C and D with approximately 78% and 55% having low serum levels respectively. Other nutrients of concern were zinc, iron and vitamin B12 with over 40% showing low levels. There is a great deal of literature available that reports on the micronutrient status of vascular surgery patients which has already been described in chapter 2, however these studies have again been conducted in a single type of vascular

disease making it difficult to compare to the current study. A number of studies report that low vitamin D is common in PAD patients (89, 107, 250, 251) and in diabetic foot infections, (165) that it worsens as disease progresses (174) and is associated with increased rates of amputation and CVD events at lower levels of vitamin D (252). Given the prevalence of vitamin D deficiency and the impact of limb amputation and CVD on morbidity, correcting vitamin D status is crucial. Suboptimal serum vitamin C was common in our sample at 78% which is higher than other studies (87) but is of concern as it acts as an antioxidant, providing protection from free-radical damage. It is also important in the healing of wounds which is relevant in this population (106). Other literature supports the current findings regarding vitamin B12 and iron (116, 253), and while prevalence may be lower than the current study there is indication that deficits of a variety of micronutrients are common in vascular surgery patients that may have implications on clinical outcomes.

4.4.3 Prevalence of sarcopenia

In the present study, the prevalence of sarcopenia was low at 5%, with no participants being classified as sarcopenic obese. This was surprising given prevalence rates ranging from 12.5-67% observed in the literature reviewed and presented in Table 9. An important distinction between this study and those presented in table xx is in the method of diagnosing sarcopenia. In all studies in Table 4, sarcopenia was diagnosed based on a measurement of skeletal muscle mass only, mainly CT-imagery and hence wasn't an accurate diagnosis of sarcopenia but rather low muscle mass. The current study incorporated additional parameters as recommended by the EWGSOP that examine not only the amount of skeletal muscle but also muscle strength and function (92) and hence is a more robust method of diagnosing sarcopenia. It has been proposed that adults with PAD have a decline in SMM or

atrophy of skeletal muscle when compared to age-matched controls (105), particularly as the disease progresses (254). These consequences are as a result of disuse due to pain from IC or ischaemic rest pain and an increased requirement for protein and energy associated with ischaemic ulcers and vascular interventions (255, 256). In addition, reduced functional ability and mobility is also common (105) which would affect gait speed. Hence, two of the parameters used in the diagnosis of sarcopenia should theoretically be impaired leading to an increased likelihood of sarcopenia. There is no definitive method of diagnosing sarcopenia and hence making comparisons with literature can be challenging. There is the potential that if this study was to examine SMM only the outcome would have differed, however at the time of this study, the EWGSOP consensus statement (92) is a well cited definition of diagnosing sarcopenia.

4.4.4 The effect of undernutrition on clinical outcomes

In this study, malnutrition according to the dietitian's comprehensive assessment was significantly associated with longer hospital LOS, increased likelihood of complications during admission and discharge to an institution rather than to their original place of residence. Similar findings have been reported in other studies. Durkin et al (83) observed higher rates of septic complications in malnourished vascular surgery patients compared to well nourished (41% vs 0%, $p<0.05$) whilst Shiraki et al (182) found an association between malnutrition risk (assessed by Geriatric Nutrition Risk Indicator (GNRI) score) and increased risk of mortality and major amputation in CLI patients 3 years post endovascular therapy. Mortality in the malnourished group was 74±5% compared with 48±5% in the nourished group ($p<0.001$). Limb salvage rate was 92±2% in the well-nourished versus 84±3% in the malnourished group ($p<0.001$). The adjusted hazard ratio for major amputation was 1.49

(95% CI, 1.13-1.97) per decrements of 10 in the GNRI score whereas for mortality the hazard ratio was 1.44 (95% CI, 1.15-1.82) per 1 SD decrement. Similar links have been observed between malnutrition and poorer outcomes in other patient groups such as those undergoing geriatric rehabilitation (220) and in the intensive care setting (81).

This study also explored the associations between micronutrient deficiencies and clinical outcomes with variable results depending on the micronutrient and outcomes studied. Much of the work regarding micronutrient and clinical outcomes in vascular disease has been conducted to investigate the effects of supplementation rather than the link between deficiencies per se and clinical outcomes. In the current study, iron deficiency was significantly associated with each of the outcomes studied including LOS which was also observed by Shah (257) who found longer LOS in vascular surgery in-patients with anaemia (mean 25 days [SD16] vs mean 12 days [SD 8] p=0.0125) compared to those who weren't anaemic. Vitamin D deficiency was associated with increased risk of admission complications in the current study. Similar associations have been observed with risk of foot ulcers in patients with diabetes with low vitamin D being predictive of foot ulcer development in multivariate analysis ($p<0.001$) (167). Vitamin D deficiency has also been shown to be predictive of poorer outcomes in other patient groups (258, 259). Further investigations of the associations between micronutrient deficiencies and LOS in the current study found a significant positive correlation between the number of deficiencies and LOS (r^2 0.243, $p<0.001$). One outcome that wasn't examined in the current study due to lack of specialised resources is wound/ulcer size and/or healing rate which is often explored in the literature as an important outcome for vascular patients and linked to nutrition status, particularly micronutrient status (90, 167, 171). Given the prevalence of suboptimal

micronutrient status in the participants of this study, exploration of wound and ulcer healing would have been a valuable inclusion.

These results all indicate that micronutrient status is important with regards to clinical outcomes. Hence, consideration of micronutrient status is important in the screening for and assessment of malnutrition in vascular surgery patients to maximise outcomes.

4.4.5 Strengths and limitations

This study has several strengths, the first of which is its large sample size, particular in comparison to other similar studies, encompassing a range of vascular pathologies making it more generalizable to the general vascular surgery population. A wide range of nutritional parameters were collected on study participants enabling researchers to assess multiple markers of nutritional status and all assessments were conducted by dietitians professionally trained to assess nutritional status. A unique aspect of this study is the exploration of nutritional biochemistry to enable a more complete assessment of nutritional status.

While this study has its strengths, it is not devoid of limitations. Reference has already been made to the heterogeneity of the sample, particularly the “other” vascular group that may have affected the results of the study. The heterogeneity may be a limitation in terms of making comparisons to previous research, however it is reflective of the patient population that clinicians are working with in a vascular surgery unit and hence the results of this pragmatic study are useful for clinicians working in the area. There is the possibility that potential participants were excluded from the study due to an admission of less than 48 hours which may have affected the prevalence data collected regarding nutritional status in this patient group. Given the results showing longer LOS in those with nutritional deficits, it

is more likely that patients excluded due to a LOS of <48 hours would be well-nourished and if included, the overall prevalence of poor nutritional status would be lower than presented. This study measured nutritional status on admission and hence any deterioration and resultant malnutrition that may have occurred during admission was not determined. Lastly, there is no definitive method to diagnose sarcopenia, however the most common, widely accepted consensus method (92) was utilised in the present study.

4.4.6 Conclusion

Despite variation in prevalence rates and methods used to identify and assess participants, vascular surgery patients are a nutritionally vulnerable group. The key questions now are how do we appropriately identify individuals with nutritional issues placing them at risk of malnutrition (malnutrition screening) and is there an instrument currently available that could be implemented in these individuals? When it comes to assessing nutritional status, it is clearly indicated from these results that the PG-SGA is unlikely to be an appropriate assessment tool in this patient group, with further research to investigate its true validity being warranted given its popularity amongst clinical dietetic practitioners. When subgroups were explored there were no significant differences in measurements of nutritional status indicating it is appropriate to explore the possibility of using one instrument across the whole vascular surgery inpatient population. Given the high rates of suboptimal micronutrient status and their crucial role in the overall health of these patients due to the inflammatory nature of their disease, likelihood of infection and wounds a more comprehensive assessment that encompasses a wider range of parameters, including micronutrient status appears warranted.

Chapter 5*:* An evaluation of the validity of commonly used nutrition screening and assessment tools in vascular surgery patients.

This chapter was used to prepare a manuscript that was published in the *British Journal of Nutrition,* a quartile one journal ranked 14th in Nutrition and Dietetics by Scimago Journal Rankings (2018). This chapter was used to prepare the manuscript, hence there is direct overlap in content and phrasing. Please see Appendix 12 for the accepted pre-print version (included with permission).

5.1 Introduction

The identification and management of malnutrition in vascular surgery patients is critical due to its reported association with poorer clinical outcomes including longer hospital length of stay, increased likelihood of infections and lower limb amputations (80, 86, 180). Results in Chapter 4 reported that approximately 75% of vascular surgery patients had nutritional deficits warranting further investigation according to a comprehensive dietitian's assessment. In the literature, rates as high as 60-90% have been reported using a variety of tools (82-84). Despite the consequences of malnutrition and the prevalence observed, malnutrition across clinical specialties remains under-recognised despite the availability of several validated malnutrition screening tools and local policies, protocols and guidelines to encourage implementation. Also, potentially problematic is that even if tools were adopted and action taken, these tools, policies, protocols and guidelines have not been developed using data exclusively from vascular surgery patients and hence it is unclear how applicable they are in this setting.

To facilitate uptake, a malnutrition screening tool should be quick and simple to administer and able to be completed by an individual with minimal training or by the patients

themselves. The four screening tools selected were the NRS-2002 (196), the MNA-SF (197) and the MUST (198) and the MST (192). These four screening tools were chosen for examination as part of this thesis as described in section 3.4.1 Baseline assessments of this thesis. In summary, each tool consists of a number of items (2 to 6) pertaining to nutritional parameters known to be associated with malnutrition, with a weighted scoring system for each item. An overall score is given with a defined cut-off score indicating possible malnutrition, warranting further investigation by a dietitian. Each of these malnutrition screening tools have been determined to have acceptable levels of validity and reliability in a variety of patient groups as outlined in section 3.4.1 Baseline assessments of this thesis.

It is well recognised that malnutrition screening tools need to be validated for the population in which they are to be administered to expedite nutrition interventions where indicated and allow resources to be used efficiently (204). To date, none of the malnutrition screening tools mentioned have been validated specifically in patients admitted to a vascular surgery unit. This is important as the setting is characterised by the heterogeneous aetiology of vascular disease and presence of complex comorbidities amongst admitted patients. Whilst they are heterogeneous in terms of disease and comorbidities, the results presented in Table 9 show that nutritional status didn't differ according to type of vascular disease hence it would be appropriate to consider them as a whole group when exploring methods of malnutrition screening and assessment.

The first step in the nutrition care process, following screening, is the nutrition assessment. A nutrition assessment is conducted by a nutrition professional using a range of parameters that contribute to nutritional status such as anthropometric assessment, dietary assessment and biochemical markers of nutritional status. In some settings a more standardised

approach is used, characterised by the use of a validated nutrition assessment tool. A commonly used tool within Australian clinical dietetic practice is the Patient- Generated Subjective Global Assessment (PG-SGA) which has been described previously in 3.4.1 Baseline assessments of this thesis and can be viewed in appendix 8. The PG-SGA has been validated in a number of patient groups including stroke (219), geriatric rehabilitation (220) and acute abdominal surgery (221) with Sn of 92-100%, Sp of 84-96.7% and receiver operating curve (ROC) area under the curve (AUC) of 0.91-0.98 showing excellent diagnostic agreement. While the PG-SGA has been validated in several patient groups, it has not been investigated in the vascular surgery population.

With an aging population and increasing prevalence of chronic disease, the number of individuals with vascular disease is also predicted to rise; hence it is critical that we investigate methods firstly to identify those who are nutritionally vulnerable and secondly to assess nutritional status to optimise their nutritional health and overall clinical outcomes. Therefore, to address thesis research question 2 'How do four commonly used nutrition screening tools perform (validity) in a heterogenous sample of acute care inpatients admitted to a vascular surgery unit?' (2.4 Research Questions), there were two aims to this study;

1. to investigate the validity of the four commonly adopted malnutrition screening tools (the MST, MUST, NRS-2002 and the MNA-SF), and the PG-SGA against a dietitian's clinical assessment (the 'gold standard') in vascular surgery inpatients.
2. to evaluate the ability of the malnutrition screening tools and the PG-SGA to predict clinical outcomes, namely length of hospital LOS, in-hospital complications, quality of life and discharge destination.

5.2 Methods

5.2.1 Study Sample

Study sample details have been described previously in 4.3 Results.

5.2.2 Data collection

Data collection occurred between October 2014 and August 2016 and has been described in section 3.3 Data Collection.

Nutrition Screening

Data required for completion of the four nutrition screening tools (MST, MUST, NRS-2002 and MNA-SF) were completed on entry to the study. A more detailed description of the nutrition screening process is available in 3.4.1 Malnutrition screening. Participants were classified as 'at risk of malnutrition' for each tool separately if they scored 2 or more on the MST or MUST, 3 or more on the NRS-2002, and 11 or less on the MNA-SF (192, 193, 196, 198).

Assessment of Nutritional Status.

Nutritional status was assessed by an Accredited Practicing Dietitian (APD) during an in-person consultation, using the scored PG-SGA as described in 3.4.1 Nutrition Assessment with each participant being awarded a PG-SGA score and a global rating of A (well nourished), B (suspected or moderately malnourished) or C (severely malnourished) (212).

Comprehensive Dietetic Assessment of Nutritional Status

The comprehensive dietitian's assessment was conducted retrospectively using all data collected during the baseline data collection as described in 3.4.1 Nutrition Assessment.

5.2.3 Ability of the screening and assessment tools to predict clinical outcomes

In-hospital complications and discharge destination were collected from the medical records following discharge to enable the evaluation of the ability of the screening tools and PG-SGA to predict clinical outcomes. In-hospital complications included infections, cardiovascular events, unplanned surgery or procedures, deterioration or development of an ulcer or wound, vascular restenosis/acute occlusion and acute renal failure.

Health-related quality of life (HRQoL) is commonly examined in the literature when investigating clinical outcomes and in this study was included as an outcome in the predictive validity analyses. In this study, HRQoL was assessed using the EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) (234) which has been described in 3.4.1 Health-related Quality of Life. Using the responses, the EQ-5D-5L utility index was calculated using a valuation algorithm (235). EQ-5D-5L index values have a range of -0.624 to 1: the maximum score of 1 representing perfect health, a score of 0 representing death while scores less than 0 represent health states that are worse than death (236-238).

5.2.4 Statistical Analysis

General statistical methods are described in 3.5 Statistical Analysis., those specific to the validity analyses are detailed below.

To determine the concurrent validity of the five tools (four screening tools and the PG-SGA), measures of diagnostic accuracy were determined. Concurrent validity is a measure of how well the tools compare to the comprehensive dietitian's assessment (reference standard) (260). Sn (malnourished/risk of malnourished correctly identified), Sp (well-nourished correctly identified), PPV (correctly identified as malnourished/risk of malnourished within

the malnourished group), and NPV (correctly identified as well-nourished within the well-nourished group) were determined against the results of the comprehensive dietitians assessment (the reference standard). In the reference standard, respondents were classified as either 'malnourished' or 'not malnourished' according to the parameters described in 3.4.1 Nutrition Assessment. To facilitate comparison to the reference standard, two levels of risk were considered for each screening tool namely 'at risk' (aggregating participants with high or moderate risk of malnutrition) and 'not at risk'. Similarly, the PG-SGA global rating was classified into 'malnourished' and 'not malnourished' with ratings B (moderately, suspected malnourished) and C (severely malnourished) aggregated into one group (malnourished) as is common practice in similar literature (186, 207, 261). Cut-off points for Sn and Sp of ≥80% indicate good validity, if both Sn and Sp are ≥50% but <80% validity is classed as fair and <50% is poor validity (128). Similar a-priori values of ≥80% for sensitivity and ≥60% for specificity were used to indicate a valid instrument by Fergusson et al (191). The diagnostic consistency between the five tools as dichotomous variables against the comprehensive dietitian's assessment was assessed by kappa (k) statistic. Kappa is an estimate of the proportion of consistency between two tools or instruments that takes into account the amount that could have occurred by chance (262). The value of k varies from 0 to 1 with values <0.2 indicating poor, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 substantial and >0.8 as almost perfect concordance. Negative kappa values indicates that the number of agreements observed is fewer than would be expected by chance indicating poor consistency overall (263).

Discriminant validity of the MST, MUST, NRS-2002 and MNA-SF and convergent validity of all five tools were also explored. To test how well the screening tools discriminated between known categorical groups (discriminant validity), statistically significant differences in

mean/median screening tool scores across clinical categorical outcomes (incidence of in-hospital complications, discharge destination and in-hospital mortality) were explored using the Independent T or Mann Whitney U test, as appropriate. To test the level of association between all five tools and continuous clinical and HRQoL outcomes (convergent validity), two different analyses were undertaken. First, correlation between tool scores and continuous clinical (LOS) and HRQoL (EQ-5D-5L) outcomes was assessed using Pearson or Spearman's Rank Order Correlation. Second, cross tabulations of tool and PG-SGA outcomes (at risk versus not at risk and malnourished versus not malnourished, respectively) and categorical clinical outcomes were assessed for statistical association using chi-square and Fishers Exact tests. Differences in median LOS and EQ-5D-5L scores between the binary outcomes for the tools and PG-SGA were assessed using Independent T or Mann Whitney U tests, as appropriate.

The ability of the five tools to predict clinical and HRQoL outcomes was tested using multivariate regression analysis. In all regressions, dichotomous screening and assessment tool variables (at risk or malnutrition/malnourished or not at risk/well-nourished) were entered as independent variables with age, gender, disease type and smoking status included as potential confounders. To predict continuous dependent variables or outcomes (LOS and EQ-5D-5L index), generalised linear models (GLM) were fitted. To identify an appropriate family for the GLM, a Modified Park Test was conducted following standard procedures with a comparison of AIC/BIC to determine the link function (139). For models where LOS was the dependent variable, coefficients of predicted dependent values in the Modified Park Test indicated that the Poisson (for models including the MST and MUST) and Inverse Gaussian (for models incorporating the NRS2002, MNA-SF and PG-SGA) family of GLM were appropriate for analysis. The OLS regression model was appropriate for all

models where the EQ-5D-5L Index was the dependent variable. To predict binary outcomes (1 = return to prior residence or to an institution such as residential aged care, rehabilitation or another hospital, 0 = other discharge destination and; 1 = in-hospital complications, 0 = no complications), binary regression models were fitted.

5.3 Results

5.3.1 Participant Characteristics

Table 12 displays the characteristics of the 322 participants. Details regarding total number of eligible and consenting patients are described in 4.3 Results. Most participants were male (69.3%) and over 65 years old (61.6%). Nearly all (95.7%) lived independently, either alone or with another person/s with the majority (82.1%) returning to their pre-admission residence on discharge. Twenty-one percent of participants had at least one in-hospital complication and the median (IQR) hospital LOS was 8 (1,15) days. Median (IQR) quality of life score was 0.72 (0.36, 1.08).

Table 13 shows the results of the malnutrition screening using the four screening tools and the proportion of participants assessed as malnourished by the PG-SGA and by the dietitian's clinical assessment. The malnutrition screening tools showed variable results ranging from 12.5% at risk of malnutrition according to the MUST up to 47.5% with the MNA-SF. According to the PG-SGA, 15.8% of participants were assessed as either moderately/suspected malnourished (PG-SGA B) or severely malnourished (PG-SGA C). The dietitian's assessment of nutritional status revealed that 75.5% of study participants had at least one nutritional deficit indicating that nutrition intervention may be warranted.

Table 12: Participant Characteristics of 322 vascular surgery patients participating in a validation study of nutrition screening and assessment tools

Characteristic	**N (%) unless indicated**
Male	223 (69.3)
Age (median, IQR)	68.0 (48,88)
Age Categories <65 years 65 and above	 123 (38.2) 199 (61.8)
Weight (kg) (Median/IQR)	85.5 (59.9, 111.1)
Median BMI (IQR) (n=320)	28.2 (20.3, 36.1)
Pre-admission living situation Lives alone Lives with another person/s SCF RACF	 105 (32.6) 203 (63.4) 2 (0.6) 12 (3.7)
EQ-5D-5L Score (Median/IQR)	0.72 (0.46, 0.82)
Proportion with in-hospital complications	69 (21.4)
Discharge Destination Return to prior living D/c to institutional care	 260 (82.0) 57 (18.0)
LOS (Median/IQR)	8 (5,12)

Table 13: Proportion of vascular surgery participants at risk of malnutrition according to the four screening tools and those assessed as malnourished according to the PG-SGA, and the comprehensive dietitian's assessment.

Nutritional Parameter	Proportion of participants (n=322)
Nutritionally at risk	
MST	93 (28.8%)
MUST (n=320)	40 (12.5%)
NRS-2002	79 (24.5%)
MNA-SF (n=320)	152 (47.5%)
PG-SGA Rating	
A (well nourished)	272 (84.2%)
B (moderately/suspected malnutrition)	50 (15.5%)
C (Severely malnourished)	1 (0.3%)
Dietitians assessment	244 (75.5)

5.3.2 Validity of the screening and assessment tools

Concurrent validity and agreement of both the malnutrition screening tools and the PG-SGA against the Comprehensive dietitian's assessment is displayed in Table 14. Overall, while the MNA-SF performed best, none of the screening tools or the PG-SGA achieved the a-priori levels for Sn, and all showed poor NPV. Diagnostic consistency between the comprehensive dietitian's assessment and the tools was also poor, with negative kappa values indicating poor consistency overall.

Table 14: Concurrent validity of four commonly used screening tools and the PG-SGA against the comprehensive dietitian's assessment of malnutrition in 323 vascular surgery patients

	MST	MUST	NRS-2002	MNA-SF	PG-SGA (%)
Sensitivity	32.8	14.9	29.9	52.5	20.9
Specificity	83.5	94.9	96.1	67.9	100
PPV	86.0	90.0	92.4	83.6	100
NPV	28.7	26.4	29.9	31.5	29
K	-0.154	-0.117	-0.223	-0.155	-0.237

PPV: Positive predictive value, NPV: negative predictive value, K: kappa statistic.

Table 15 show the discriminant and convergent validity of the malnutrition screening tools, as continuous variables, when compared against clinical and HRQoL outcomes. The MST, MNA-SF and NRS-2002 scores were all able to discriminate between discharge destination with those exhibiting a higher risk of malnutrition being more likely to be discharged to an institution ($p=0.002$, <0.001 and 0.005 respectively). In terms of convergent validity, a small but statistically significant correlation was observed between both the MNA-SF ($r = -0.145$, $p=0.009$) and NRS-2002 ($r = 0.199$, $p<0.001$) scores and LOS with longer median LOS observed in at risk participants. A small but significant correlation was also observed between MNA-SF score and EQ-5D-5L Index with lower quality of life score in those at risk of

malnutrition (r = 0.237, p<0.001). MUST score was not related to either of the clinical outcomes examined.

Table 16 displays further convergent validity results where dichotomised tool outcomes are compared against clinical outcomes. Overall, there were no significant relationships between the MUST and any of the outcomes investigated. However, the MST, NRS-2002 and the MNA-SF all showed a significant association with discharge destination with a higher proportion of those deemed at nutritional risk being discharged to an institution (p=0.002, 0.005 and <0.001 respectively). Both the NRS-2002 and MNA-SF were significantly associated with HRQoL with the 'at risk' participants scoring a lower EQ5D-5L score compared to those not at risk (p=0.033 and 0.009 respectively). Both tools were also significantly associated with hospital LOS with the at-risk participants having a 1.5 day longer median LOS compared to the not at-risk group (NRS-2002: 9 (6, 14) days vs 7.5 (4, 11) p=0.005. MNA-SF: 8.5 (5,14) vs 7 (4,11) p=0.025). Significant associations were observed between PG-SGA and discharge destination, LOS and quality of life (EQ5D) with malnourished participants having the poorer outcomes (p = 0.003, p<0.001 and p = 0.016 respectively).

Results of the regression analyses are displayed in Tables 17 and 18. A significant association was observed between LOS and four tools (the MST, MUST, NRS-2002 and PG-SGA), however the direction of the relationship differed. The MST and PG-SGA had positive associations (Coefficient (SE) 0.1061 (0.0376), p=0.005 and 5.02 (1.33), p<0.001 respectively) indicating that those who were at risk of malnutrition or already malnourished had a longer LOS while the reverse was true for the MUST (-0.00006 (0.00003), p=0.029) and NRS-2002 (-0.004 (0.002), p=0.045). No significant association was observed between LOS and MNA-SF.

Associations were also observed between LOS and disease type and age in some of the models. No significant associations were observed in the models for EQ-5D-5L Index indicating no association between the predictor variables and HRQoL. Results of the logistic regression analyses are shown in Table 18. MST, NRS-2002 and PG-SGA all showed a significant association with discharge destination when all confounders were included with participants at risk of malnutrition or already malnourished being at least 2.3 times more likely to be discharged to another institution (OR(SE), 2.36 (0.71), p=0.004, 2.38(0.74) p=0.005 and 2.91 (1.03), p=0.003 respectively). There were no other significant associations identified with discharge destination. When in-hospital complications were examined, only NRS-2002 had a significant association with at risk participants being 1.85 (0.56) (OR(SE)) times more likely to have complication when confounders were controlled for.

Table 15: Discriminant and Convergent Validity of the MUST, MST, NRS-2002, MNA-SF scores against clinical outcomes in 323 vascular surgery patients

Clinical Outcome		MUST Scores Median (IQR)	MST Scores Median (IQR)	MNA-SF Scores Median (IQR)	NRS-2002 Scores Median (IQR)
Discriminant validity					
In-hospital complications	Yes	0	1 (0, 2)	12 (8, 16)	2 (0, 4)
	No	0	0	12 (8, 16)	1 (0,2)
	Test (p value)	Z = -0.503 (0.615)	Z = -0.180 (0.858)	Z = -0.465 (0.648)	Z = -1.612 (0.107)
Discharge destination	Home	0	0 (2)	12 (8, 16)	1 (0, 2)
	Other Institution	0	1(2)	10 (6, 14)	2 (0, 4)
	Test (p value)	Z = -0.423 (0.673)	Z = -3.17 (0.002)	Z = -4.494 (<0.001)	Z = -2.825 (0.005)
In-hospital mortality	Yes	0.5 (-)	0.5 (-)	9.5 (-)	2 (-)
	No	0	1 (2)	12 (8, 16)	1 (0,2)
	Test (p value)	Z = -0.714 (0.475)	Z = -0.53 (0.595)	Z = -1.062 (0.288)	Z = -0.727 (0.467)
Convergent validity					
Length of Stay	r (p value)	0.048 (0.395)	0.10 (0.087)	-0.145 (0.009)	0.199 (<0.001)
EQ5D Index	r (p value)	0.005 (0.922)	-0.081 (0.145)	0.237 (<0.001)	-0.109 (0.051)

Table 16: Convergent validity of the MUST, MST, NRS-2002, MNA-SF & PG-SGA (Dichotomous variables) against clinical outcomes in vascular surgery patients

	MUST (n=318)			MST (n=322)			NRS-2002 (322)			MNA-SF (320)			PG-SGA (322)		
Clinical Outcome	**At risk**	**No risk**	**P-value**	**At risk**	**No risk**	**P-value**	**At risk**	**No risk**	**P-value**	**At risk**	**No risk**	**P-value**	**A**	**B/C**	**P-value**
Any in-hospital complications	8/40	61/280	0.898	16/93	53/230	0.408	24/79	45/244	0.070	34/152	35/168	0.606	54/271	15/51	0.130
In-hospital mortality	0/40	2/279	0.591	0/93	2/229	0.366	0/79	2/243	0.419	2/152	0/167	0.137	0/271	2/51	0.103
Discharge destination			0.174			0.002			0.005			<0.001			0.003
Home	35/39	223/276		66/92	195/226		55/77	206/241		107/148	151/167		228/269	33/49	
Institution	4/39	53/276		26/92	31/226		22/77	35/241		41/148	16/167		41/269	16/49	
EQ-5D, median IQR	0.66 (0.50, 0.86)	0.72 (0.45, 0.82)	0.470	0.70 (0.48, 0.82)	0.72 (0.46, 0.82)	0.734	0.64 (0.40, 0.80)	0.73 (0.51, 0.83)	0.033	0.65 (0.41, 0.82)	0.76 (0.54, 0.83)	0.009	0.74 (0.36)	0.63 (0.38)	0.016
Length of stay, median IQR	8 (4, 11.75)	8 (5, 12)	0.694	8 (5, 14.5)	8 (5, 12)	0.342	9 (6, 14)	7.5 (4, 11)	0.005	8.5 (5, 14)	7 (4, 11)	0.025	7 (0,14)	10 (11)	<0.001

Table 17: Generalised Linear Model (GLM) results

	Dependent variable = Length of Stay (LOS)									
	Model inc MST[a]		**Model inc MUST[a]**		**Model inc NRS2002[b]**		**Model inc MNA-SF[b]**		**Model inc PG-SGA[b]**	
Predictors	Coefficient (SEM)[d]	P value	Coefficient (SEM) [d]	P value	Coefficient (SEM) [d]	P value	Coefficient (SEM) [d]	P value	Coefficient (SEM) [d]	P value
MST	0.1061 (0.0376)	0.005	-		-		-		-	
MUST	-		-0.00006 (0.00003)	0.029	-		-		-	
NRS-2002	-		-		-0.004 (0.002)	0.045	-		-	
MNA-SF	-		-		-		0.00001 (8.08e-6)	0.183	-	
PG-SGA	-		-		-		-		5.02 (1.33)	<0.001
Gender	0.0087 (0.0385)	0.821	0.004 (0.038)	0.913	-0.0003 (0.002)	0.889	-0.0003(0.002)	0.875	0.28 (1.04)	0.785
Smoker	0.012 (0.052)	0.819	0.0096 (0.052)	0.852	-0.0004 (0.003)	0.890	-0.0002(0.003)	0.936	0.22 (1.39)	0.874
Age	0.004 (0.001)	0.004	0.0041 (0.001)	0.003	6.00E-05(0.0001)	0.378	-0.00009 (0.00007)	0.230	0.02 (0.04)	0.636
Venous	-0.22 (0.11)	0.05	-0.203 (0.11)	0.065	0.009 (0.008)	0.301	0.007 (0.008)	0.372	-2.51 (2.49)	0.313
Aneurysmal	0.335 (0.08)	<0.0001	0.351 (0.083)	<0.0001	-0.007 (0.005)	0.155	-0.008 (0.005)	0.113	2.76 (2.18)	0.206
PAD	0.256 (0.07)	<0.0001	0.26 (0.073)	<0.001	-0.006 (0.005)	0.211	-0.006 (0.005)	0.191	1.63 (1.84)	0.173
DM limb	0.32 (0.07)	<0.001	0.324 (0.074)	<0.001	-0.007 (0.004)	0.127	-0.007 (0.005)	0.114	2.53 (1.85)	0.173
Other vascular	0.150 (0.08)	0.06	0.170 (0.08)	0.033	-0.004 (0.005)	0.442	-0.004 (0.005)	0.398	0.60 (1.99)	0.763
Constant	1.79 (0.123)	<0.001	1.82 (0.123)	<0.001	0.02 (0.007)	0.003	0.021 (0.007)	0.002	6.62 (3.14)	0.036

	Dependent variable = EQ-5D-5L Index									
	Model inc MST[d]		Model inc MUST[d]		Model inc NRS2002[d]		Model inc MNA-SF[d]		Model inc PG-SGA[d]	
Predictors	Coefficient (SEM)[c]	P value	Coefficient (SEM) [c]	P value	Coefficient (SEM) [c]	P value	Coefficient (SEM) [c]	P value	Coefficient (SEM) [c]	P value
MST	54.15 (87.10)	0.535	-		-		-		-	
MUST	-		0.0005 (0.047)	0.992	-		-		-	
NRS2002	-		-		70.40 (91.95)	0.444	-		-	
MNASF	-		-		-		-0.0005 (0.057)	0.994	-	
PG-SGA	-		-		-		-		-85.1 (110.2)	0.441
Gender	-58.23 (86.30)	0.50	-60.69 (86.26)	0.482	-56.96 (86.31)	0.510	-60.61 (86.66)	0.485	-65.15 (86.37)	0.451
Age	3.51 (3.04)	0.249	3.52 (3.04)	0.249	3.35 (3.05)	0.273	3.52 (3.06)	0.251	3.88 (3.07)	0.208
Smoker	198.93 (115.09)	0.085	199.13 (115.20)	0.085	200.46 (115.06)	0.082	199.08 (115.36)	0.085	197.32 (115.07)	0.087
Venous	14.11 (206.11)	0.945	8.599 (207.13)	0.967	9.28 (205.87)	0.964	9.03 (208.01)	0.965	23.79 (206.77)	0.908
Aneurysmal	-24.50 (180.8)	0.892	-15.95 (180.35)	0.930	-24.69 (180.54)	0.891	-15.83 (181.64)	0.931	-3.33 (180.91)	0.985
PAD	79.95 (151.75)	0.599	82.01 (151.80)	0.589	78.48 (151.73)	0.605	82.09 (152.05)	0.590	95.96 (152.72)	0.530
DM limb	129.40 (153.40)	0.400	132.10 (153.43)	0.390	129.67 (153.32)	0.398	132.12 (153.68)	0.391	141.92 (153.81)	0.357
Other vascular	14.03 (164.76)	0.932	15.81 (165.63)	0.924	15.54 (164.68)	0.925	16.07 (165.43)	0.923	29.13 (165.56)	0.860
Constant	-247.99 (261.45)	0.344	-233.460 (260.75)	0.371	-239.19 (260.44)	0.359	-233.85 (262.36)	0.373	-252.48 (261.48)	0.335

[a] GLM model family for LOS model that included results of the malnutrition screening tool (MST) and malnutrition Universal Screening Tool (MUST) assessments (both coded as 1 = at risk and 0 = not at risk) was Poisson and link was log; [b] GLM model family for LOS model that included results of the Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF) assessments (both coded as 1 = at risk and 0 = not at risk) was Inverse Gaussian and link was power $^{-2}$; [c] SEM = Standard Error of the Mean, [d] Regression model for EQ-5D-5L model that included results of the Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF) assessments (both coded as 1 = at risk and 0 = not at risk) was ordinary least squares (OLS).

Table 18: Binary Logistic Regressions results

	Dependent variable = Discharge Destination									
	Model inc MST		**Model inc MUST**		**Model inc NRS2002**		**Model inc MNASF**		**Model inc PG-SGA**	
Predictors	OR (SE)[a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value
MST	2.36 (0.71)	0.004	-		-		-		-	
MUST	-		0.58 (0.30)	0.295	-		-		-	
NRS-2002	-		-		2.38 (0.74)	0.005	-		-	
MNASF	-		-		-		1.0 (0.003)	0.821	-	
PG-SGA	-		-		-		-		2.91 (1.03)	0.003
Gender	0.98 (0.31)	0.937	0.89 (0.28)	0.698	0.96 (0.30)	0.90	0.94 (0.29)	0.843	0.98 (0.31)	0.953
Age	1.00 (0.01)	0.710	1.00 (0.01)	0.774	1.00 (0.01)	0.90	1.01 (0.01)	0.641	1.00 (0.01)	0.943
Smoker	0.53 (0.26)	0.194	0.55 (0.27)	0.215	0.55 (0.27)	0.22	0.55 (0.27)	0.217	0.54 (0.27)	0.211
Venous	0.44 (0.39)	0.356	0.45 (0.40)	0.363	0.41 (0.37)	0.32	0.44 (0.39)	0.349	0.31 (0.28)	0.196
Aneurysmal	0.40 (0.29)	0.206	0.52 (0.38)	0.369	0.41 (0.3)	0.22	0.49 (0.35)	0.313	0.37 (0.27)	0.176
PAD	1.19 (0.63)	0.748	1.26 (0.66)	0.655	1.17 (0.62)	0.76	1.21 (0.63)	0.714	1.00 (0.53)	0.999
DM limb	0.80 (0.44)	0.684	0.91 (0.50)	0.863	0.82 (0.45)	0.72	0.85 (0.46)	0.759	0.72 (0.40)	0.552
Other vascular	0.84 (0.50)	0.771	1.02 (0.60)	0.974	0.87 (0.52)	0.82	0.90 (0.52)	0.853	0.71 (0.42)	0.559
Constant	0.17 (0.17)	0.067	0.25 (0.24)	0.147	0.22 (0.20)	0.10	0.21 (0.2)	0.10	0.30 (0.28)	0.200

	Dependent variable = In-hospital Complications									
	Model inc MST		Model inc MUST		Model inc NRS2002		Model inc MNASF		Model inc PG-SGA	
Predictors	OR (SE)[a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value
MST	0.64 (0.20)	0.159	-		-		-		-	-
MUST	-		0.87 (0.38)	0.754	-		-		-	
NRS2002	-		-		1.85 (0.56)	0.039	-		-	
MNASF	-		-		-		1.00 (0.14)	0.945	-	
PG-SGA	-		-		-		-		1.72 (0.61)	0.128
Gender	0.98 (0.30)	0.951	0.99 (0.30)	0.970	1.03 (0.31)	0.916	1.02 (0.31)	0.956	1.02 (0.31)	0.932
Age	1.00 (0.01)	0.965	1.00 (0.01)	0.956	0.99 (0.01)	0.825	1.00 (0.01)	0.973	1.00 (0.01)	0.778
Smoker	1.19 (0.46)	0.654	1.17 (0.45)	0.678	1.21 (0.47)	0.626	1.18 (0.46)	0.673	1.20 (0.46)	0.642
Venous	0.39 (0.34)	0.282	0.43 (0.38)	0.340	0.40 (0.35)	0.300	0.43 (0.38)	0.337	0.36 (0.32)	0.253
Aneurysmal	1.36 (0.83)	0.618	1.30 (0.80)	0.670	1.17 (0.72)	0.796	1.31 (0.80)	0.661	1.16 (0.71)	0.805
PAD	1.20 (0.63)	0.726	1.19 (0.62)	0.736	1.17 (0.72)	0.796	1.18 (0.61)	0.755	1.07 (0.56)	0.898
DM Limb	1.11 (0.59)	0.843	1.11 (0.59)	0.842	1.06 (0.56)	0.913	1.09 (0.58)	0.869	1.02 (0.54)	0.977
Other vascular	0.76 (0.45)	0.638	0.80 (0.48)	0.716	0.74 (0.44)	0.609	0.77 (0.45)	0.653	0.68 (0.40)	0.516
Constant	0.31 (0.28)	0.200	0.28 (0.26)	0.169	0.26 (0.24)	0.147	0.26 (0.24)	0.141	0.32 (0.29)	0.211

[a] OR (SEM) = Odds ratio (standard error of the mean

5.4 Discussion

This is the first study to evaluate the validity of malnutrition screening tools as well as a nutrition assessment tool (PG-SGA) commonly used in dietetic practice, exclusively in vascular surgery patients.

5.4.1 Concurrent Validity

The MNA-SF achieved a better concurrent validity than the other screening tools when compared to the comprehensive dietitian's assessment in this heterogeneous sample of vascular surgery patients. However, like all tools, it did not achieve the a-priori acceptable levels for Sn and Sp and had low NPV indicating that they all underestimated the presence of malnutrition in the participants. Similar results were found when the concurrent validity of the PG-SGA was investigated against the comprehensive dietitian's assessment, with the PG-SGA underestimating the presence of malnutrition with very low negative predictive values and poor sensitivity. There was poor diagnostic consistency and diagnostic accuracy between the screening tools and the comprehensive dietitian's assessment and between the PG-SGA and comprehensive dietitian's assessment according to Kappa values and AUC values.

The MST and the MUST were both developed for use in the acute care setting and validated in several patient groups. However, in this study, we have demonstrated that they fail to perform adequately in the vascular surgery setting. The NRS-2002 was used by De Waele et al (82) as a nutrition screen in vascular surgery patients who were all subsequently assessed by a dietitian. They found that the NRS-2002 did not result in any false positives, however they did not mention whether there were any false negatives, which was found to be high in

the present study. The present study and the study by De Waele et al (82) are quite different in terms of sample size (n=23 participants versus n=322 in the current study) and the type of vascular patients included, making comparisons difficult. De Waele et al (82) included only elective surgery patients and excluded those needing urgent surgery and/or limb amputations whereas our sample included all surgery types, and both elective and emergency patients making it a more representative sample of a routinely heterogeneous acute vascular surgery unit.

The suboptimal performance of the malnutrition screening tools, and the PG-SGA is likely related to the parameters included in each of these tools, which are of less relevance to this patient group. Malnutrition screening tools traditionally focus on weight and/or BMI status, unintentional weight loss and reduced appetite/oral intake. The NRS-2002 also accounts for disease severity and age while the MNA-SF incorporates parameters known to impact on nutritional status that may be more relevant to this patient group; suboptimal mobility, (264) increased psychological stress and depression (19-21). The participants in this study were mostly overweight or obese with minimal reporting of unintentional weight loss hence they would not score highly on the tools that focus solely on these parameters. The MNA-SF identified the highest proportion of 'at risk' participants likely due to the inclusion of broader parameters. Overall, all malnutrition screening tools and the PG-SGA performed poorly as they failed to account for micronutrient status which we found to be a key nutritional issue in the participants of this study. Incorporating micronutrient status into the comprehensive dietitian's assessment provides a more comprehensive determination of nutritional status and this study has demonstrated that any malnutrition screening tools or assessment tools that neglect this important area will likely be grossly inadequate for implementation in a vascular surgery setting. In this thesis, suboptimal micronutrient status,

and therefore undernutrition, was allocated to a participant when one or more micronutrient was deemed suboptimal. It is acknowledged that classifying undernutrition based on being suboptimal in one micronutrient could be interpreted as increasing the likelihood of false positive results, however given the importance of each micronutrient studied in these participants for their overall and vascular health, poor status in one micronutrient could have a detrimental impact on outcomes and should be rectified.

Micronutrients are crucial in this patient group for wound healing (106), and vascular health (107) hence ensuring adequate micronutrient status is critical to ensure optimal perioperative and long-term outcomes. With the majority of participants in this study being overweight or obese the risk of malnutrition would not be of primary concern even to an astute clinician and yet there was a high prevalence of micronutrient deficiencies which appears to be masked by the participant's weight status and are not being identified by the tools examined in this study. This is an issue that needs to be addressed. The malnutrition screening tools that are currently available in the existing literature do not include biochemical assessment of micronutrients as this contravenes the premise that a screening tool should be quick and simple to administer by any trained person or the patient themselves. The inclusion of serum analysis requires additional resources and time rendering it not quick or simple and accrues additional financial cost. Traditionally it would not be plausible to include them in a malnutrition screening tool, however, given the prevalence of micronutrient deficits in this patient group (265), the results presented in chapter 4.3 Results and the importance of micronutrients in vascular health, inclusion appears warranted in a screening tool specifically for this population. A cost-benefit analysis should be undertaken to confirm whether the inclusion of serum analysis is acceptable.

5.4.2 Predictive Validity

Discriminant and convergent validity testing of the screening tools showed variable results. The MNA-SF performed best with significant associations observed between the MNA-SF score and 3 of the 5 outcomes studied followed by the NRS-2002 (2 out of 5) and MST (1 out of 5).

Results of the regression analyses investigating the ability of the tools to predict short-term clinical outcomes were variable. Whilst the MNA-SF was the better performer on validity testing, it performed lowest in predicting outcomes, with no significant associations observed between MNA-SF and the outcomes studied after controlling for confounders. The NRS-2002 showed the best predictive ability, with significant associations observed with discharge destination, in-hospital complications and hospital LOS indicating poorer outcomes in those classified as at risk of malnutrition.

Existing literature that has looked at the ability of the MUST, MST, NRS-2002 and MNA-SF to predict outcomes has also reported variable results, depending on the population studied, sample size and setting. Wang et al (266) found the NRS-2002 to be predictive of LOS, non-infectious complications and higher cost and mortality in Chinese GI patients and when compared to other tools in a Brazilian study, Raslan et al (267) found that the NRS-2002 performed better than that MUST and MNA-SF despite it identifying the lowest proportion of nutritional risk out of the three tools studied. Both studies were conducted in acute care patients. However when the NRS-2002 was studied in nursing home residents, it was found to have a lower predictive ability along with the MUST when compared to the MNA-SF (261). The authors postulated this was due to the lack of functional, cognitive and psychological parameters in the MUST and NRS-2002. The MNA-SF has been studied more

extensively, particularly in the older age groups, showing that it is associated with increased risk of discharge to institutional care (268) and longer LOS in geriatric rehabilitation (268, 269) and also long-term mortality (4-year follow-up) in elderly Taiwanese (270). In younger populations, the results are not clear cut. Asiimwe et al (271) found the MNA-SF to be strongly associated with mortality in younger Ugandan adults, whereas Wegener et al (272) found a trend towards longer LOS and increased likelihood of readmission in younger rehabilitation patients but the results failed to reach significance as the study was underpowered. In the current study, the MST was predictive of discharge destination and LOS. Similar to the other screening tools, the literature is variable with the MST being predictive of LOS in acute care patients (192) but not in renal patients (273) and not predictive of any clinical outcomes in geriatric rehabilitation (205). The variable results in the current study and also in existing literature highlight that no one screening tool is suitable for use across a range of population groups and hence the tool selected needs to be valid for the population for which it is intended (127).

S.4.3 Strengths and Limitations

It is important to consider the strengths and limitation of this study when drawing conclusions. This study is the first of its kind to investigate a range of screening tools in the vascular surgery population. It has a large sample size of 322 participants that are heterogeneous and therefore representative of the spectrum of vascular disease. Nutrition assessment bias was minimised by having an APD conduct the PG-SGA who was not involved in the screening process and all measurements were conducted by a trained APD. Nursing staff that conducted the nutrition screening were trained via in-service education sessions and individual support by research team members.

While the study has many strengths, it is not devoid of limitations. The comprehensive dietitian's assessment was completed retrospectively utilising information collected via the screening and nutrition assessment processes. As this was done retrospectively, the dietitian was not able to clarify information with individual participants and this may have influenced the assessment results. When investigating the validity of the tools, participants at moderate and high risk of malnutrition according to the MNA-SF, MUST and the PG-SGA were merged for analysis so the relationship between the different levels of risk or malnutrition with clinical outcomes could not be explored. Due to the small proportion of severely malnourished participants in this sample, it is unlikely that any statistically significant relationships would have been observed. This study measured nutritional status on admission and hence any deterioration and resultant malnutrition that may have occurred during admission was not determined

5.4.4 Conclusion

Vascular surgery patients are complex with a range of pathologies influenced by nutrition. This study found a high prevalence of malnutrition secondary to suboptimal micronutrient status that was not identified by the four commonly used nutrition screening tools investigated or the PG-SGA indicating that vascular disease-specific screening and assessment tools are warranted to ensure that those at nutritional risk receive appropriate nutritional care to optimise patient and clinical outcomes. Given the results of this study it is appropriate that further research is conducted to develop alternative instruments to identify malnutrition in this patient group that encompass additional parameters of relevance such as micronutrients and mobility measures that are predictive of relevant clinical outcomes.

Chapter 6: Is it possible to develop a malnutrition screening tool for use in vascular surgery inpatients that has improved validity compared to commonly used malnutrition screening tools?

6.1 Introduction

The literature presented in chapter 2 of this thesis indicates that patients with vascular disease are at risk of poor nutritional health. Research presented in chapter 4 supports the existing literature with approximately 75% of a sample of vascular surgery patients being malnourished according to a comprehensive dietitian's assessment.

Poor nutritional health (malnutrition) has significant consequences for these individuals such as higher rates of infections (180), longer hospital LOS (86) and increased risk of lower limb amputations in those with diabetic foot infection (80). This in turn has consequences to the health care system. Similar findings are presented in chapter 4 with patients assessed as malnourished on the comprehensive dietitian's assessment exhibiting a significantly longer median hospital LOS, increased likelihood of complications during admission and increased likelihood of discharge to an institution. There were also significant associations found between deficiencies in vitamins A, C, D and iron and poorer clinical outcomes.

Identification of vascular disease patients with malnutrition or at risk of malnutrition is paramount in ensuring timely and appropriate nutritional intervention to maximise nutritional health and clinical outcomes. However, results presented in 5.3.2 Validity of the screening and assessment tools indicate that four commonly used malnutrition screening tools (MUST, MST, NRS-2002 and MNA-SF) as well as the PG-SGA are ineffective in identifying malnutrition or risk of malnutrition and a more specific instrument is required for this patient group. Identification of patients at risk of malnutrition (malnutrition screening)

is crucial to initiate appropriate dietetic input and as earlier work presented in chapter 2 this thesis highlighted that there isn't a screening tool that has been developed or validated in the vascular surgery population, and hence the focus of this research is on this crucial initial step of malnutrition screening rather than nutrition assessment.

Commonly used screening tools focus on parameters such as weight loss, weight and/or BMI status, poor appetite and/or intake, parameters that were found to be less relevant in the participants presented in this thesis. Parameters that are linked to poorer nutritional status and of more relevance in this group were found to include suboptimal mobility (264), increased psychological stress and depression (19-21). The tool that included some or all of these parameters (MNA-SF) performed the best in the studies presented in previous chapters; however, it did not reach the a-priori levels for Sn and Sp (191) at 52.5% and 67.9% respectively compared to a comprehensive dietitians assessment.

Suboptimal micronutrient status has been identified as an issue in the vascular surgery patient group, both within the literature (Table 5) and in research presented in chapter 4 (Table 9) which unearthed a high prevalence of suboptimal micronutrient status, particularly in vitamin C, vitamin D, vitamin B12, zinc and iron. Malnutrition screening tools that are currently available do not include analysis of micronutrient status as their inclusion contradicts the ideal that screening tools should be simple to administer using only data that is routinely available on administration of the screening tool. Adequate micronutrient status is critical in vascular surgery patients for overall vascular health (107) and also to promote optimal wound healing (106). So, it seems plausible to include micronutrient status in a screening tool when biochemical analysis is conducted as part of routine admission medical assessment. The inclusion of micronutrient analysis within a screening

tool provides potential for a valid screening tool to be developed for this important patient group. Therefore, to address thesis research question 3, In the absence of an adequate/appropriate screening tool for use in this population, can a valid screening tool be developed that performs better than tools that are currently available?' (2.4 Research Questions), and prior work presented in chapter 5 highlighting that commonly used screening tools are not adequate, the aim of this study was to develop a short screening tool for identifying risk of malnutrition that would be valid for use in the vascular surgery disease inpatient setting.

6.2 Methods

The methods of data collections methods for data used in this chapter of the thesis have been described in full in 3.4 Assessment of Participants. Only the framework for the analysis specific to this chapter is presented.

6.2.1 Instrument construction:

Key items (variables) that are incorporated into available malnutrition screening and assessment tools were extracted from supplementary files relating to a systematic review of nutrition screening tools for the hospital setting (128) for potential inclusion in the new tool and supplemented with variables included within additional screening tools identified as part of the literature review presented in 2.2.3 What malnutrition screening tools are valid and/or reliable for use in surgical patients?. In addition, other key indicators of nutritional status that are of relevance in this population based on the literature and previous findings described in chapters 4 and 5, such as biochemical factors and mobility were also included as potential variables. Table 19 displays the collated variables of interest.

Table 19: Items for potential inclusion in the Vascular Malnutrition Screening Tool

Nutrition Impact Symptoms	**Physical/Anthropometric Factors**
Poor/no appetite	Weight
Swallowing difficulties	Height
Depression/dementia	Body Mass Index
Psychological stress	
Acute illness	Grip strength
Nausea and/or vomiting	Mid-arm muscle circumference
Mouth sores	Triceps skin fold thickness
Taste changes	Physical signs of muscle wasting
Food smells bother client	
Early satiety	Age
Pain	
Altered bowels/digestive problems	
Any other symptoms affecting intake	
Weight loss	**Food intake changes**
Weight change in past 2 weeks	Decline in intake in past 3 months
Weight loss in last 3-6 months	Decline in intake in 1 month
Percentage weight loss	Decline in intake in past 1 week
	No nutrition likely for 5 days.
Biochemical Factors	**Mobility/Activity Factors**
Albumin status	Reduced mobility in past month
Vitamin D status	Activity compared to usual in the
Vitamin C status	past month.
Vitamin A status	
Vitamin E status	
Zinc status	
Selenium Status	

Items that require expertise to measure and/or are not routinely collected on admission were removed based on the premise that a screening tool should have the potential to be completed by a non-nutrition professional using routinely collected data (274). The resulting set of items were included as potential predictors in the proposed screening tool. The convergent, construct and concurrent validity of the tool was thereafter assessed.

6.2.2 Statistical analysis

Continuous variables were assessed for normality using the Shapiro-Wilk test and reported as mean (standard deviation, SD) or median (interquartile range, IQR). Descriptive statistics were expressed as frequencies (n, %) with Chi-square analysis or Fishers Exact Test used to determine differences between groups for categorical variables. Continuous variables were compared using Independent–samples t-test/Mann-Whitney U test or One-way ANOVA/Kruskal-Wallis Test.

6.2.3 Selection of variables to include in screening tool

As the underlying constructs of the items of interest were not known a priori, exploratory factor analysis (EFA) was utilised to explore the underlying factor structure of these items (275). The EFA was used as a data reduction technique to identify which items can be collapsed into interpretable underlying factors and thereafter included in the tool. In line with the literature, a combination of Eigen values greater than 1.0 and scree plots were used to determine the optimum number of factors to retain (276). To enable selection of only variables that loaded sufficiently onto the factors, just those with factor loadings of at least 0.4 were considered. Factor loadings of 0.4 or greater are most commonly used in the literature with a third of 402 factor analyses examined by Peterson (277) using this cut-off and Hair et al (cited in (278)) categorising 0.4 as important whereas loadings of 0.3 were

categorised as minimal. Polychoric correlations were also incorporated in the EFA to index the association between the variables of interest and factors due to the presence of categorical items (279).

The Varimax (orthogonal technique) rotation method was used to refine/optimise each model due to the exploratory nature of this phase. Varimax rotation maximises the sum of the squared factor loadings across the columns, which tends to force each item to load highly on as few factors as possible (280). The loadings can be considered as the estimated correlation between each item and each factor (281).

6.2.4 Determining the optimum number of variables to be included in the tool

A screening tool should be quick to administer, inexpensive and non-invasive to ensure the burden on resources and on patients is minimised (274). Hence the principle of parsimony was considered to determine the number of variables for inclusion in the tool in the event where the EFA resulted in many variables. This refinement would be based on the inclusion of items that are common to the majority of screening tools (weight status and recent changes, appetite changes, declining food intake), issues that are prominent in the vascular surgery population (mobility, micronutrient deficiencies) and that loaded highly during the factor analysis. While biochemical nutritional markers are not routinely collected and have additional cost and burden associated with their collection, they were included in the following analyses for completeness with the view to informing routine practice if these markers were of higher relevance/importance.

6.2.5 Determination of decision thresholds

Within the new tool, each variable was coded as a binary variable with 1 assigned to a positive result/presence of that indicator and 0 assigned to the absence of the variable. Each variable was then tallied to give a final total score for each participant with a higher score representing a higher risk of malnutrition.

6.2.6 Cross-validation of candidate vascular malnutrition screening tools

In the absence of an independent data set for a validation study, the k-fold cross validation technique was employed to assess the performance and generalisability of candidate tools if they were implemented in an independent sample of vascular surgery patients. In this method, the original data set is randomly partitioned into k equal subsamples (folds) with each fold being used once as the validation data while the rest of the folds (k-1) are used as the training sample. The results from the k folds can then be averaged to produce one single estimate. The advantage of this method is that each observation is used for both training (the original tool development phase) and in the validation, and each observation is used only once in the validation (282). k is an unfixed parameter, and while a large k appears more desirable as it gives more performance estimates and the training set is closer to the full data set, the overlap between the training sets increases and the size of the test set decreases leading to measurements of the performance metric being less precise. Considering all of these factors, the consensus is that k=10 is a good compromise (283). Hence the data set of 322 participants was randomly subdivided into 10 subsamples with approximately 10% of the original data set in each sub sample.

Evaluation of the performance of the candidate tools considered discrimination and calibration in the 10-fold cross validation. Discrimination of the tools was assessed using the

average area under the curve (AUC) from the receiver operator characteristics (ROC) analysis. The AUC can be interpreted as the concordance probability that the value from a subject in one group is greater than that for a subject in the other group (284) and has been shown to be desirable as a performance measure in machine learning algorithms such as the k-fold (285). Based on the established equivalence between the concordance statistics (C-statistic) for assessing discrimination and AUC (286), AUC ≥ 0.9 was considered to represent outstanding discrimination, 0.8 ≤ AUC < 0.9 excellent, 0.7 ≤ AUC < 0.6 acceptable and AUC=0.5 no discrimination while AUC < 0.5 was negative discrimination (287). The Brier score, an overall goodness-of-fit check for binary and categorical variables, was used to assess calibration. The commonly used Hosmer-Lemeshow test wasn't possible in assessing calibration of the candidate tools as regression modelling wasn't employed. The Brier score has a range of 0 to 1 with a perfect model achieving a score of 0 (288).

Youden Index (J) is used as an additional criterion for choosing the optimal threshold value for which the performance of a test is maximised (289, 290). The index can be defined as *J= (sensitivity – (1-specificity))* and ranges between 0 and 1. Maximising the Youden Index allows us to find the cut-off point that has the largest value in the sum of sensitivity and specificity or in the difference between sensitivity and the false positive rate (284). Tool scores greater than the threshold were determined to be 'at risk' of malnutrition with scores below the threshold being 'not at risk' of malnutrition.

The tool that performed best in terms of discrimination and calibration in the validation exercise was chosen as the optimum one.

6.2.7 Determination of optimal cut-off thresholds

The goal of the tool is to predict whether individuals would be at risk of malnutrition or not i.e. dichotomised outcome. Therefore, ROC analysis was used to (1) determine the accuracy of the instrument in separating individuals into those at risk of malnutrition and those not at risk of malnutrition and (2) to determine the optimal cut-off point that maximises the likelihood ratio for positive results while minimising the likelihood ratio for negative results. To determine the optimal cut-off, the maximised Youden Index and another criterion, namely 'closest-to-(0,1)' were examined. The 'closest –to-(0,1) selects the cut-off point that minimises the distance between the ROC curve and an ideal point (0,1) representing zero false positives and perfect sensitivity. This criterion can be defined as the square root of ((1-sensitivity)^2 + (1-specificity)^2) (284).

Both the Youden Index and the closest-to-(0,1) index consider Sn and Sp to be of equal importance/value. However when developing an instrument to detect malnutrition, Sn (probability of correctly classifying those with malnutrition) is considered of higher importance over Sp (probability of correctly classifying those without malnutrition) with a-priori levels of 80% and 60% respectively cited in the literature (191). Hence, where these cut-off points differ, the cut-off point that would allow the tool to meet a-priori levels was considered for further analyses.

6.2.8 Comparison of the Vascular Malnutrition Screening Tool to commonly used malnutrition screening tools.

The concurrent validity (Sn, Sp, NPV and PPV) of the new tool against the comprehensive dietitian's assessment was compared to that of the four commonly used screening tools

investigated in 5.3.2 Validity of the screening and assessment tools. Diagnostic consistency assessed by kappa (k) statistic was also compared.

The discriminant and convergent validity of the new tool was examined. Discriminant validity was explored using the Independent T or Mann Whitney U test, as appropriate, to examine differences in mean/median screening tool scores across clinical categorical outcomes (incidence of in-hospital complications during admission and discharge destination). Convergent validity was tested using correlation between tool scores and continuous clinical (LOS) and HRQoL (EQ-5D-5L) outcomes and was assessed using Pearson or Spearman's Rank Order Correlation. The discriminant and convergent validity of the new tool was then compared to the four commonly used screening tools; MST, MNA-SF, MUST and NRS-2002.

The ability of the tool to predict clinical and HRQoL outcomes was tested via multivariate regression analysis. The dichotomous screening tool variable (at risk of malnutrition/malnourished or not at risk/well-nourished) was entered as independent variables with age, gender, disease type and smoking status included as potential cofounders. To predict continuous dependent variables or outcomes (length of stay and EQ-5D-5L scores), generalised linear models (GLM) were fitted using a Modified Park Test to identify the appropriate GLM family with comparison of AIC/BIC for determining the link function. For the LOS model, coefficients of predicted dependent values in the Modified Park Test indicated that the Inverse Gaussian family was appropriate. The OLS regression model was used for the EQ5D-5L model (139). To predict binary outcomes (1 = return to prior residence or to an institution such as residential aged care, rehabilitation or another

hospital, 0 = other discharge destination and; 1 = in-hospital complications, 0 = no complications), binary regression models were fitted.

6.3 Results

6.3.1 Participants

Table 20 displays the characteristics of the 322 participants recruited from the vascular surgery inpatient unit at SALHN. Details regarding recruitment,total number of eligible and consenting patients are described in 4.3 Results.

Table 20: Participant characteristics

Variable	N (%) unless specified
Males	223 (69.3)
Age	
Median (IQR)	68.0 (48,88)
<65 Years	123 (38.2)
65 years and above	199 (61.8)
BMI (n=320)*	
Median (IQR)	28.2 (20.3, 35.2)
Underweight	28 (8.8)
Normal	86 (26.9)
Overweight/Obese	206 (64.4)
Vascular disease type	
Aneurysmal	35 (10.9)
PAD	94 (29.2)
Occlusive other	28 (8.7)
Venous	20 (6.2)
DM Foot Infection	92 (28.6)
Other	53 (16.5)
Living situation	
Lives alone	105 (32.6)
Lives with another person/s	86 (63.0)
SCF	2 (0.6)
RACF	12 (3.7)
EQ5D-5L Index Median (IQR)	0.72 (0.36, 1.08)
In-hospital complications	69 (21.4)
Median LOS (IQR)	8 (1,15)
Discharge destination (n,%)	
Return to prior place of residence	260 (82.0)
Discharge to institutional care	57 (18.0)

** n=320 as height was not available on 2 participants*

6.3.2 Selection of variables for inclusion in tool

After the removal of duplicates and measurements that require expertise to collect (upper arm anthropometry), 25 potential items were available for inclusion. The potential items are listed in Table 21. All nutritional biochemistry were retained due to their relevance and prevalence of deficiency in this population (265).

The 25 items were entered into the EFA revealing nine factors with eigenvalues greater than 1 (Table 22), explaining 75.7% of the variance. Examination of the scree plot (Figure 2) revealed an “elbow/break” at the third factor. Consideration of both the eigen values and scree plot together indicated that two factors should be retained for further investigation. (278)

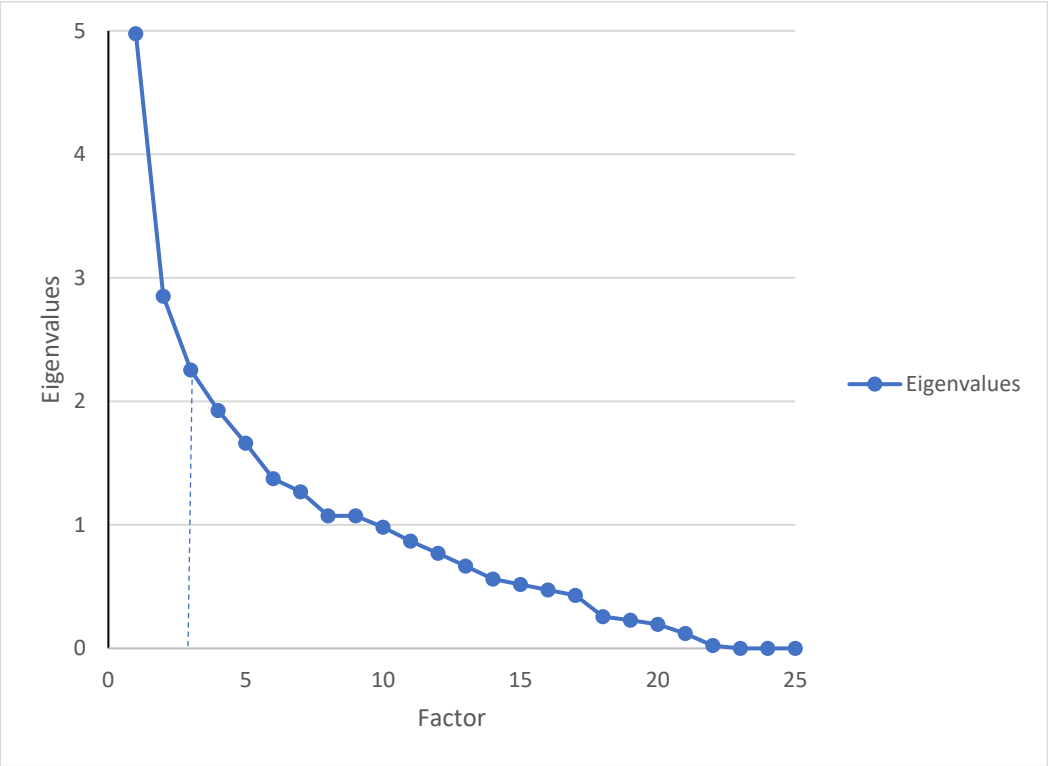
Table 21: Potential items for inclusion into the newly developed vascular screening tool

	Questions	**Possible Responses**
1	How old is the patient?	
2	What is the patient's Body mass Index (BMI)?	
3	Has the patient lost weight in the last 3-6 months without trying	No, yes, unsure
4	What is the patient's grip strength?	
5	During the past 2 weeks has your body weight decreased?	Yes or no
6	Over the past month would you describe your activity as low or suboptimal?	Yes or no
7	Has food intake declined in past 3 months?	Yes or no
8	In the past month I would rate my food intake as less than normal	Yes or no
9	Has food intake declined in past week?	Yes or no
10	Does the patient complain of a poor or no appetite?	Yes or no
11	Does the patient report swallowing problems?	Yes or no
12	Has the patient suffered psychological stress or acute disease in the past 3 months?	Yes or no
13	Is the patient acutely unwell?	Yes or no
14	Is there the presence of depression or dementia?	Yes or no
15	Does the patient report any nausea and/or vomiting that has affected intake in past 1 month?	Yes or no
16	Does the patient report any pain that has affected intake in the past 1 month?	Yes or no
17	Does the patient report any other symptoms that has affected intake in the past 1 month?	Yes or no
18	What is the overall rating of muscle deficit on physical examination?	Nil, mild, moderate, severe
19	Is the patient's albumin low with a normal CRP?	Yes or no
20	Is the patient's vitamin D low?	Yes or no
21	Is the patient's vitamin C low?	Yes or no
22	Is the patient's Zinc low?	Yes or no
23	Is the patient's selenium low?	Yes or no
24	Is the patient's vitamin A low?	Yes or no
25	Is the patient's vitamin E low?	Yes or no

Table 22: Results of the Exploratory Factor Analysis

Factor	Eigenvalue	Difference	Proportion	Cumulative
1	4.97600	2.12511	0.1990	0.1990
2	2.85089	0.62553	0.1140	0.3131
3	2.2536	0.30034	0.0890	0.4021
4	1.92502	0.26431	0.0770	0.4791
5	1.66071	0.09379	0.0664	0.5455
6	1.37373	0.19320	0.0627	0.6082
7	1.26736	0.10636	0.0549	0.6631
8	1.07250	0.19486	0.0507	0.7138
9	1.07250	0.09201	0.0429	0.7567
10	0.98050	0.11329	0.0392	0.7960
11	0.86721	0.09773	0.0347	0.8306
12	0.76948	0.10482	0.0308	0.8614
13	0.66566	0.10379	0.0266	0.8880
14	0.56087	0.04385	0.0224	0.9104
15	0.51702	0.04440	0.0207	0.9311
16	0.47262	0.04418	0.0189	0.9500
17	0.42844	0.17192	0.0171	0.9672
18	0.25653	0.02836	0.0103	0.9774
19	0.22816	0.03394	0.0091	0.9866
20	0.19422	0.07475	0.0078	0.9943
21	0.11947	0.09715	0.0048	0.9991
22	0.02232	0.02232	0.0009	1.0000
23	0.00000	0.00000	0.0000	1.0000
24	-0.0000	0.00000	0.0000	1.0000
25	-0.0000	0.00000	0.0000	1.0000

Figure 2 Scree Plot of Eigenvalues



The rotated solution revealed 10 items loaded highly onto factor 1 and 6 onto factor 2 and hence were appropriate for inclusion into the new tool. Factor 1 loadings explained 64.3% of the variance while those for factor 2 explained 35.7% of the variation (Table 23).

Table 23: Rotated Factor Loadings and unique variances

	Item	Factor 1	Factor 2	Uniqueness
1	How old is the patient?			0.9938
2	What is the patient's Body mass Index (BMI)?			0.9337
3	Has the patient lost weight in the last 3-6 months without trying?	0.4554		0.7878
4	What is the patient's grip strength?			0.9553
5	During the past 2 weeks has your body weight decreased?			0.8430
6	Over the past month would you describe your activity as normal or suboptimal?	-0.4811		0.7417
7	Has food intake declined in past 3 months?	0.7163		0.4797
8	In the past month I would rate my food intake as less than normal	0.6420		0.5878
9	Has food intake declined in past week?	0.5487		0.6854
10	Does the patient complain of a poor or no appetite?	0.7613		0.4065
11	Does the patient report swallowing problems?	0.6328		0.5607
12	Has the patient suffered psychological stress or acute disease in the past 3 months?			0.8999
13	Is the patient acutely unwell?			0.8142
14	Is there the presence of depression or dementia?			0.9141
15	Does the patient report any nausea and/or vomiting that has affected intake in past 1 month?	0.6726		0.5258
16	Does the patient report any pain that has affected intake in the past 1 month?	0.4272		0.8171
17	Does the patient report any other symptoms that has affected intake in the past 1 month?	0.4891		0.7313
18	What is the overall rating of muscle deficit on physical examination?			0.9497
19	Is the patient's albumin low with a normal CRP?		0.8305	0.3063
20	Is the patient's vitamin D low?			0.9622
21	Is the patient's vitamin C low?		0.4392	0.8608
22	Is the patient's Zinc low?		0.5140	0.7312
23	Is the patient's selenium low?		0.5915	0.5343
24	Is the patient's vitamin A low?		0.5496	0.6605
25	Is the patient's vitamin E low?		0.5255	0.7225
	% of the variance explained	64.3	35.7	

A 16-item instrument was deemed to contradict the parsimony premise of a screening tool, hence further refinement occurred. Hence a decision was made to reduce the number of items based on parsimony principles to include items that are common to the majority of screening tools (weight status and recent changes, appetite changes, declining food intake), issues that are prominent in the vascular disease population (reduced mobility,

micronutrient deficiencies) and that loaded highly during the factor analysis. Nutritional biochemistry analyses are not routinely included in a malnutrition screening tool due to their invasiveness and the costs associated with the laboratory analysis. However it is known that vascular surgery patients have a high prevalence of micronutrient deficiencies (116, 162, 170) and previous work presented in chapter 4 revealed a high prevalence of suboptimal micronutrient status, particularly for vitamin C. Serum albumin level loaded highly (0.8305) in the factor analyses, hence its inclusion in the proposed tools. The use of serum albumin as a nutritional marker is controversial due to the significant number of variables in a clinical setting that can affect albumin levels rendering it less useful as a nutritional marker in that setting (291, 292). The inclusion of serum albumin could have affected the level of specificity of the tool however in this study, low albumin was only included in the presence of a normal CRP level and hence would be considered a more reliable indicator of nutritional status than when CRP is elevated indicating inflammation which impacts negatively on albumin level (291). Another important consideration is that serum albumin continues to be a significant marker of clinical outcomes and hence its inclusion appeared warranted when developing a tool that is aimed to be predictive of clinical outcomes (293-295).

The following items (Table 24) were selected for inclusion in a shorter screening instrument with the aim of combining these items to achieve the optimal tool.

Table 24: Potential items selected for inclusion in a short screening instrument based on factor loadings within the Exploratory Factor Analysis

Item No.	Item	Potential Responses
3	Has the patient lost weight in the last 3-6 months without trying?	Yes or No
6	Over the past month would you describe your activity as normal of suboptimal?	Normal or Suboptimal
7	Has food intake declined in past 3 months?	Yes or No
8	In the past month I would rate my food intake less than usual	Yes or No
10	Does the patient complain of a poor or no appetite?	Yes or No
19	Is the patient's albumin low with a normal CRP?	Yes or No
21	Is the patient's vitamin C low?	Yes or No

The items were selected based on their factor loadings and whilst vitamin C status didn't load as highly as other micronutrients, it was selected based on its known importance in this patient group. The following four proposed variable combinations (Table 25) were entered into the remaining analyses to determine the optimal tool.

Table 25: The combination of items included in each of the four candidate short screening tools.

Candidate Tool	Nutrition Impact Symptom Items	Biochemical Items
1	3 Has the patient lost weight in the last 3-6 months without trying? 6 Over the past month would the patient describe their activity as normal or suboptimal? 7. Has the patient's food intake declined in the past **3** months? 10. Does the patient complain of a poor or no appetite?	19. Is the patients Albumin low with normal CRP?
2	3 Has the patient lost weight in the last 3-6 months without trying? 6. Over the past month would the patient describe their activity as normal or suboptimal? 7. Has the patient's food intake declined in past **3** months? 10. Does the patient complain of a poor or no appetite?	19. Is the patients Albumin low with normal CRP? 21. Is the patient's vitamin C low?
3	3 Has the patient lost weight in the last 3-6 months without trying? 6. Over the past month does the patient describe their activity as normal or suboptimal? 8. In the past 1 month has the patient's food intake been less than normal? 10. Does the patient complain of a poor or no appetite?	19. Is the patients Albumin low with normal CRP?
4	3 Has the patient lost weight in the last 3-6 months without trying? 6. Over the past month does the patient describe their activity as normal or suboptimal? 8. In the past 1 month has the patient's food intake been less than normal? 10. Does the patient complain of a poor or no appetite?	19. Is the patients Albumin low with normal CRP? 21. Is the patient's vitamin C low?

6.3.3 Cross-Validation of candidate Vascular Malnutrition Screening Tools

Table 26 displays the results of the k-fold validation (k=10) of the four candidate tools including the mean AUC, Sn and Sp at the level of maximum Youden Index and the Brier Scores for calibration.

Assessment of the mean AUC and Brier score showed similar results across the four tools. Mean AUC values indicate fair accuracy. Likewise, Brier scores were similar across the four tools, with a slightly lower mean validation score of 0.210 for tool 2. Sensitivity and specificity were similar with tools 2 and 4 having slightly higher sensitivity values compared to tools 1 and 2 (Table 26). While results were similar, candidate tool 2 was selected as the optimal tool based on the combination of AUC (0.788), Sn (77%), Sp (74%) and Briers score of calibration (0.210).

Table 26: k-fold Validation of the four candidate tools

Candidate Tool 1				
K fold	**AUC**	**Sensitivity**	**Specificity**	**Briers**
Estimation 1	0.754	0.7	0.67	.314
E2	0.756	0.47	0.89	.447
E3	0.738	0.71	0.63	.304
E4	0.745	0.70	0.64	.312
E5	0.739	0.44	0.88	.469
E6	0.758	0.70	0.65	.310
E7	0.740	0.69	0.65	.318
E8	0.744	0.45	0.87	.469
E9	0.742	0.7	0.63	.307
E10	0.747	0.72	0.62	.302
Mean	**0.746**	**0.63**	**0.71**	**.355**
Validation 1	0.635	0.32	1.0	.586
V2	0.635	0.65	0.6	.357
V3	0.865	0.92	0.75	0.107
V4	0.758	0.74	0.62	0.24
V5	0.801	0.75	0.71	0.258
V6	0.711	0.6	0.78	0.345
V7	0.815	0.64	1.0	0.31
V8	0.758	0.74	0.71	0.267
V9	0.804	0.64	1.0	0.333

V10	0.745	0.55	0.8	0.4
Mean	**0.753**	**0.65**	**0.8**	**0.320**
Candidate tool 2				
K fold	**AUC**	**Sn**	**Sp**	**Briers**
Estimation 1	.789	0.62	0.79	0.352
E2	.789	0.88	0.53	0.175
E3	.778	0.64	0.77	0.34
E4	.788	0.63	0.76	0.353
E5	.767	0.63	0.75	0.35
E6	.818	0.63	0.83	0.34
E7	.787	0.63	0.76	0.346
E8	.792	0.65	0.77	0.335
E9	.782	0.88	0.52	0.171
E10	.788	0.65	0.78	0.327
Mean	**.788**	**0.68**	**0.73**	**.309**
Validation 1	.74	0.88	0.5	0.154
V2	.778	0.62	1.0	0.333
V3	.869	0.9	0.75	0.125
V4	.80	0.6	0.75	0.269
V5	.991	0.68	1.0	0.045
V6	.625	0.94	0.2	0.238
V7	.738	0.67	1.0	0.318
V8	.75	0.85	0.5	0.208
V9	.815	0.62	1.0	0.32
V10	.781	0.95	0.66	0.091
Mean	**.788**	**0.77**	**0.74**	**.210**
Candidate tool 3				
K fold	**AUC**	**Sn**	**Sp**	**Briers**
Estimation 1	.755	0.68	0.7	.314
E2	.753	0.7	0.68	.302
E3	.741	0.7	0.67	.290
E4	.742	0.69	0.68	.309
E5	.738	0.69	0.67	.312
E6	.754	0.69	0.7	.309
E7	.734	0.69	0.67	.318
E8	.743	0.69	0.67	.315
E9	.736	0.7	0.65	.311
E10	.744	0.7	0.66	.306
Mean	**.744**	**0.69**	**0.68**	**.309**
Validation 1	.548	0.28	1.0	.621
V2	.648	0.61	0.6	.379
V3	.802	0.92	0.5	.50
V4	.758	0.39	1.0	.452
V5	.792	0.71	0.71	.290
V6	.725	0.45	0.89	.414
V7	.835	0.64	1.0	.310

V8	.748	0.74	0.71	.267
V9	.812	0.64	1.0	.3
V10	.750	0.6	0.8	.36
Mean	**.742**	**0.6**	**0.82**	**.389**
Candidate Tool 4				
K fold	**AUC**	**Sn**	**Sp**	**Briers**
Estimation 1	.794	0.63	0.79	.348
E2	.794	0.64	0.75	.34
E3	.790	0.64	0.77	.334
E4	.789	0.63	0.76	.352
E5	.772	0.63	0.76	.346
E6	.819	0.63	0.76	.340
E7	.791	0.87	0.53	.350
E8	.799	0.65	0.77	.335
E9	.780	0.64	0.74	.346
E10	.792	0.64	0.78	.337
Mean	**.789**	**0.66**	**0.74**	**0.343**
Validation 1	.729	0.92	0.5	.115
V2	.762	0.57	1.0	.375
V3	.80	0.9	0.5	.167
V4	.808	0.7	0.83	.385
V5	.991	0.95	1.0	.045
V6	.656	0.44	0.8	.476
V7	.738	0.71	1.0	.273
V8	.731	0.8	0.5	.25
V9	.863	0.62	1.0	.32
V10	.789	0.9	0.67	.136
Mean	**.787**	**0.75**	**0.78**	**.254**

Figure 3 Proposed Vascular Malnutrition Screening Tool (VMST)

Does the patient have:

- Limitations to activity over the past month? YES NO
- A reduced appetite? YES NO
- A loss of weight in the past 3-6 months without trying? YES NO
- Reduced food intake in the past 3 months? YES NO

Does the patient have:

- A low albumin level with normal CRP? YES NO
- A low vitamin C level? YES NO

Allocate a score of 1 for each YES

TOTAL SCORE: ____/6____

6.3.4 Determination of Accuracy and cut-off Thresholds

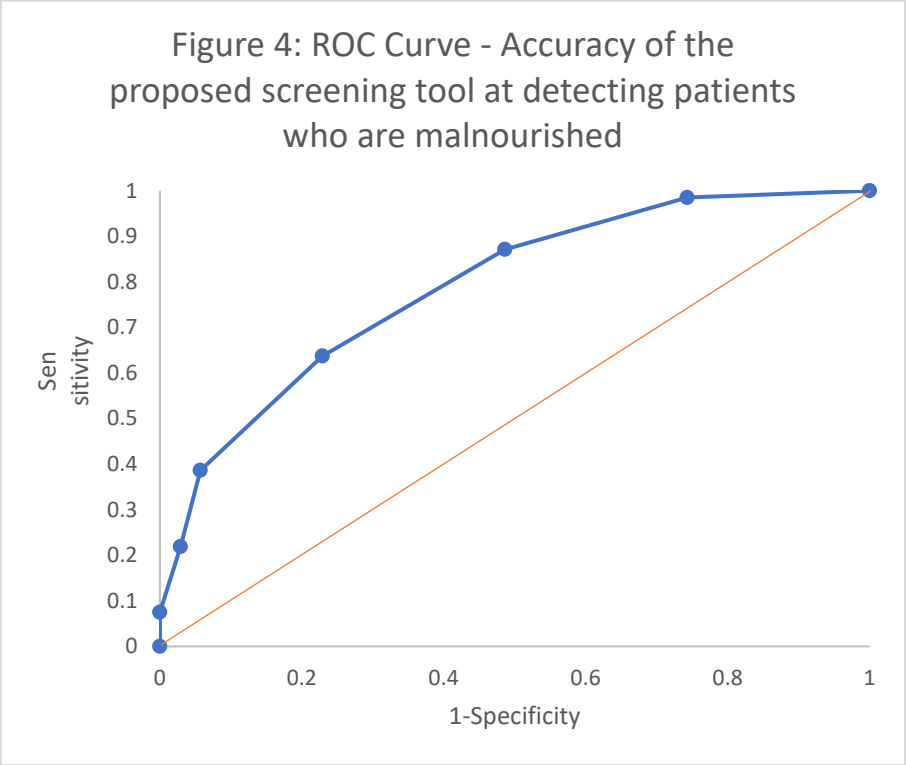
The proposed Vascular Malnutrition Screening Tool (VMST) shown in figure 3 was subsequently used in ROC analysis to determine its cut-off threshold and ability to diagnose those who were malnourished on the comprehensive dietitian's assessment.

Table 27 displays the Sn, Sp, Youden and closest-to-(0,1) values at varying thresholds for the proposed tool. The values of Youden Max and closest-to-(0,1) were 0.408 and 0.429 respectively, both of which indicate an optimal cut-off score of greater than or equal to 3 out of 6 when Sn and Sp are considered equally important. When higher Sn at the expense of Sp (a priori of 80% and 60% respectively) was considered the optimal cut-off score was identified at greater than or equal to 2 out of 6 with Sn of 87.1% and Sp of 51.4%.

Table 27: Sensitivity, Specificity, Youden and closest-to-(0,1) at varying thresholds of the proposed Vascular Malnutrition Screening Tool

Cut-point	Sensitivity	Specificity	Youden Index	closest-to-(0,1)
≥0	1.0	0.000	0	1
≥1	0.985	0.257	0.242	0.743
≥2	0.871	0.514	0.385	0.503
≥3	0.637	0.771	0.408	0.429
≥4	0.3863	0.943	0.326	0.620
≥5	0.219	0.971	0.190	0.782
≥6	0.075	1.000	0.075	0.925
>6	0.00	1.000	0	1

Figure 4 displays the results of the ROC analysis of total tool score (maximum score of 6) when compared with a clinical assessment of nutritional status. A statistically significant ($p<0.001$) AUC of 0.788 (SE 0.041, 95% CI 0.707 – 0.868) was observed showing that the tool has a fair level of accuracy at determining risk of malnutrition.



6.3.5 Comparison of the Vascular Malnutrition Screening Tool to readily available malnutrition screening tools.

The concurrent validity of the new tool (with the cut-off score of ≥ 2 indicating risk of malnutrition) in the sample of 322 vascular patients, was compared to the concurrent validity of the four commonly used screening tools (MNA-SF, MUST, MST, NRS-2002) examined in 5.3.2 Validity of the screening and assessment tools using the comprehensive dietitians assessment as the reference assessment. (Table 28). Sensitivity was 87.1% compared with 14.9-52.5% across the other tools, whilst specificity was 51.4% compared with 67.9-96.1%. Positive predictive value and NPV were 91.1% and 40.9% compared to 83.6-92.4% and 26.4-31.5% respectively. The new tool had a kappa value of 0.348 indicating fair consistency (263) with the comprehensive dietitians assessment compared to kappa

values of 0.117-0.223 across the other tools which indicate poor consistency. The AUC of the new tool was 0.788 ($p<0.001$) indicating fair diagnostic accuracy compared with AUC = 0.5797 - 0.678 across the other tools.

The discriminant and convergent validity of the new tool showed significant associations between screening scores and each of the outcomes studied (Table 29). The new tool was able to discriminate between discharge destination and in-hospital complications with participants classified as at risk of malnutrition being more likely to have poorer outcomes ($p=0.001$ and 0.005 respectively). The results for the 4 existing tools were inconsistent. In terms of convergent validity, a statistically significant moderate correlation of 0.356 ($p<0.001$) was observed between vascular screening scores and LOS, indicating a longer LOS with increasing score (increasing risk of malnutrition). A small but significant correlation (r – 0.172, $p=0.008$) was also observed between vascular screening scores and the HRQoL outcome EQ5D-5L Index indicating poorer HRQoL with increasing vascular screening score.

Table 28: Concurrent validity of the Proposed Vascular Malnutrition Screening Tool and 4 commonly used malnutrition screening tools using a dietitian's clinical assessment as the comparator in 322 vascular surgery participants.

	Vascular Malnutrition Screening Tool	MST	MUST	NRS-2002	MNA-SF
Sensitivity	87.1	32.8	14.9	29.9	52.5
Specificity	51.4	83.5	94.9	96.1	67.9
PPV	91.1	86.0	90.0	92.4	83.6
NPV	40.9	28.7	26.4	29.9	31.5
K	0.348	-0.154	-0.117	-0.223	-0.155
AUC	0.788 (<0.001)	0.653 (<0.001)	0.597 (0.01)	0.678 (<0.001)	0.643 (0.001)

Sn: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: negative predictive value, K: kappa statistic, AUC: area under the curve

Table 29: Discriminant and convergent validity of the newly developed Vascular Malnutrition Screening Tool and the MUST, MST, NRS-2002, MNA-SF scores against discharge clinical outcomes in vascular surgery patients

Clinical Outcome		**Vascular Nutrition screening tool scores Median (IQR)**	**MUST Scores Median (IQR)**	**MST Scores Median (IQR)**	**MNA-SF Scores Median (IQR)**	**NRS-2002 Scores Median (IQR)**
In-hospital Complications	Yes	3 (2,5)	0	1 (0, 2)	12 (8, 16)	2 (0, 4)
	No	3 (2,4)	0	0	12 (8, 16)	1 (0,2)
	Test (p value)	Z = -2.799 (0.005)	Z = -0.503 (0.615)	Z = -0.180 (0.858)	Z = -0.465 (0.648)	Z = -1.612 (0.107)
Discharge destination	Home	3 (2,4)	0	0 (2)	12 (8, 16)	1 (0, 2)
	Other Institution	4 (2,5)	0	1(2)	10 (6, 14)	2 (0, 4)
	Test (p value)	Z = -3.180 (0.001)	Z = -0.423 (0.673)	Z = -3.17 (0.002)	Z = -4.494 (<0.001)	Z = -2.825 (0.005)
Length of Stay median (IQR)	correlation (p value)	r=0.356 (<0.001)	r = 0.048 (0.395)	r = 0.10 (0.087)	r = -0.145 (0.009)	r = 0.199 (<0.001)
EQ5D Index Median (IQR)	correlation (p value)	r= -.172 (0.008)	R = 0.005 (0.922)	R = -0.081 (0.145)	R = 0.237 (<0.001)	R = -0.109 (0.051)

GLM models were used to investigate the relationship between LOS and EQ5D-5L Index (dependent variables) with the vascular screening tool as a dichotomous variable (at risk of malnutrition/not at risk of malnutrition). Gender, age, smoking status and vascular disease type were included as confounders. Results of the analyses and comparisons to analyses conducted in the four commonly used tools are displayed in Table 30. A significant association was observed between the vascular screening tool and LOS (coefficient (SEM) -0.531 (0.11) $p<0.001$) indicating that those who were classified as not at risk had a shorter LOS. The same association was observed for the MUST, MST and NRS-2002, but not the MNA-SF. A significant association was observed between nutrition risk on the vascular screening tool and EQ5D5L Index (Coefficient (SE) -0.026 (0.01), p=0.011). There were no significant associations for the other tools.

Binary logistic regression results are shown in Table 31. There was no statistically significant association between the vascular screening tool and discharge destination when confounders were included (OR (SEM) 2.66 (0.56), p=0.083). The MUST and MNA-SF also showed no significant association (p=0.295 and 0.821 respectively). A significant association was observed between the Vascular Malnutrition Screening Tool and in-hospital complications with those who were classified at risk of malnutrition being 5.4 times more likely to encounter a complication compared to those who weren't at risk of malnutrition (OR (SEM) 5.41 (0.63), p=0.007). Three of the commonly used screening tools (MUST, MNA-SF and MST) showed no association with in-hospital complications whilst the NRS-2002 did show an association (OR (SEM) 1.85 (0.56), p=0.039).

Table 30: Generalised Linear Model (GLM) Results

	Dependent variable = Length of Stay (LOS)									
	Model inc Vascular Tool[b]		Model inc MUST[a]		Model inc NRS2002[b]		Model inc MNASF[b]		Model inc MST[a]	
Predictors	**Coefficient (SEM)[d]**	**P value**	**Coefficient (SEM) [d]**	**P value**	**Coefficient (SEM)[d]**	**P value**	**Coefficient (SEM) [d]**	**P value**	**Coefficient (SEM)[d]**	**P value**
Vascular Tool	-0.531 (0.11)	<0.001	-		-		-		-	
MUST	-		-0.00006 (0.00003)	0.029	-		-		-	
NRS-2002	-		-		-0.004 (0.002)	0.045	-		-	
MNA-SF	-		-		-		0.00001 (8.08e-6)	0.183	-	
MST	-		-		-		-		0.1061 (0.0376)	0.005
Gender	-0.048 (0.09)	0.609	0.004 (0.038)	0.913	-0.0003 (0.002)	0.889	-0.0003(0.002)	0.875	0.0087 (0.0385)	0.821
Smoker	-0.044 (0.13)	0.729	0.0096 (0.052)	0.852	-0.0004 (0.003)	0.890	-0.0002(0.003)	0.936	0.012 (0.052)	0.819
Age	0.001 (0.003)	0.656	0.0041 (0.001)	0.003	6.00E-05(0.0001)	0.378	-0.00009 (0.00007)	0.230	0.004 (0.001)	0.004
Venous	0.257 (0.23)	0.275	-0.203 (0.11)	0.065	0.009 (0.008)	0.301	0.007 (0.008)	0.372	-0.22 (0.11)	0.05
Aneurysmal	-0.381 (0.21)	0.063	0.351 (0.083)	<0.0001	-0.007 (0.005)	0.155	-0.008 (0.005)	0.113	0.335 (0.08)	<0.0001
PAD	-0.235 (0.18)	0.182	0.26 (0.073)	<0.001	-0.006 (0.005)	0.211	-0.006 (0.005)	0.191	0.256 (0.07)	<0.0001
DM limb	-0.224 (0.17)	0.195	0.324 (0.074)	<0.001	-0.007 (0.004)	0.127	-0.007 (0.005)	0.114	0.32 (0.07)	<0.001
Other vascular	-0.160 (0.19)	0.402	0.170 (0.08)	0.033	-0.004 (0.005)	0.442	-0.004 (0.005)	0.398	0.150	0.06
Constant	2.946 (0.75)	<0.001	1.82 (0.123)	<0.001	0.02 (0.007)	0.003	0.021 (0.007)	0.002	1.79	<0.001

	Dependent variable = EQ-5D-5L Index									
	Model inc Vascular Screening Tool[d]		Model inc MUST[d]		Model inc NRS2002[d]		Model inc MNASF[d]		Model inc MST[d]	
Predictors	**Coefficient (SEM)[c]**	**P value**	**Coefficient (SEM) [c]**	**P value**	**Coefficient (SEM) [c]**	**P value**	**Coefficient (SEM) [c]**	**P value**	**Coefficient (SEM)[c]**	**P value**
Vascular Tool	-0.026 (0.01)	0.011	-		-		-		-	
MUST	-		0.0005 (0.047)	0.992	-		-		-	
NRS2002	-		-		70.40 (91.95)	0.444	-		-	
MNASF	-		-		-		-0.0005 (0.057)	0.994	-	
MST	-		-		-		-		54.15 (87.10)	0.535
Gender	-0.016 (0.034)	0.648	-60.69 (86.26)	0.482	-56.96 (86.31)	0.510	-60.61 (86.66)	0.485	-58.23 (86.30)	0.50
Age	0.00 (0.001)	0.733	3.52 (3.04)	0.249	3.35 (3.05)	0.273	3.52 (3.06)	0.251	3.51 (3.04)	0.249
Smoker	-0.077 (0.046)	0.096	199.13 (115.20)	0.085	200.46 (115.06)	0.082	199.08 (115.36)	0.085	198.93 (115.09)	0.085
Venous	0.017 (0.086)	0.845	8.599 (207.13)	0.967	9.28 (205.87)	0.964	9.03 (208.01)	0.965	14.11 (206.11)	0.945
Aneurysmal	0.099 (0.074)	0.185	-15.95 (180.35)	0.930	-24.69 (180.54)	0.891	-15.83 (181.64)	0.931	-24.50 (180.8)	0.892
PAD	-0.024 (0.064)	0.707	82.01 (151.80)	0.589	78.48 (151.73)	0.605	82.09 (152.05)	0.590	79.95 (151.75)	0.599
DM limb	0.021 (0.064)	0.742	132.10 (153.43)	0.390	129.67 (153.32)	0.398	132.12 (153.68)	0.391	129.40 (153.40)	0.400
Other vascular	-0.089 (0.07)	0.206	15.81 (165.63)	0.924	15.54 (164.68)	0.925	16.07 (165.43)	0.923	14.03 (164.76)	0.932
Constant	0.722 (0.101)	<0.001	-233.460 (260.75)	0.371	-239.19 (260.44)	0.359	-233.85 (262.36)	0.373	-247.99 (261.45)	0.344

[a] GLM model family for LOS model that included results of the malnutrition screening tool (MST) and malnutrition Universal Screening Tool (MUST) assessments (both coded as 1 = at risk and 0 = not at risk) was Poisson and link was log; [b] GLM model family for LOS model that included results of the vascular screening tool, Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF) assessments (both coded as 1 = at risk and 0 = not at risk) was Inverse Gaussian and link was power $^{-2}$; [c] SEM = Standard Error of the Mean
[d] Regression model for EQ-5D-5L model that included results of the vascular screening tool, malnutrition screening tool (MST), malnutrition Universal Screening Tool (MUST) Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF) assessments (both coded as 1 = at risk and 0 = not at risk) was ordinary least squares (OLS).

Table 31: Binary Logistic Regressions results

	Dependent variable = Discharge Destination									
	Model inc vascular screening tool		Model inc MUST		Model inc NRS2002		Model inc MNASF		Model inc MST	
Predictors	**OR (SE)[a]**	**P value**	**OR (SE) [a]**	**P value**	**OR (SE) [a]**	**P value**	**OR (SE) [a]**	**P value**	**OR (SE)[a]**	**P value**
Vascular tool	2.66 (0.56)	0.083	-		-		-		-	
MUST	-		0.58 (0.30)	0.295	-		-		-	
NRS-2002	-		-		2.38 (0.74)	0.005	-		-	
MNASF	-		-		-		1.0 (0.003)	0.821	-	
MST	-		-		-		-		2.36 (0.71)	0.004
Gender	0.94 (0.38)	0.872	0.89 (0.28)	0.698	0.96 (0.30)	0.90	0.94 (0.29)	0.843	0.98 (0.31)	0.937
Age	1.01 (0.01)	0.653	1.00 (0.01)	0.774	1.00 (0.01)	0.90	1.01 (0.01)	0.641	1.00 (0.01)	0.710
Smoker	1.02 (0.52)	0.964	0.55 (0.27)	0.215	0.55 (0.27)	0.22	0.55 (0.27)	0.217	0.53 (0.26)	0.194
Venous	0.26 (1.2)	0.26	0.45 (0.40)	0.363	0.41 (0.37)	0.32	0.44 (0.39)	0.349	0.44 (0.39)	0.356
Aneurysmal	0.501 (1.19)	0.56	0.52 (0.38)	0.369	0.41 (0.3)	0.22	0.49 (0.35)	0.313	0.40 (0.29)	0.206
PAD	0.29 (1.19)	0.25	1.26 (0.66)	0.655	1.17 (0.62)	0.76	1.21 (0.63)	0.714	1.19 (0.63)	0.748
DM limb	0.496 (1.10)	0.52	0.91 (0.50)	0.863	0.82 (0.45)	0.72	0.85 (0.46)	0.759	0.80 (0.44)	0.684
Other vascular	0.294 (1.13)	0.28	1.02 (0.60)	0.974	0.87 (0.52)	0.82	0.90 (0.52)	0.853	0.84 (0.50)	0.771
Constant	4.53 (4.4)	0.73	0.25 (0.24)	0.147	0.22 (0.20)	0.10	0.21 (0.2)	0.10	0.17 (0.17)	0.067

	Dependent variable = In-hospital Complications									
	Model inc vascular tool		Model inc MUST		Model inc NRS2002		Model inc MNASF		Model inc MST	
Predictors	**OR (SE)[a]**	**P value**	**OR (SE) [a]**	**P value**	**OR (SE) [a]**	**P value**	**OR (SE) [a]**	**P value**	**OR (SE) [a]**	**P value**
Vascular tool	5.41 (0.63)	0.007	-		-		-		-	
MUST	-		0.87 (0.38)	0.754	-		-		-	
NRS2002	-		-		1.85 (0.56)	0.039	-		-	
MNASF	-		-		-		1.00 (0.14)	0.945	-	
MST	-		-		-		-		0.64 (0.20)	0.159
Gender	1.42 (0.36)	0.329	0.99 (0.30)	0.970	1.03 (0.31)	0.916	1.02 (0.31)	0.956	0.98 (0.30)	0.951
Age	1.001 (0.012)	0.938	1.00 (0.01)	0.956	0.99 (0.01)	0.825	1.00 (0.01)	0.973	1.00 (0.01)	0.965
Smoker	1.16 (0.460)	0.746	1.17 (0.45)	0.678	1.21 (0.47)	0.626	1.18 (0.46)	0.673	1.19 (0.46)	0.654
Venous	0.254 (1.204)	0.255	0.43 (0.38)	0.340	0.40 (0.35)	0.300	0.43 (0.38)	0.337	0.39 (0.34)	0.282
Aneurysmal	0.850 (0.767)	0.833	1.30 (0.80)	0.670	1.17 (0.72)	0.796	1.31 (0.80)	0.661	1.36 (0.83)	0.618
PAD	1.21 (0.652)	0.772	1.19 (0.62)	0.736	1.17 (0.72)	0.796	1.18 (0.61)	0.755	1.20 (0.63)	0.726
DM Limb	0.817 (0.654)	0.758	1.11 (0.59)	0.842	1.06 (0.56)	0.913	1.09 (0.58)	0.869	1.11 (0.59)	0.843
Other vascular	1.016 (0.72)	0.982	0.80 (0.48)	0.716	0.74 (0.44)	0.609	0.77 (0.45)	0.653	0.76 (0.45)	0.638
Constant	0.054 (1.169)	0.013	0.28 (0.26)	0.169	0.26 (0.24)	0.147	0.26 (0.24)	0.141	0.31 (0.28)	0.200

[a] OR (SEM) = Odds ratio (standard error of the mean)

6.4 Discussion

This is the first study that has aimed to develop a malnutrition screening tool for use specifically within the vascular disease inpatient population following previous research presented in 5.3.2 Validity of the screening and assessment tools which revealed that four commonly used malnutrition screening tools (MUST, MST, NRS-2002 and MNA-SF) did not perform well in terms of concurrent, discriminant and convergent validity.

The new tool that was developed consists of six items and shows good diagnostic accuracy according to AUC and high sensitivity when a cut off score of ≥2 is implemented against a comprehensive dietitian's assessment. Specificity didn't meet the a-priori level of 60% and has the tendency to incorrectly classify well-nourished participants as malnourished, which has implications in terms of unnecessary referrals for full nutrition assessment by a nutritional professional and hence unnecessary utilisation of resources. Whilst this is an issue, the high sensitivity indicates that the tool can correctly classify those participants who warrant further assessment and given the impact of poor nutritional health in these patients, higher sensitivity at the expense of specificity can be justified.

When developing a new instrument, it is important to determine whether it is an improvement on existing instruments. When compared to the existing four screening tools examined, the new tool had improved Sn, PPV and NPV along with an improved kappa value when compared to the reference assessment. Specificity was lower than existing tools, however this was deemed of lower importance than the higher sensitivity and the tools ability to correctly classify individuals who were at risk of malnutrition. The AUC was also higher indicating a better diagnostic accuracy than the other tools. These results combined indicate that the new tool has more optimal concurrent validity in vascular surgery patients

than the other tools examined. Similarly, the new tool showed better discriminant and convergent validity with statistically significant associations with all four outcomes (in-hospital complications, discharge destination, LOS and EQ5D-5L Index), whereas the other tools were inconsistent. The MUST did not show any significant associations, the MST was associated with 1 outcome, the NRS-2002 with 2 outcomes and the MNA-SF with 3 outcomes. Correlations between the new tool and LOS and EQ5D-5L Index were stronger compared to those observed in the MNA-SF and NRS-2002.

When multivariate analyses were conducted the new tool was significantly associated with three (LOS, EQ5D-5L Index, and in-hospital complications) of the four outcomes explored, as was the NRS-2002 (LOS, discharge destination, in-hospital complications). Whilst both tools showed an association with in-hospital complications, the OR was higher for the new tool than the NRS-2002 (OR (SEM) 5.41 (0.63), p=0.007 vs OR (SEM) 1.85 (0.56), p=0.039). The MST and MUST were associated with 2 (LOS and discharge destination) and 1 (LOS) outcome respectively, whereas the MNA-SF did not have any significant associations when confounders were considered.

When all validity results are examined, the new tool outperforms the four existing tools in the vascular surgery population and therefore is more appropriate for use in the identification of 'at risk' patients and implementation into clinical practice is justified.

Exploratory factor analysis is a commonly used statistical method for developing instruments and measures in the psychology field and health sectors. It has the ability to reduce a large number of variables (or factors) into a smaller set of variables, examine the relationship between variables, evaluate construct validity, address multi-collinearity and develop theoretical constructs (278). Given the aim of this study, it was an appropriate

method to employ. Sample size is an important consideration when undertaking EFA and there is debate on how to determine a minimum sample size. Tabachnick & Fidell (296) suggested that a minimum sample size of 300 is required for factor analysis where as another method is the subject to item ratio, where the "rule of thumb" often used is 10:1 (297). The current study had a sample of 322, which exceeds the minimum sample using both guidelines. It has been suggested that multiple approaches be employed to determine factor extraction (278). In this study two approaches were used: Kaisers criteria (eigenvalue>1) and the scree test, the latter being the best choice (297). Rotation method is also an important decision, with Orthogonal varimax rotation being the most commonly used and was used in this study. This method produces factor structures that are uncorrelated and produces more easily interpretable results (297). In the current study, sixteen items loaded onto 2 factor structures indicating a tool of sixteen items. A sixteen-item instrument was deemed to contravene the premise that a screening tool should be quick to administer, inexpensive and non-invasive to ensure burden on resources and on patients is minimised. Hence a decision was made to reduce the number of items based on parsimony principles to include items that are common to the majority of screening tools, issues that are prominent in the vascular disease population and those that loaded highly during the factor analysis. Nutritional biochemistry analyses are not routinely included in a malnutrition screening tool due to their invasiveness and the costs associated with the laboratory analysis. However it is known that vascular surgery patients have a high prevalence of micronutrient deficiencies (116, 162, 170) and previous work presented in chapter 4 revealed a high prevalence of suboptimal micronutrient status, particularly for vitamin C. Serum albumin level loaded highly (0.8305) in the factor analyses, hence its inclusion in the proposed tools. The use of serum albumin as a nutritional marker is

controversial due to the significant number of variables in a clinical setting that can affect albumin levels rendering it less useful as a nutritional marker in that setting (291, 292). The inclusion of serum albumin could have affected the level of specificity of the tool however in this study, low albumin was only included in the presence of a normal CRP level and hence would be considered a more reliable indicator of nutritional status than when CRP is elevated indicating inflammation which impacts negatively on albumin level (291). Another important consideration is that serum albumin continues to be a significant marker of clinical outcomes and hence its inclusion appeared warranted when developing a tool that is aimed to be predictive of clinical outcomes (293-295).

When it comes to statistical model selection, multivariable regression modelling is commonly used, with logistic regression being the common method for predicting binary outcomes such as whether a patient is malnourished or not (298). The current study opted to not employ this method to develop the screening model due to the method of how the resultant tool needed to be applied in the clinical setting. Malnutrition screening tools are administered on admission, 'at the bed-side' or even by the patient themselves. Hence a simple scoring system with a threshold at which nutritional risk is indicated is warranted. Prediction modelling using regression methodology results in coefficients and equations which are difficult to implement in routine practice and would also not enable the comparison of the newly developed tool to existing screening tools.

Newly created tools require validation to determine whether the performance of the tool is precise and generalizable when conducted in a population external to the sample in which it was created. In the current study, we were unable to undertake validation in a separate sample due to resource and time constraints and so an internal cross-validation using the k-

fold method (k=10) for the four candidate tools was conducted. The AUC from ROC analyses (diagnostic accuracy) was the performance indicator employed in the 10-fold with an average of the AUC being used as the final measure. A study by Bradley (285) concluded that AUC should be used as the preference for single number evaluation of machine learning algorithms when compared to the more conventional accuracy measures. Random subsampling was conducted to minimise estimation bias and ensured that there was no overlap of data used for validation in the same "fold". Discrimination of the tools was assessed using the mean AUC, with calibration being assessed using the Brier score which is appropriate for binary variables.

It is important that both discrimination and calibration of predictive models is examined which was the case in the current study. In the clinical setting Sn and Sp of the model is also of relevance due to the impact on diagnosis and subsequent referral and resource utilisation. In this study, discrimination, calibration as well as Sn and Sp were examined which can be considered a strength of the study. With malnutrition screening, Sn is of high importance to ensure patients in need of nutritional support are identified accurately and is given higher priority than Sp (191). A tool can have good discriminatory accuracy but suboptimal Sn, rendering it inadequate for implementation in the clinical setting (288).

It is important to consider the strengths and limitations of the study. Robust methodology, including the use of polychoric correlations within the EFA, orthogonal rotation method and the use of both scree plot and eigenvalues to determine the number of retained factors, was used to develop the new malnutrition screening. Regression modelling for developing predictive models is a preferred method, however given the proposed implementation of the tool to be administered by untrained personnel, a simple scoring system with a cut-

point to determine the presence of risk was required which is not possible with regression modelling.

A limitation of the study is the method of validation employed. The most robust method of validation would be to validate in a population external to that which was involved in the development of the tool however this wasn't possible in the current study. While the k-fold has its limitations pertaining to small samples of performance estimation, overlapping training data and elevated type 1 error for comparison, it has been deemed an accurate performance estimation in the absence of an external validation sample. A further potential limitation is the equal weighting assigned to each item in the VMST and the use of unweighted kappa to assess diagnostic consistency which also attributes equal weighting to each item. The weighting of the individual items in the allocation of scores is an area for further exploration in the translation of the VMST into clinical practice.

6.4.1 Conclusions

In conclusion, the vascular surgery inpatient population is a nutritionally vulnerable population which requires an accurate and valid screening tool to detect nutritional risk. Four existing tools were shown in chapter 5 to not have an adequate level of accuracy or validity and hence a new malnutrition screening tool has been developed using robust methodology which has improved accuracy and validity in this patient group with the ability to predict clinical outcomes. The superior performance of the new tool compared with commonly used malnutrition screening tool justifies a change to malnutrition screening practices and the implementation of the new tool into routine clinical practice within a vascular surgery inpatient setting. Future research should focus on determining the cost comparison between screening all patients admitted to the vascular surgery unit using the

newly developed VMST in addition to the costs of full nutrition assessments on those deemed at risk versus a full nutrition assessment for all admitted patients given the high prevalence of nutritional deficits in this group. This will be discussed further in chapter 8.

Chapter 7: What are the health care costs and clinical outcomes for vascular surgery inpatients over 12-months of follow-up and can they be predicted by the Vascular Malnutrition Screening Tool?

7.1 Introduction

Poor nutritional status has been demonstrated in the literature to have a negative impact on several patient outcomes across clinical specialities, including in patients with vascular disease.

Increased rates of leg ulcers recurrence and more proximal level of limb amputations have been observed in poorly nourished vascular patients (80, 133), and poor nutritional status has also been associated with increased mortality (141, 149, 151). The majority of studies reviewed in the literature review of this thesis (presented in Table 3) have examined clinical outcomes over time periods of 30 days-6 months, with the majority at 30 days post-discharge and those that have explored mortality over a longer time period have been retrospective in design. In addition, all studies except for one were conducted in a single disease type (152). Inpatients under the care of vascular surgery units are heterogenous in their clinical pathologies and disease types and hence when implementing strategies to identify those with poor nutritional health they should be valid across all vascular disease types.

In previous work presented in chapter 4 of this thesis, vascular surgery patients with poor nutritional status were more likely to experience complications during their admission, have a longer length of stay and to be discharged to a place other than their prior residence than those who were adequately nourished. Exploration of commonly used screening tools (5.3.2 Validity of the screening and assessment tools) showed inadequate validity and

demonstrated that there was a need for a vascular disease specific malnutrition screening tool to identify patients who would require further nutritional assessment and intervention. Subsequently, the VMST was developed (Figure 3) which had an improved level of accuracy, sensitivity and specificity when compared to four commonly used malnutrition screening tools (MST, MUST, NRS-2002 and MNA-SF) and was a better predictor of short-term clinical and HRQoL outcomes, however it is not known how the VMST performs in predicting outcomes over a longer period of time. Whilst patient outcomes have been examined in the literature and in this thesis previously, no studies have been located that have explored the ability of a malnutrition screening tool to predict clinical outcomes over a longer follow-up period in vascular surgery patients.

With a rapidly ageing population world-wide, the cost of health care into the future is an important consideration and with evidence demonstrating the impact of poor nutrition on clinical outcomes, it would be reasonable to assume that poor nutrition would also impact on health care costs. Increased health care costs have been linked to poor nutritional status (as measured by a Geriatric Nutritional Risk Index (GNRI) in community-dwelling older adults over a 10-year follow-up period (299). In that study, individuals of poor nutritional status at baseline had 47% higher total costs than those who were of normal nutritional status and the GNRI was identified as being predictive of increased future health care costs. No further studies were located that explore the ability of a malnutrition screening tool to predict higher health care costs. Much of the health economic research in malnutrition has focussed on the economic costs and/or savings associated with nutrition interventions (300-303). Data presented in chapter 1 indicated that vascular surgery patients incur significant costs to the health care system. The presented data represents singular vascular disease types and the availability of health care cost data for Australian patients is limited, hence it

is worthwhile to explore health care costs incurred by a sample of Australian vascular disease patients over a 12-month period.

Therefore, to address thesis research question 4 ' What are the clinical outcomes and health care costs for vascular surgery patients over 12-months of follow-up and can they be predicted by a malnutrition screening tool developed for use in vascular surgery patients?' (2.4 Research Questions), this study aims to explore the health care costs and clinical outcomes of a sample of vascular surgery inpatients over 12-months and to determine the ability of the newly developed VMST to predict health care costs and clinical outcomes over the same time period. The health care costs examined in this study relate only to costs attributed to health care providers and medication costs. Costs such as lost productivity, personal 'out of pocket' expenses and costs related to government pensions/financial support are not accounted for in this study.

7.2 Methods

In addition to ethical and governance approval from the Southern Adelaide Health Research and Ethics Committee (approval number 258.14) and Flinders Medical Centre, governance approval was also obtained from Northern Adelaide Local Health Network (NALHN), Central Adelaide Local Health Network (CALHN) and Country Health SA (CHSA) for access to and provision of health service utilisation and costs data. Approval was also provided by the Australian Department of Health (DoH) for the provision of and usage of Medicare Benefit Scheme (MBS) and Pharmaceutical Benefit Scheme (PBS) data (approval number MI 1986).

7.2.1 Study Sample

Participants were recruited consecutively from the Southern Adelaide Health Local

Network (SALHN) Vascular Surgery Unit, Adelaide Australia according to inclusion and exclusion criteria outlined in 3.2 Recruitment. On entry into the study, consent was sought to allow access to health care data via the MBS and PBS.

7.2.2 Data collection

Twelve-month data were collected between October 2015 and August 2017. Prior to contacting participants, Oacis was consulted to check for mortality. Data were also collected from Oacis regarding admissions to the SA public health system, vascular surgery follow-up to determine whether there was documented arterial/vascular stenosis, ulcer development/deterioration, surgeries or procedures (e.g. angiogram/plasty, stenting, revascularisation), cardiovascular events and any other surgeries/procedures. Dates and details of any events were recorded. In addition to data collected via Oacis, participants were followed up via telephone during which they were asked whether they had experienced any of the listed events, in particular, admissions or events that occurred in the private health system, or outside of South Australia which are not recorded on the Oacis system. Re-admission to hospital, deterioration in or newly developed vascular conditions, surgeries/procedures and cardiovascular events were all classified as an adverse outcome for the purpose of analyses. Participants also completed the EQ-5D-5L during the phone-call. Three attempts were made to contact participants during the 1- week period following the 12-month follow-up date. When this was not successful, a questionnaire was forwarded to the participant via the mail with a reply-paid envelope to enable collection of the data. If the questionnaire was not returned within six weeks, participants were recorded as 'missing data' for the information collected via the questionnaire.

7.2.3 Health Care Costing Analysis

Out of hospital health care costs were obtained via the Medicare Benefits Scheme (MBS). The MBS covers services that are provided out-of-hospital such as General Practitioner and primary health care visits, tests and investigations, medical consultations and treatments. Medication costs were obtained via the Pharmaceutical Benefits Scheme (PBS), utilising the public subsidy paid for each medication used. All costs were collected for the 12-month period following each participant's individual discharge date from hospital at baseline. Hence, the 12-month collection start and end dates varied for each participant.

In-hospital admission, emergency department visits and outpatient data and costings were collected from each local health network in South Australia; SALHN, CALHN, NALHN and CHSALHN for each participant individually, using actual length of stay and individual encounters, complications and procedures. Inpatient encounters were costed according to Diagnosis Related Group (DRG), and attributed costs as per the Independent Hospital Pricing Authorities (IHPA) National Hospital Cost Data Collection (NHCDC) costing standards (304). The definition of the costs included within the NHCDC standards can be viewed at appendix 13. Non-admitted care was classified and costed according to the IHPA standards for Tier 2 Non-admitted care services and emergency department encounters were classified and costed according to Urgency Related Groups (URGs) as per IHPA guidelines (305). Total costs per hospital encounter were tallied to give a total hospital health care cost per participant over the twelve-month period. Hospital costings, MBS and PBS costings were all tallied to give a total health care cost for each study participant over the twelve-month follow-up period.

7.2.4 Statistical Analysis

Descriptive statistics were developed and presented as frequencies and means ± SD or as median (IQR) if non-parametric. Differences in outcomes across the vascular disease types, were examined using Kruskal-Wallis with post-hoc analyses to determine which groups were significantly different. Bonferroni adjustments were made to control for type 1 errors. Chi-square analysis or the Fishers Exact Test was used to determine differences in categorical variables (death, complications over 12months, whether readmitted in 12 months) between participants classified as 'at nutritional risk' or 'not at risk' according to the VMST. The Mann-Whitney U Test was used for exploring differences in continuous variables (time to readmission, EQ-5D-5L Utility Score, health care costs) according to risk status according to VMST. Generalised Linear Modelling (GLM) was used to test whether nutritional risk was predictive of continuous variables (time to first admission, EQ5D Index, total health care costs). Potential confounders (Age, gender, disease type and smoking status) for 12-month outcomes were examined for significant associations with the dependent variables (bivariate analyses). Confounders found to have a statistically significant relationship were then included in multivariate regression models. To identify the appropriate family for the GLM, a Modified Park Test was conducted following standard procedures with comparison of AIC/BIC to determine the link function (139). For the model where the time to first admission was the dependent variable, coefficients of predicted dependent values indicated that the Poisson family (coefficient 1.3) of GLM with a log link was appropriate for analysis. Where EQ-5D-5L Utility Score was the dependent variable, the Gamma family (coefficient: 1.833) with a log link was appropriate. The Gamma family (coefficient: 1.83) with a power 0.5 link was deemed appropriate when total health care cost was the dependent variable.

Binary logistic regression models were utilised to determine whether nutritional risk (VMST) predicted binary outcomes (1 = death during follow-up, 0 = alive at follow-up and; 1 = adverse clinical events, 0 = no adverse clinical events and; 1 = was admitted to hospital during follow-up, 0= no admission during follow-up).

7.3 Results

7.3.1 Health Care Costs

Of the 322 participants enrolled in the study, 307 participants consented to the provision of health care costs via the MBS and PBS and were subsequently included in the analysis for health care costings over the twelve months. The total health care costs (MBS, PBS and SA Health Service costs) for the 307 participants was $10,539,161.97 with median (IQR) cost of $14, 471 (5147.61, 43472.56) per participant. Across the subgroups (Table 32), median costs varied from $5991 to $22,997. A significant difference in total health costs was observed across the subgroups (p = 0.001), with the 'other' participants incurring higher costs than the aneurysmal and occlusive-other participants (p=0.002 and 0.001 respectively). The DM limb participants were also found to accrue higher costs than the occlusive-other and aneurysmal participants (p=0.001 and 0.003). Similarly, there was a significant difference across in-hospital costs (p=0.001) and out-of-hospital costs (p=0.049) across the subgroups. The median out-of-hospital costs for the 'other' group was significantly higher than the occlusive-other group (p=0.014). For in-hospital costs, the 'other' group had a significantly higher median cost that the aneurysmal (p<0.0001) and the occlusive – other groups (p<0.0001) and the DM limb group had a higher median cost than the aneurysmal (p=0.004) and occlusive-other groups (p=0.002).

Table 32: Median (IQR) Health care costs according to vascular disease subtype over 12-months

Disease Type	Total Health Care Costs ($)	Out of hospital costs ($)	In-hospital costs ($)
Venous (n=19)	8603.15 (3896.11, 32561.01)	2272.83 (460.52, 6466.95)	5309.37 (2217.81, 24831.88)
Aneurysmal (n=34)	8940.93$^{*\,\beta}$ (4168.63, 15009.19)	3775.55 (2427.18, 5812.15)	4154.42$^{*\,\ddagger}$ (1301.62, 10136.72)
PAD (n=90)	14967.16 (4062.55, 43296.14)	3469.63 (2227.05, 6078.47)	10406.63 (1364.11, 34774.99)
DM Limb (n=87)	16394.37$^{\ddagger\,\beta}$ (7226.69, 57914.35)	4418.87 (2004.03, 6695.26)	11410.06$^{\ddagger\,\beta}$ (2857.68, 47452.23)
Occlusive – other (n=26)	5991.02$^{\#\,\ddagger}$ (2660.04, 16920.60)	2068.35* (1579.54, 4745.82)	1813.28$^{\#\,\beta}$ (522.10, 15146.24)
Other (n=51)	22997.42$^{*\,\#}$ (11050.30, 57122.21)	4842.80* (2366.72, 7741.10)	16642.47$^{*\#}$ (6471.19, 51163.86)
Total sample (n=307)	14471.53 (5147.61, 43472.56)	3673.18 (1974.07, 6432.92)	8916.24 (1707.22, 35986.74)

$^{*\,\#\,\ddagger\,\beta}$ denotes statistically significant differences in costs between subgroups within the three types of health care costs.

7.3.2 Twelve-month Outcomes

Two hundred and eighteen participants (67.7%) were followed-up either by telephone or by returned questionnaire at 12-months and were able to provide the full suite of follow-up clinical and HRQoL data. Of the remaining participants, 15 (4.7%) had withdrawn from follow-up (reasons included extended travel, admission to aged care facilities, too unwell for phone calls or didn't want to be disturbed with phone calls), but agreed to data being collected from medical records and 23 (7.1%) were deceased. Sixty-six participants (20.5%) were not able to be reached by telephone and did not return the questionnaire and hence were lost to follow-up. Data were collected from medical records where possible for the 66 participants which resulted in varying participant numbers across some outcomes.

Table 33: Sample characteristics for 12-month follow-up outcomes

Variable	Total (n=322)
Males (n, %)	223 (69.3)
Females (n, %)	99 (30.7)
***Age (years)**	68.0 (48, 88)
Disease type (n, %)	
Venous	20 (6.2)
Aneurysmal	35 (10.9)
PAD	94 (29.2)
Diabetic Limb	92 (28.6)
Occlusive other	28 (8.7)
Other	53 (16.5)
Death (n=284) (n, %)	23 (8.1)
Admitted to hospital (n=281) (n, %)	157 (55.9)
***Days to first admission (n=206)**	49.5 (13,127.5)
Experienced Adverse Clinical Outcomes (n=294) (n, %)	242 (82.3)
EQ-5D-5L utility score (n= 217)	Median (IQR) 0.83 (0.69, 1.0) Mean (SD) 0.79 (0.21)

*Median (IQR)

Table 33 displays the sample characteristics and 12-month outcome data for study participants. Eight per cent of participants had died and over half were admitted to hospital, with a median time to re-admission of 49.5 days. Further analysis showed that 25.2% (52/206) of participants were re-admitted to a hospital within 14 days post discharge. The majority of participants experienced at least 1 of the adverse outcomes studied (82.3%).

7.3.3 Ability of the VMST to predict health care costs and outcomes at 12-months

Two hundred and thirty-nine participants had a full data set to allow completion of the VMST. Table 34 shows the sample characteristics of these participants. One-hundred and ninety-two participants (80.3%) were deemed at risk of malnutrition. There were no differences in the demographics (age, gender, disease type) of participants deemed at risk or not at risk. When 12-month outcomes were examined, statistically significant differences

were observed in the proportion of participants deceased at 12-months (10.1% vs 0%, p=0.027), proportion admitted to hospital (60.6% vs 43.2%, p=0.041), the proportion of participants who experienced adverse clinical outcomes (85.6% vs 71.7%, p=0.024) and the time to first re-admission (43 (12,122.5) days vs 96 (19.5, 169.0) days, p=0.011). In all these outcomes, participants deemed at risk of malnutrition had the poorer outcomes. There was also a significant difference in median (IQR) total health care costs between the two groups, with the at-risk participants costing almost double that of the not at-risk participants (p=0.024). No difference was observed in HRQoL between the groups (p=0.261).

Table 34: Sample characteristics of 239 participants who were screened using the new VMST

Variable	At risk of malnutrition (n=192)	Not at risk of malnutrition (n=47)	p value
Males (n, %)	134 (69.8)	36 (76.6)	0.378^
***Age (years)**	74 (61.5, 80)	64.0 (57.5, 77.0)	0.198#
Disease type (n, %)			0.606^
Venous	10 (5.2)	3 (6.4)	
Aneurysmal	21 (10.9)	7 (14.9)	
PAD	57 (29.7)	15 (31.9)	
Diabetic Limb	65 (33.9)	10 (21.3)	
Occlusive other	13 (6.8)	4 (8.5)	
Other	26 (13.5)	8 (17.0)	
Death (n=212) (n, %)	17/169 (10.1)	0/43 (0)	0.027^
Admitted to hospital (n=192) (n, %)	100/165 (60.6)	19/44 (43.2)	0.041^
***Days to first admission (n=206)**	43 (12, 122.5)	96 (19.5, 169.0)	0.011#
Experienced Adverse Clinical Outcomes (n=192) (n, %)	148/171 (86.5)	33/46 (71.7)	0.024^
***EQ-5D-5L Utility Score (n= 217)**	0.81 (0.58, 0.94)	0.82 (0.78, 1.0)	0.261#
***Total Health Care Costs ($)**	15896.25 (5589.69, 53995.29)	8775.18 (4665.38, 22349.58)	0.024#

*Median (IQR) ^Chi-Square Test. #Mann-Whitney U Test

Table 35 displays the results for the examination of associations between potential confounding variables (age, gender, smoking status and disease type) and the 12-month outcomes. Where death was the outcome, both age and smoking status showed significant associations (p=0.001 and p=0.028 respectively). For HRQoL (EQ-5D-5L Index), disease type was significantly associated (p=0.020) and where total health care costs was the outcome, both disease type and age showed significant associations (p=0.001 and p= 0.032 respectively). The potential confounders were not associated with time to first re-admission, adverse events or whether participants were admitted to hospital in the 12-months of follow-up.

Table 35 Associations between 12-month outcomes and potential confounders.

	12-month Outcomes					
	Death	**Admissions**	**Adverse events**	**Total health care costs**	**Time to first admission**	**EQ-5D-5L Utility Score**
Age	z= -3.452* p=0.001	z= -0.958* p=0.338	z=-1.800* p=0.072	r=0.123^ p=0.032	r= -0.08^ p=0.256	r=0.039^ p=0.570
Gender	p=0.817§	p=0.532§	p=0.392§	z=-0.222* p=0.824	z= -0.708* p=0.479	z=-0.773* p=0.439
Smoking	p=0.028§	p=0.923§	p=0.369§	z=-0.375* p=0.708	z= -0.898* p=0.369	z=-0.533* p=0.594
Disease type	p=0.753‡	p=0.274§	p=0.151‡	p=0.001#	p=0.320#	p=0.020#

*Mann-Whitney U Test, ^ Spearman's Rho Correlation, #Kruskal Wallis, §Chi-Square Analysis, ‡Fishers Exact Test

Table 36 and 37 displays the results of the GLM and logistic regression analyses for the VMST. The VMST was predictive of time taken to next admission (coefficient (SEM) 5.88e-6 (2.6e-7), p<0.0001) adverse events (OR 2.54 95%CI 1.17-5.52, p=0.019) and hospital admission (OR 2.02 95%CI 1.03-3.97, p=0.04) but not EQ-5D-5L Index (coefficient (SEM) 8.59e-6 (0.00002), p=0.708), total health care costs (coefficient (SEM) -0.003 (0.002),

p=0.191), or death (OR 1.0 95%CI 0.99-1.00, p=0.571) within the follow-up period when confounders were included.

Table 36 Generalised Linear Models investigating the association between the nutritional risk on the VMST and clinical outcomes at 12-months.

Predictors	**Coefficient**	**Standard Error**	**p value**
	Dependent Variable: Time to first admission		
VMST	$5.88e^{-6}$	2.60^{e-7}	<0.0001
Constant	7.98	0.001	<0.0001
	Dependent Variable: EQ5D-5L Index		
VMST	-8.59e-6	0.00002	0.708
Venous disease	-0.002	0.457	0.996
Aneurysmal disease	-0.577	0.398	0.147
PAD	0.347	0.341	0.308
DM Limb	0.404	0.339	0.233
Other vascular	0.352	0.365	0.335
Constant	7.74	0.308	<0.0001
	Dependent Variable: Total Health Care Costs		
VMST	-0.003	0.002	0.191
Age	1.733	0.521	0.001
Venous disease	25.522	28.271	0.367
Aneurysmal disease	16.876	25.902	0.515
PAD	67.781	21.798	0.002
DM Limb	94.355	23.001	<0.0001
Other vascular	85.345	24.699	0.001
Constant	6.725	37.921	0.859

Table 37: Results of Logistic regression analyses to examine associations between nutritional risk on the VMST and categorical 12-month clinical outcomes

	Dependent Variable: Adverse Events within 12 months		
Predictors	Odds Ratio	95% Confidence Interval	p value
VMST	2.535	1.17-5.52	0.019
Constant	2.538		0.004
	Dependent Variable: Hospital admission within 12 months		
VMST	2.02	1.03-3.97	0.04
Constant	-0.274		0.367
	Dependent Variable: Death within 12 months		
VMST	1.0	0.99-1.00	0.571
Age	1.01	0.98-1.03	0.650
Smoking Status	0.249	0.73-0.85	0.026
Constant	0.184	0.04-0.81	0.025

7.4 Discussion

This is the first study to investigate the health care costs associated with a heterogeneous sample of vascular surgery patients. It is also the first study to explore clinical and HRQoL outcomes in this patient group over 12-months and whether a vascular surgery-specific malnutrition screening tool can predict these outcomes and health care costs.

7.4.1 Health Care Costs and 12-month outcomes

The results showed that a high proportion of participants experienced adverse outcomes over the follow-up period with approximately 55% being re-admitted to hospital during that time and 83% experiencing at least one adverse outcome. Median time to re-admission was approximately 7 weeks, however further analysis showed that 25% of participants with follow-up data were re-admitted within less than 14 days. This proportion appears to be higher than that observed in the literature with reports of 18% readmission at 30 days post lower-extremity bypass (306). This is likely due to hospital admissions in this study incorporating admissions to rehabilitation which occur within 1-2 days post discharge from

in-patient services and hence inflates the proportion of early admissions. Death occurred in 8% of participants within 12-months which appears to agree with the study by Senda et al who observed a 25% mortality rate in 3 years of follow-up in a group of PAD patients (135) and reflects the burden of atherosclerotic disease in this group of patients.

Health-related quality of life was examined using the EQ-5D-5L utility score which has been described previously in 3.4.1 Health-related Quality of Life. The mean (SD) utility score in the sample was 0.79 (0.21) which is lower than the normative values (mean 0.91, SD 0.14) estimated for community-living individuals in South Australia (307) indicating that vascular surgery patients have lower health-related quality of life than the general population in South Australia.

Health care costs in this sample exceeded $10 million over the 12 months with the 'other group' having significantly higher associated health care costs, along with the DM limb group having significantly higher in-hospital costs than some of the other groups. It is not surprising that the 'other' group has high associated costs due to the inclusion of renal access patients who then underwent dialysis during the follow-up period. It is also not surprising that the DM limb group accrued higher costs given the high costs associated with diabetic foot ulcers in Australia (69). As a patient group, the vascular surgery population incurs significant cost given the chronic and multimorbid nature of the conditions managed by vascular surgeons. A systematic review examining the health care utilisation of elderly persons with multiple chronic conditions found a positive association with chronic conditions and that costs and health care utilisation increased significantly with each additional condition (308). When comparing to other health care conditions, the costs attributed to vascular disease are comparable to those attributable to cancer in Australia.

Recent research conducted for the Cancer Council of New South Wales revealed that cancer costs Australian health services approximately $6.3billion (309). When the available health care costs on vascular diseases (presented in chapter 1) are tallied, diabetic foot disease and cerebrovascular disease combined cost approximately $4 billion which doesn't account for venous disease or peripheral arterial disease which are chronic conditions associated with significant health care requirements.

7.4.2 Ability of the VMST to predict health care costs and outcomes

In clinical practice, malnutrition screening is the recommended process for identifying individuals that are at risk of malnutrition and the initiation of nutritional assessment and intervention. In 6.3.5 Comparison of the Vascular Malnutrition Screening Tool to readily available malnutrition screening tools., the newly developed VMST was examined for diagnostic agreement and validity against the dietitian's assessment and was found to have improved validity and agreement compared to commonly used screening tools. The VMST was also associated with short-term clinical outcomes, particularly LOS, complications during admission, discharge destination and health related QOL. When confounders were included, the association remained significant for LOS, health-related QOL and in-hospital complications. Again, these results were an improvement on commonly used screening tools. In this current study, the VMST was further examined to determine whether the associations between nutritional risk on the VMST and clinical outcomes remained at 12-months and to also determine whether the VMST was predictive of total health care costs. Significant differences were found in the proportion of participants who had died (p=0.027), experienced adverse clinical outcomes (p=0.024) and been re-admitted to hospital

(p=0.041) during follow-up with the 'at risk' of malnutrition participants having the higher proportion across each outcome. The 'at risk' group also had a much shorter time to re-admission during the follow-up at a median (IQR) of 43 (12, 122.5) vs 96 (19.5, 169) days (p=0.011). The significant associations remained for time to re-admission (p<0.0001), being admitted to hospital (p=0.04) and encountering adverse clinical outcomes (p=0.019) over 12-months during regression analyses but not for mortality. Health-related QOL was the same for both groups.

When total health care costs were examined according to VMST, the 'at risk' group had a significantly higher median cost compared to the 'no risk' group ($15896.25 (5589.69, 53995.29) vs $8775.18 (4665.38, 22349.58), p=0.024). However, when confounders were included, the association was no longer significant (p=0.191). Being older age and having PAD, diabetic limb or "other" vascular disease were significantly associated with higher total health care costs.

Overall results indicate that the VMST has predictive ability when it comes to clinical outcomes at 12-months indicating that it has promise for translation into clinical practice.

7.4.3 Strengths and Limitations

When considering future research and translation into clinical practice it is important to consider the strengths and limitations of this study. This study is the first of its kind to investigate longer-term clinical and health care outcomes in the vascular surgery population. It is also the first study to examine the ability of a vascular disease specific malnutrition screening tool to predict clinical outcomes and health care costs in this patient group. The study has a large sample that is heterogeneous and therefore representative of the spectrum of vascular disease. A further strength is the use of reliable and robust data

from the MBS, PBS and South Australian Local Health Networks in the determination of health care costs.

Study limitations are related to the data that was not available to calculate total health care costs, primarily, health care utilisation in the private sector was not included. In addition, any public 'in-hospital' costs outside of South Australia were not included. Hence, health care costs are likely to be under-estimated in this study.

Self-reported data relating to clinical outcomes were also included in this study, particularly data regarding admission to private hospitals, surgeries and procedures conducted in the private sector and changes in vascular disease where vascular review was conducted in the private sector. This may have some influence on the reliability of data such as timelines and dates (eg hospital admissions) which should be considered when interpreting results. Future research should incorporate a method to access private health care and health care outside of SA Health utilisation data as well as cost data from private health funds. Adverse events and admission to hospital were analysed as a dichotomous variable (yes/no) and this did not allow exploration of outcomes that are specific to disease types which is an important consideration for further research.

7.4.4 Future directions

The VMST has good validity and predictive ability for short-term outcomes and shows significant associations with being re-admitted to hospital, a shorter time frame to re-admission and adverse clinical outcomes when confounders were accounted for. Future research should also examine the cost-effectiveness of whether identification of malnutrition using the VMST and appropriate intervention will lead to a reduction in health expenditure amongst vascular surgery patients as cost-effectiveness in this patient group is

yet to be explored. Research in this area within other patient groups is also limited. A systematic review examining cost-effectiveness of malnutrition screening published in 2016, was unable to draw definitive conclusions as only 3 studies were eligible for review and the methods and patients included were too heterogenous (310). A systematic review examining the costs of malnutrition in institutionalised and community dwelling older adults included 5 studies that examined the impact of health care interventions on malnutrition costs after identifying that malnutrition incurs significant health care costs (311). The impact of malnutrition screening/identification of malnutrition was not considered, and interventions varied including nutritional supplements, education and vitamin supplements. Positive effects on costs were observed in some studies, with the costs of the interventions being offset by reduced hospital admissions and medical visits. However due to the limited number of studies, the authors were not able to draw firm conclusions. Research within general surgery patients has shown that within the clinical setting, every $1 spent on nutrition therapy for hospitalised patients saves $52 in hospital dollars, with 75% of surgeons believing that nutrition input reduces complications (312). We could postulate that given the research presented in this thesis highlights the negative impact of undernutrition on outcomes, that financial investment in nutrition intervention would yield cost savings in vascular surgery patients. Overall, literature regarding the cost-effectiveness of identifying and treating malnutrition is limited and an important gap in nutrition research.

It is appropriate to conclude that the VMST warrants consideration for translation into clinical practice including examination of cost-effectiveness.

Chapter 8: Discussion

8.1 Summary of Research Findings

The research presented in this thesis is the first to explore the nutritional status and prevalence of sarcopenia in a heterogeneous sample of vascular surgery inpatients. A high prevalence of undernutrition was observed during a comprehensive dietitian's assessment (75%) which was utilised as the reference standard within this thesis. Suboptimal micronutrient status (>44% with suboptimal zinc, iron, vitamin D or vitamin C) was particularly prevalent. Both undernutrition according to the dietitian's assessment and undernutrition according to suboptimal micronutrient status was found to be associated with poorer outcomes, in particular a longer hospital LOS, increased likelihood of in-hospital complications and increased likelihood of discharge to a destination other than their place of residence (e.g. residential aged care). Only a small proportion (5%) were classified as having sarcopenia which is lower than in the literature and likely attributable to differences in the methods employed to diagnose sarcopenia.

Research conducted as part of this thesis was the first to evaluate commonly used malnutrition screening tools that have been examined in other surgical specialties to determine whether they were valid in vascular surgery patients. The validity of the PG-SGA, a commonly used nutrition assessment tool, was also explored. In all cases, the comprehensive dietitian's assessment was the reference standard. The results showed that neither tool performed adequately in terms of diagnostic accuracy and consistency, concurrent, convergent and discriminant validity. The ability of the four screening tools (MST, MUST, MNA-SF and NRS-2002) to predict discharge outcomes was variable. The conclusion drawn from these results was that a screening tool specific for vascular surgery

patients was warranted as the tools examined did not meet an acceptable level of validity likely due to the absence of parameters that are relevant to the vascular surgery population, such as micronutrient status which was found to be a key issue in this sample and functional capacity/physical activity which has been shown to be an issue in the literature (17, 105).

Exploratory Factor Analysis and k-fold cross validation techniques were utilised to develop a malnutrition screening tool specifically for use within the vascular surgery population. This research is the first to develop an instrument (VMST) for use in this highly vulnerable patient group, which has good sensitivity (87%), fair diagnostic accuracy and consistency which were all improved compared to the existing tools that were examined. The VMST also has improved discriminant and convergent validity whilst being predictive or a number of short-term (discharge) outcomes (LOS, HRQoL, in-hospital complications) and outcomes at 12-months post discharge (whether re-admitted to hospital or not and the time taken to re-admission, whether adverse events were experienced).

Examination of health care costs revealed that the study sample accrued a total cost of $10,539,161.97 in public health spending. This value doesn't include costs accrued in the private health system, in-hospital costs accrued outside of South Australia, or any 'out of pocket' expenses covered by the participant themselves relating to out of hospital costs such as over the counter medication. Hence, the total cost is likely to be under-estimated in this thesis, but it is indicative of a population group that is associated with high health care costs. The 'other' vascular group and the DM limb group were the more 'expensive' groups accruing higher median costs than other vascular disease types which was not surprising given the inclusion of renal access patients and associated dialysis and the high costs associated with DM foot ulcers in Australia (69).

Following on from the results of this body of research, it is important to consider the future implications of the findings and how the VMST will be utilised in clinical practice. Currently within the SA Health acute care setting, malnutrition screening is completed on admission by ward nursing staff using the MUST. This research has shown that the MUST is not valid in vascular surgery patients as it is not able to identify the patients who are at risk of malnutrition, hence it is reasonable to consider the implementation of the VMST in this patient group. Completion of the VMST in clinical practice would require the inclusion of serum albumin, CRP and vitamin C levels which traditionally contradicts the premise that malnutrition screening should be non-invasive and use routinely collected data (204). However, in the vascular surgery unit studied, serum albumin and CRP are routine measures included in the admission blood tests ordered by the surgical team, with local vascular surgeons indicating that these would be routine measures in the vascular surgery arena. So, albumin and CRP are arguably routinely collected data, does not increase burden on the patient and doesn't incur additional costs which is also another important consideration for malnutrition screening. Currently, vitamin C level isn't routinely measured and hence this would incur additional health care costs at approximately $15.00 per patient screened, but not additional phlebotomist resourcing as it can be collected during routine blood collection. The other parameters collected within the VMST are already routinely collected by nursing staff during current malnutrition screening processes and hence would not necessitate a change in nursing staff practice or increase burden on staff or patients. Theoretically, the implementation of the VMST would result in an additional health care cost of $15.00 per patient for the vitamin C level plus the costs associated with staff time (nursing) to access and read the biochemical test results (an additional 1 to 2 minutes of nursing staff time) and the resources required to provide training to staff to complete the

VMST. Whilst the costs associated with applying the VMST could be deemed small, implementation of the screening tool would result is more patients being identified as requiring dietetic input and hence there would be an increase in dietetic service-related costs, some of which would be related to assessments of 'false positive' patients. Future work is necessary to examine whether the additional costs of dietetic input are offset by the benefits to the patient and/or the health care system. A cost-benefit analysis has not been conducted as part of this thesis as this requires implementation of the malnutrition screening process which is beyond the scope of this thesis. However, the results have shown that vascular surgery patients are costly in terms of health care dollars and that those who were identified 'at risk' on the VMST had poorer outcomes upon discharge but also at 12-month follow-up. So, it would be reasonable to assume that correct identification of 'at risk' patients would enable timely interventions to occur with the aim to address issues and improve outcomes over the short and long-term. A relatively small financial investment in screening has the potential to lead to cost-savings via appropriate intervention strategies. At this stage, we can only postulate that this would be the case and a cost-benefit analysis should be conducted to investigate this further.

This body of research showed that the majority of participants had nutritional deficits so there could be an argument that routine malnutrition screening in vascular surgery patients isn't warranted given the majority would be deemed 'at risk' and require a full assessment by a dietitian. If this was the case, there would be cost savings related to nursing staff resources to complete the screening, including the interpretation of biochemistry. There would be an increase in dietetic resource utilisation in order to assess all patients, however based on the results of this research, only 1 in 5 patients (79% of participants had at least one deficit (vitamin C)) would receive an assessment by a dietitian who wouldn't require

one. Whilst this could be viewed as unnecessary utilisation of dietetic resources, it would be important to examine the differences in costs between implementing malnutrition screening to identify 79% of participants with a deficit versus routine nutrition assessment by a dietitian whereby 1 in 5 would not have been necessary.

8.2 Future directions

This research has led to the development of a malnutrition screening tool specifically for use on vascular surgery patients, hence it is important to consider future directions regarding potential changes to clinical practice and future research.

The next step would be to explore the translation of this research into clinical practice using an established translational research framework to determine whether the implementation of the screening tool would work in the environment for which it was developed and to determine what conditions or factors impact on whether implementation is successful or unsuccessful. A translational research framework has been developed by the SAX Institute (313), consisting of seven steps, starting with idea generation which has already developed from the research presented in this thesis.

Whilst the VMST has been shown to be valid, it is important to explore the feasibility, whether the tool is practical to implement and acceptable in the inpatient setting (313). Research in the literature has shown low completion of malnutrition screening in the clinical setting. In a study of nursing staff in an Australian hospital, only 61% of screens were completed on a gastroenterology ward and 17% on a general medical ward with nursing staff listing time pressures, higher prioritisation of other documentation (e.g. Observation charts) and a lack of recognition of the value of, or need for a screening tool (314). They also cited training and making a tool 'simpler' as enablers to successful completion (314). A

formalised implementation process was undertaken in a second study in Australia to improve compliance in completing a nutrition risk screening program by nursing staff across six hospital sites (315). Whilst they found a significant increase in compliance from 7.1% to 37.9% in 12 months ($p<0.001$) overall compliance remained well below the target of 75% that the authors were aiming for and a need for more regular education, auditing and established ward routines and practices were reported (315). It is imperative that all relevant stakeholders are involved in this step, including nursing and medical staff and potentially patients to be reflective of a broad range of views and experiences (313).

Following on from examining the feasibility of the VMST, it is important to explore efficacy and whether the implementation of the VMST would make a positive difference to patient outcomes (313). Questions such as whether the screening process can initiate appropriate referrals to dietetic services and that appropriate interventions are available, was the screening and referral process delivered as planned? During this step of the process, cost and resource implications should also be examined (313). Given the potential for increased workload for dietetic services due to more appropriate screening with the VMST, it is important to ensure that there is sufficient dietitian availability and sufficient nutrition support to enable appropriate interventions and whether the impact on patient outcomes warrants the additional resources.

If deemed efficacious, the replicability and adaptability of the screening process using the VMST should be examined and whether the screening process is effective in improving patient outcomes (313). To enable this, a randomised trial comparing outcomes of patients who were screened using the VMST and managed via the resultant pathways to outcomes in patients who receive usual care would be necessary. This would allow exploration not only

of the impact on direct patient outcomes, but also allow assessment of costs relative to benefits.

Finally, future considerations for the VMST surround the ability of the tool to be digitalised in-line with the local transition to electronic health records and incorporation of such instruments into the software platforms utilised by health care settings. There is also the potential for consideration of developing the tool into an app format suitable for mobile devices for use by health care practitioners.

8.3 Strengths and Limitations of the Research Presented in this Thesis

It is important to consider the strengths and limitations of the research presented in this thesis when planning future research.

Firstly, the sample of vascular surgery patients who took part in the study was relatively large and included patients across a range of pathologies that are managed under a vascular surgery team. Most studies in vascular surgery patients focus on single pathologies and hence are less generalisable to all patients. When investigating health service practices such as malnutrition screening in vascular surgery patients, it is important to ensure that the range of pathologies are captured and that the malnutrition screening is valid across the whole group rather than needing different screening practices for sub-groups of patients within a service which is not feasible.

A wide range of parameters were collected to determine nutritional status in the study participants. Traditional methods such as weight status/history, changes in appetite and dietary intake were included as well as more unique parameters that are not routinely used

in the clinical setting, namely micronutrient status and assessment of sarcopenia. The wider range of parameters was crucial in this patient population as it revealed the primary nutritional issue for the participants was micronutrient deficits, which is not routinely investigated and hence goes under-diagnosed. A high proportion of the patients were overweight and obese and hence undernutrition would not have been detected without the inclusion of micronutrient assessment. To determine sarcopenia, three parameters were measured to assess muscle mass (DEXA), function (gait speed) and strength (grip strength) which were then used in the algorithm recommended by the EWGSOP to diagnose sarcopenia (92). The EWGSOP consensus is a well-recognised method for determining sarcopenia and includes the three facets of muscle mentioned above. This is a strength compared to most studies in vascular surgery patients (Table 4) who have used CT imagery only to determine muscle mass and have not accounted for function or strength. It explains why the prevalence of sarcopenia was much lower in this study than in those presented in Table 4.

A key outcome of this body of research is the development of the Vascular Surgery Malnutrition Screening Tool (VMST). Robust methodology was employed to develop the VMST, including the use of polychoric correlations within the EFA to account for the categorical variables, orthogonal rotation method and the use of two methods to determine the number of retained factors (scree plot and eigenvalue) (281). It is important that both discrimination and calibration of predictive models is examined which was the case in the development of the VMST, as well as sensitivity and specificity which is a strength in this study.

The healthcare costs of participants were explored in this study using robust, nationally collected data from the MBS and PBS which accounts for the costs of medical services and pharmaceuticals covered by the Australian Government with data collected and managed by the Australian Department of Health. In addition, health-related costs for in-hospital services were collected from local health networks which is again robust data using standardised methods for attributing costs based on diagnosis related groups and associated in-direct costs (304).

Consideration of the limitations of the work presented in this thesis is important, with an obvious one being the method of validation employed for the VMST. The most robust method of validation would be to validate in a population external to that which was involved in the development of the tool (external validation) however this wasn't possible in the current study due to insufficient resources and time constraints. While the k-fold has its limitations, in particular, small samples of performance estimation, overlapping training data and elevated type 1 error for comparison, it is an accurate performance estimation in the absence of an external validation sample and hence was selected for use in this study. Whilst the VMST hasn't been externally validated, the k-fold validation has shown that the VMST is an improvement on previously available malnutrition screening tools. Further research could be undertaken in an external population to determine whether items within the VMST should receive different weightings within the scoring system to further improve its validity.

There are other limitations within this research that may have affected the results presented. Firstly, since the analyses were completed for results chapters 4 and 5, the criteria for determining a low BMI for older adults (>65 years) have changed. In this study, a

BMI of < 22kgm^2 was employed to determine low BMI in participants aged over 65 years (222), however more recent guidelines suggest a BMI of 24-31kgm^2 is optimal in older adults (316). The impact of this within the research presented is that the prevalence of low BMI in study participants could have been under-estimated compared with if the more recent guidelines were applied.

In order to collect data to determine the validity of commonly used malnutrition screening tools in the study participants (chapter 5), a pooled questionnaire was completed by nursing staff to reduce burden for nursing staff and patients (one questionnaire as opposed to four separate screening tools) and reduce bias during data collection. Inter-rater reliability (IRR) testing of the nursing staff involved wasn't undertaken which is a limitation in this study. Inter-rater reliability testing would determine the agreement in the data collected between the different nursing staff involved and hence determine the level of consensus in the information collected. As this wasn't undertaken, the level of consensus wasn't determined and hence there may have been differences in how the data were collected which would affect the robustness of the data presented in chapters 5 and 6. In addition, IRR testing was not undertaken for the completion of the PG-SGA, only upper-arm anthropometric measures collected by the research dietitians, which were subsequently not included in this thesis. Inadequate completion or reporting of IRR testing has been observed in other tool development and validation studies (191, 210, 317-319) with a systematic review published in 2013 finding only 13% of 199 articles examining the SGA reported IRR (320). Any implementation of the VMST must include inter-rater reliability testing to ensure reliability. Whilst there is a question as to whether there was sufficient consensus between nursing staff, the questions in the questionnaire were very clear and nursing staff were well trained in completing the questions and physical measures (body weight and ulna length).

Similarly, the dietitians involved in the completion of the PG-SGA all received training from the one experienced dietitian which would minimise the differences between assessors, however it is noted as a study limitation and should be noted for further research.

To explore patient outcomes over 12-months (chapter 7), data were collected from the Oacis system but as this only captures information related to utilisation of SA Health services, patient recounts were also collected to determine whether any outcomes had occurred within the private health sector or outside of South Australia. When outcomes were reported by participants that weren't included in the Oacis data, the outcome was recorded as an event, however as timelines could not reliably be determined information was not recorded for 'time to admission'. The impact of this is that the number of participants (n) varies across the variables collected at 12-months which could affect results; however, sample numbers are still relatively large across the variables.

To conclude, there is an increasing prevalence of vascular disease with significant health care burden associated with the management of this patient group. Links between nutrition and poor vascular health are well known and in more recent times, the prevalence of undernutrition in this patient group has been unearthed along with the negative outcomes associated with undernutrition. Poor dietary intake in vascular patients has been well-reported (177, 178, 321) and hence nutrition and dietetic input to improve the nutritional health of these patients is critical and has potential to improve patient outcomes, quality of life and reduce health care spending. This thesis presents original research that is the first to comprehensively examine the nutritional status of a heterogenous sample of vascular surgery inpatients and explore the validity of commonly used malnutrition screening tools to determine their appropriateness at identifying those patients at risk of nutritional issues.

Additionally, this study is the first to develop a malnutrition screening tool (VMST) for use specifically in vascular surgery patients that has improved validity and ability to predict clinical and health care cost outcomes. Future research should focus on exploring the potential implementation of the VMST and subsequent impact of nutrition screening and dietetic input on vascular surgery inpatients.

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Appendices

Appendix 1: Search Strategies for literature review questions

Search strategy for literature review question 1 (What is the prevalence of malnutrition (undernutrition and sarcopenia/suboptimal muscle mass) in vascular disease patients and how does it affect clinical outcomes?

#	Searches
1	Body Mass Index/ or Body Weight/ or Waist-Height Ratio/ or Body Height/ or Waist Circumference/ or Body Size/ or Anthropometry/ or Body Composition/ or Body Size/ or Waist-Hip Ratio/ or Body Weight/ or Body Fat Distribution/ or Malnutrition/ or Overweight/ or Obesity/ or Body Weight.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2	("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcop?en* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "skeletal muscle mass" or over-nutrition or "over nutrition" or "over nourish*" or "under nourish*" or malnutrition).tw,kf.
3	1 or 2
4	vascular diseases/ or aneurysm/ or aortic aneurysm/ or aortic aneurysm, abdominal/ or aortic aneurysm, thoracic/ or arterial occlusive diseases/ or diabetic angiopathies/ or diabetic foot/ or peripheral vascular diseases/ or peripheral arterial disease/ or Intermittent Claudication/
5	(peripheral adj3 disease*).tw,kf.
6	((foot or feet or limb* or toe* or leg*) adj3 isch?emi*).tw,kf.
7	claudica*.tw,kf.
8	((aort* or abdomin* or thorac* or thorax) adj3 aneur?sm*).tw,kf.
9	(diabet* adj3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)).tw,kf.
10	or/4-9

11	3 and 10
12	(hospital* or inpatient*).tw,kf.
13	(patient* adj4 (admitted or admission)).tw,kf.
14	(operati* or preoperati* or perioperati* or postoperativ* or surg* or presurg* or perisurg* or postsurg*).tw,kf.
15	su.fs.
16	or/12-15
17	11 and 16
18	(exp infant/ or exp child/ or adolescent/) not (exp adult/ or young adult/)
19	(child* or infan* or preschool* or pre-school* or adolescen* or teen* or p?ediatric*).ti.
20	exp animals/ not humans/
21	(rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or swine or horse* or equine or monkey*).ti.
22	(case reports or comment or editorial or letter or news).pt.
23	or/18-22
24	17 not 23
25	11 not 23
26	limit 24 to english
27	limit 25 to english
28	1 and 10
29	28 and 17
30	29 not 23
31	limit 30 to english

Scopus:

TITLE-ABS-KEY (("Body mass index" OR bmi OR "Body weight" OR "height" OR "anthropomet*" OR "body shape" OR "waist-hip ratio" OR "body fat percentage" OR "muscle mass" OR "fat free mass" OR "body fat" OR "fat mass" OR "lean body mass" OR

lbm OR lbw OR "body weight" OR "body distribution" OR "body fat distribution" OR "muscle distribution" OR "skeletal muscle" OR "body mass" OR malnutrition OR malnourish* OR undernourish* OR starv* OR sarcop*en* OR "skin fold*" OR "body composition" OR overweight OR obese OR "excess weight" OR "skeletal muscle mass" OR "over nutrition" OR "over nourish*" OR "under nutrition" OR "under nourish*") AND ((peripheral W/3 disease*) OR ((foot OR feet OR limb* OR toe* OR leg*) w3 AND isch*emi*) OR claudica* OR ((aort* OR abdomin* OR thorac* OR thorax) W/3 aneur*sm*) OR (diabet* W/3 (ulcer* OR limb* OR foot OR toe* OR wound* OR infection* OR angiopath*)) OR ((vascular OR venous OR arterial OR occlusive) W/2 (disease* OR condition* OR insufficien* OR ulcer*)))) AND NOT (TITLE ((rat OR rats OR mice OR murine OR mouse OR rodent* OR pig OR pigs OR swine OR bovine OR swine OR horse* OR equine OR monkey* OR child* OR infan* OR preschool* OR "pre-school*" OR adolescen* OR teen* OR p*ediatric*))) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , " re ")) AND (LIMIT-TO (LANGUAGE , "English "))

Cochrane:

("Body mass index" or BMI or "Body weight or low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcop?en* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or "over nourish*" or "under-nutrition" or "undernourish*" or "under nourish*") AND ((peripheral NEAR/3 disease*) OR ((foot or feet or limb* or toe* or leg*) NEAR/3 isc$emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) NEAR/3 aneur$sm*) OR (diabet* NEAR/3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) NEAR/2 (disease* or condition* or insufficien* or ulcer*)))

Cinahl:

#	Query	Limiters/Expanders
S1	TI ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or	Search modes - Boolean/Phrase

	LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR AB ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2	

	(disease* or condition* or insufficien* or ulcer*)))) OR MW ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*))))	
S2	TI ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or	Narrow by Language: - english Search modes - Boolean/Phrase

	"over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR AB ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR MW ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or	

	malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*))))	
S3	TI ((("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR AB ((("Body mass index" or BMI or "Body weight" or	Narrow by SubjectAge: - all adult Narrow by Language: - english Search modes - Boolean/Phrase

	“low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR MW ((("Body mass index" or BMI or "Body weight” or “low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcopaen* or sarcopen* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "protein calorie deficiency" or "protein-calorie deficiency" or "skeletal muscle mass" or "protein deficiency" or "protein energy deficiency" or "protein-energy deficiency" or over-nutrition or "over nutrition" or "over nourish*" or "under-nutrition" or "under-nourish*" or "under nourish*") AND ((peripheral N3 disease*) OR	

	((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*))))	

Database(s): PsycINFO

#	Searches
1	Body Mass Index/ or Body Weight/ or Waist-Height Ratio/ or Body Height/ or Waist Circumference/ or Body Size/ or Anthropometry/ or Body Composition/ or Body Size/ or Waist-Hip Ratio/ or Body Weight/ or Body Fat Distribution/ or Malnutrition/ or Overweight/ or Obesity/ or Body Weight.mp.
2	("Body mass index" or BMI or "Body weight" or "low body mass" or "height" or "anthropomet*" or stature or physique or figure or "body shape" or "height-for-weight" or "weight-for-age" or "waist-hip ratio" or "body fat percentage" or "muscle mass" or "fat free mass" or "body fat" or "fat mass" or "lean body mass" or LBM or LBW or "low body weight" or "body distribution" or "body fat distribution" or "muscle distribution" or "skeletal muscle" or mass or malnourish* or undernourish* or starv* or sarcop?en* or "skin fold*" or "skin fold thickness" or "body composition" or overweight or obese or "excess weight" or "skeletal muscle mass" or over-nutrition or "over nutrition" or "over nourish*" or "under nourish*" or malnutrition).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3	1 or 2
4	vascular diseases/ or aneurysm/ or aortic aneurysm/ or aortic aneurysm, abdominal/ or aortic aneurysm, thoracic/ or arterial occlusive diseases/ or diabetic angiopathies/ or diabetic foot/ or peripheral vascular diseases/ or peripheral arterial disease/ or Intermittent Claudication/
5	(peripheral adj3 disease*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
6	((foot or feet or limb* or toe* or leg*) adj3 isch?emi*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7	claudica*.mp.

8	((aort* or abdomin* or thorac* or thorax) adj3 aneur?sm*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
9	(diabet* adj3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
10	or/4-9
11	3 and 10
12	(child* or infan* or preschool* or pre-school* or adolescen* or teen* or p?ediatric*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
13	(rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or swine or horse* or equine or monkey*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
14	or/12-13
15	11 not 14
16	limit 15 to english

Search strategies for literature review question 2 (Are individuals with vascular disease at risk of poor micronutrient status?)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

#	Searches
1	Vitamin A/ or beta carotene/ or thiamine/ or riboflavin/ or Niacin/ or nicotinamide/ or Pantothenic Acid/ or Vitamin B 6/ or Pyridoxine/ or Folic Acid/ or Vitamin B 12/ or Biotin/ or Ascorbic Acid/ or Vitamin D/ or 25-hydroxyvitamin d/ or calcitriol/ or vitamin E/ or alpha-tocopherol/ or micronutrients/
2	Trace elements/ or Iron/ or ferritins/ or copper/ or magnesium/ or zinc/ or selenium/
3	avitaminosis/ or exp ascorbic acid deficiency/ or vitamin a deficiency/ or exp vitamin b deficiency/ or exp vitamin d deficiency/ or exp vitamin e deficiency/ or exp vitamin k deficiency/
4	or/1-3
5	(("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) adj3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)).tw,kf.
6	4 or 5
7	vascular diseases/ or aneurysm/ or aortic aneurysm/ or aortic aneurysm, abdominal/ or aortic aneurysm, thoracic/ or arterial occlusive diseases/ or diabetic angiopathies/ or diabetic foot/ or peripheral vascular diseases/ or peripheral arterial disease/ or Intermittent Claudication/
8	(peripheral adj3 disease*).tw,kf.
9	((foot or feet or limb* or toe* or leg*) adj3 isch?emi*).tw,kf.
10	claudica*.tw,kf.

11	((aort* or abdomin* or thorac* or thorax) adj3 aneur?sm*).tw,kf.
12	(diabet* adj3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)).tw,kf.
13	((vascular or venous or arterial or occlusive) adj2 (disease* or condition* or insufficien* or ulcer*)).tw,kf.
14	or/7-13
15	6 and 14
16	Postoperative Complications/ or Postoperative Care/
17	Preoperative Care/
18	Perioperative Care/
19	Hospitalization/
20	Inpatients/
21	exp hospital units/
22	(Hospital* or inpatient*).tw,kf.
23	(patient* adj4 (admitted or admission)).tw,kf.
24	(operati* or preoperati* or perioperati* or postoperativ* or surg* or presurg* or perisurg* or postsurg*).tw,kf.
25	su.fs.
26	or/16-25
27	15 and 26
28	(exp infant/ or exp child/ or adolescent/) not (exp adult/ or young adult/)
29	(child* or infan* or preschool* or pre-school* or adolescen* or teen* or p?ediatric*).ti.
30	exp animals/ not humans/
31	(rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or swine or horse* or equine or monkey*).ti.
32	(case reports or comment or editorial or letter or news).pt.
33	or/28-32
34	15 not 33
35	27 not 33
36	limit 34 to english language
37	limit 35 to english language

MEDLINE SEARCH 2

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

#	Searches
1	Vitamin A/ or beta carotene/ or thiamine/ or riboflavin/ or Niacin/ or nicotinamide/ or Pantothenic Acid/ or Vitamin B 6/ or Pyridoxine/ or Folic Acid/ or Vitamin B 12/ or Biotin/ or Ascorbic Acid/ or Vitamin D/ or 25-hydroxyvitamin d/ or calcitriol/ or vitamin E/ or alpha-tocopherol/ or micronutrients/
2	(("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) adj3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)).tw,kf.
3	vascular diseases/ or aneurysm/ or aortic aneurysm/ or aortic aneurysm, abdominal/ or aortic aneurysm, thoracic/ or arterial occlusive diseases/ or diabetic angiopathies/ or diabetic foot/ or peripheral vascular diseases/ or peripheral arterial disease/ or Intermittent Claudication/
4	(peripheral adj3 disease*).tw,kf.
5	((foot or feet or limb* or toe* or leg*) adj3 isch?emi*).tw,kf.
6	claudica*.tw,kf.
7	(diabet* adj3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)).tw,kf.
8	((vascular or venous or arterial or occlusive) adj2 (disease* or condition* or insufficien* or ulcer*)).tw,kf.
9	((aort* or abdomin* or thorac* or thorax) adj3 aneur?sm*).tw,kf.
10	or/4-9
11	1 or 2
12	10 and 11

13	(exp infant/ or exp child/ or adolescent/) not (exp adult/ or young adult/)
14	(child* or infan* or preschool* or pre-school* or adolescen* or teen* or p?ediatric*).ti.
15	exp animals/ not humans/
16	(rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or swine or horse* or equine or monkey*).ti.
17	or/13-16
18	12 not 17
19	limit 18 to english
20	avitaminosis/ or exp ascorbic acid deficiency/ or vitamin a deficiency/ or exp vitamin b deficiency/ or exp vitamin d deficiency/ or exp vitamin e deficiency/ or exp vitamin k deficiency/
21	19 and 20

Scopus:

(TITLE-ABS-KEY ((("Vitamin A" OR "beta carotene" OR retinol OR "Vitamin B1" OR "Vitamin b 1" OR thiamine OR thiamin OR "Vitamin B2" OR "Vitamin B 2" OR riboflavin OR "Vitamin B 3" OR "vitamin B3" OR niacin OR nicotinamide OR "Vitamin B 5" OR "Vitamin B5" OR "Pantothenic Acid" OR pantothenate OR "Vitamin B 6" OR "vitamin b6" OR pyridoxine OR "Vitamin B 9" OR "vitamin b9" OR folate OR "Folic Acid" OR "Vitamin B 12" OR "vitamin b12" OR cobalamin OR biotin OR "Vitamin C" OR "ascorbic acid" OR "Vitamin D*" OR "25-hydroxyvitamin d*" OR calciferol OR calcitriol OR "vitamin E" OR "alpha-tocopherol" OR "vitamin k" OR micronutrient* OR "micro nutrient*" OR "Trace element*" OR iron OR ferritin* OR copper OR magnesium OR zinc OR selenium) W/2 (deficien* OR deficit OR low OR inadequa* OR adequa* OR insufficien* OR sufficien* OR excessive OR high OR optimal* OR optimum OR normal OR "sub-optimal*" OR "sub-optimum" OR suboptimal* OR ideal OR status OR amount OR total OR quantit*)) AND ((peripheral W/3 disease*) OR ((foot OR feet OR limb* OR toe* OR leg*) W/3 isch*emi*) OR claudica* OR ((aort* OR abdomin* OR thorac* OR thorax) W/3 aneur*sm*) OR (diabet* W/3 (ulcer* OR limb* OR foot OR toe* OR wound* OR infection* OR angiopath*)) OR (("vascular" OR venous OR arterial OR occlusive) W/2 (disease* OR condition* OR insufficien* OR ulcer*))))) AND NOT (TITLE ((rat OR rats OR mice OR neuropathy OR murine OR mouse OR rodent* OR pig OR chicken OR pigs OR swine OR bovine OR swine OR horse* OR equine OR monkey* OR poultry OR child* OR haem* OR nephro* OR stroke OR neurological OR pulmonary OR nerve* OR infan* OR preschool* OR "pre-school*" OR adolescen* OR teen* OR p*ediatric*))) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , " re ") OR LIMIT-TO (DOCTYPE , " ip ")) AND (LIMIT-TO (LANGUAGE , "English "))

Cochrane Library:

(("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) NEAR/3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral NEAR/3 disease*) OR ((foot or feet or limb* or toe* or leg*) NEAR/3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) NEAR/3 aneur*sm*) OR (diabet* NEAR/3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) NEAR/2 (disease* or condition* or insufficien* or ulcer*)))

CINAHL

#	Query	Limiters/Expanders
S1	TI ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or	Search modes - Boolean/Phrase

	limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR AB ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR MW ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or	

	"vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*))))	
S2	TI ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR AB ((("Vitamin A" or	Narrow by Language: - english Search modes - Boolean/Phrase

	"beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR MW ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*"	

	or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*))))	
S3	TI ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR AB ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or	Narrow by SubjectAge: - all adult Narrow by Language: - english Search modes - Boolean/Phrase

	"vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*)))) OR MW ((("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) N3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)) AND ((peripheral N3 disease*) OR ((foot or feet or limb* or toe* or leg*) N3 isch*emi*) OR claudica* OR ((aort* or abdomin* or thorac* or thorax) N3 aneur*sm*) OR (diabet* N3 (ulcer* or limb* or foot or toe* or wound* or infection* or	

	angiopath*)) OR ((vascular or venous or arterial or occlusive) N2 (disease* or condition* or insufficien* or ulcer*))))	

Database(s): **PsycINFO**

Search Strategy:

#	Searches
1	Vitamin A/ or beta carotene/ or thiamine/ or riboflavin/ or Niacin/ or nicotinamide/ or Pantothenic Acid/ or Vitamin B 6/ or Pyridoxine/ or Folic Acid/ or Vitamin B 12/ or Biotin/ or Ascorbic Acid/ or Vitamin D/ or 25-hydroxyvitamin d/ or calcitriol/ or vitamin E/ or alpha-tocopherol/ or micronutrients/
2	Trace elements/ or Iron/ or ferritins/ or copper/ or magnesium/ or zinc/ or selenium/
3	avitaminosis.mp. or exp ascorbic acid deficiency/ or vitamin a deficiency.mp. or exp vitamin b deficiency/ or exp vitamin d deficiency/ or exp vitamin e deficiency/ or exp vitamin k deficiency/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
4	1 or 2 or 3
5	(("Vitamin A" or "beta carotene" or retinol or "Vitamin B1" or "Vitamin b 1" or Thiamine or thiamin or "Vitamin B2" or "Vitamin B 2" or Riboflavin or "Vitamin B 3" or "vitamin B3" or Niacin or nicotinamide or "Vitamin B 5" or "Vitamin B5" or "Pantothenic Acid" or pantothenate or "Vitamin B 6" or "vitamin b6" or Pyridoxine or "Vitamin B 9" or "vitamin b9" or Folate or "Folic Acid" or "Vitamin B 12" or "vitamin b12" or Cobalamin or Biotin or "Vitamin C" or "ascorbic acid" or "Vitamin D*" or "25-hydroxyvitamin d*" or calciferol or calcitriol or "vitamin E" or "alpha-tocopherol" or "vitamin k" or micronutrient* or "micro nutrient*" or "Trace element*" or Iron or ferritin* or copper or magnesium or zinc or selenium) adj3 (Deficien* or deficit or low or inadequa* or adequa* or insufficien* or sufficien* or excessive or high or optimal* or optimum or normal or "sub-optimal*" or "sub-optimum" or suboptimal* or ideal or status or amount or total or quantit*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
6	4 or 5
7	(peripheral adj3 disease*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
8	((foot or feet or limb* or toe* or leg*) adj3 isch?emi*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

9	((aort* or abdomin* or thorac* or thorax) adj3 aneur?sm*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
10	(diabet* adj3 (ulcer* or limb* or foot or toe* or wound* or infection* or angiopath*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
11	((vascular or venous or arterial or occlusive) adj2 (disease* or condition* or insufficien* or ulcer*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
12	or/7-11
13	6 and 12
14	(rat or rats or mice or murine or mouse or rodent* or pig or pigs or swine or bovine or swine or horse* or equine or monkey*).ti.
15	13 not 14
16	limit 15 to english

Cochrane:

(vascular diseases or aneurysm or aortic aneurysm or aortic aneurism or abdominal aneurysm or abdominal aneurism or thoracic arterial occlusive disease or thoracic arterial occlusive disease or diabetic angiopathies or diabetic foot or peripheral vascular diseases or peripheral arterial disease or Intermittent Claudication) AND (Vitamin A or beta carotene or retinol or Vitamin B1 or thiamin or Vitamin B2 or Vitamin B 2 or Riboflavin or vitamin B3 or Niacin or nicotinamide or Vitamin B 5 or Vitamin B5 or Pantothenic Acid or pantothenate or vitamin b6 or Pyridoxine or vitamin b9 or Folate or Folic Acid or Vitamin B 12 or vitamin b12 or Cobalamin or Biotin or Vitamin C or ascorbic acid or Vitamin D or 25-hydroxyvitamin d or calciferol or calcitriol or vitamin E or alpha-tocopherol or vitamin k or micronutrient or Trace element or Iron or ferritin or copper or magnesium or zinc or selenium)

Search strategy for literature review question 3 (What malnutrition screening tools are valid and/or reliable for use in patients undergoing surgery?)

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

#	Searches
1	malnutrition/
2	Nutrition Assessment/
3	((screening or assessment) adj2 tool).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	1 or 2
5	3 and 4
6	(MUST or MST or "NRS 2002" or "MNA-SF" or "malnutrition screening tool").mp.
7	(operati* or preoperati* or perioperati* or postoperativ* or surg* or presurg* or perisurg* or postsurg*).tw,kf.
8	su.fs.
9	5 and 6
10	7 and 8
11	9 and 10

MEDLINE SEARCH 2:

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

#	Searches
1	malnutrition/
2	Nutrition Assessment/
3	nutrition.mp.
4	((screening or assessment) adj2 tool).mp.
5	1 or 2 or 3
6	4 and 5
7	("malnutrition universal screening tool" or "Malnutrition Screening Tool" or "Mini Nutritional Assessment – Short Form" or "Nutritional Risk Screening 2002").mp.
8	6 and 7
9	(operati* or preoperati* or perioperati* or postoperativ* or surg* or presurg* or perisurg* or postsurg*).tw,kf.
10	su.fs.
11	9 or 10
12	8 and 11

Psychinfo

Database(s): **PsycINFO** Search Strategy:

#	Searches
1	malnutrition/
2	malnutrition.mp.
3	nutrition.mp.
4	((screening or assessment) adj2 tool).mp.
5	1 or 2 or 3
6	4 and 5
7	("malnutrition universal screening tool" or "Malnutrition Screening Tool" or "Mini Nutritional Assessment – Short Form" or "Nutritional Risk Screening 2002").mp.
8	6 or 7

9	(operati* or preoperati* or perioperati* or postoperativ* or surg* or presurg* or perisurg* or postsurg*).tw.
10	8 and 9

Scopus

TITLE-ABS-KEY (((malnutrition OR nutrition) AND ((screening OR assessment) W/2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) AND (LIMIT-TO (LANGUAGE , "English "))

Cochrane:

((malnutrition OR nutrition) AND (screening tool OR assessment tool) OR ("malnutrition universal screening tool" OR Malnutrition Screening Tool OR Mini Nutritional Assessment-Short Form OR Nutritional Risk Screening 2002) AND (operative or operation OR preoperative or preperation OR perioperative or perioperation OR postoperative or postoperation OR surgery or surgical OR presurgery or presurgical OR perisurgical or perisurgery OR postsurgery or postsurgical))

Cinahl

	Query	Limiters/Expanders
S3	TI (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) OR AB (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) OR MW (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*)))	Narrow by SubjectAge: - all adult Narrow by Language: - english Search modes - Boolean/Phrase
S2	TI (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) OR AB (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) OR MW (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*)))	Narrow by Language: - english Search modes - Boolean/Phrase
S1	TI (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) OR AB (((malnutrition OR nutrition) AND	Search modes - Boolean/Phrase

	((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*))) OR MW (((malnutrition OR nutrition) AND ((screening OR assessment) N2 tool) OR ("malnutrition universal screening tool" OR "Malnutrition Screening Tool" OR "Mini Nutritional Assessment-Short Form" OR "Nutritional Risk Screening 2002") AND (operati* OR preoperati* OR perioperati* OR postoperativ* OR surg* OR presurg* OR perisurg* OR postsurg*)))	

Appendix 2: Article Screening Summary

Literature review question 1: What is the prevalence of malnutrition in vascular disease patients and how does it affect clinical outcomes?

	Number of articles
Medline	701
Cochrane	37
PsychInfo	134
Scopus	2128
Cinahl	610
Total	3610
Removal of duplicates	50
Total post title and abstract screen	166
Manual duplicate removal	8
Total post full text screening	17
Hand-search of references list	0
Total included in review	17

Literature review question 2: Are individuals with vascular disease at risk of poor micronutrient status?

	Number of articles
Medline	362
Cochrane	31
PsychInfo	63
Scopus	1822
Cinahl	99
Total	2377
Removal of duplicates	127
Total post title and abstract screen	246
Manual duplicate removal	15
Total post full text screening	15
Hand-search of references list	10
Total included in review	25

Literature review question 4: What malnutrition screening tools are valid and/or reliable for use in patients with undergoing surgery?

	Number of articles
Medline	87
Cochrane	57
PsychInfo	15
Scopus	491
Cinahl	345
Total	995
Removal of duplicates	132
Total post title and abstract screen	106
Manual duplicate removal	5
Total post full text screening	9
Hand-search of references list	0
Total included in review	9

Appendix 3: Quality Appraisal of Articles included in the literature review: What is the prevalence of malnutrition in vascular surgery patients and how does it impact on clinical outcomes?

Author	NHMRC level of evidence[a]	Class of evidence[b]	Quality Rating[c]	Domains									
				1	2	3	4	5	6	7	8	9	10
	Undernutrition												
	Venous Disease												
Finalyson, 2009	III-2	B	-	U	U	Y	NA	N	NA	Y	Y	Y	Y
	Diabetic Foot Disease												
Gau, 2016	II	B	□	Y	Y	Y	NA	N	NA	Y	U	Y	Y
Zhang, 2013	II	B	-	N	U	U	U	N	NA	Y	Y	Y	U
	Occlusive Disease												
Giles, 2010	III-2	B	□	Y	U	Y	NA	N	NA	U	Y	Y	N
Senda, 2018	II	B	□	Y	U	Y	NA	N	NA	Y	Y	Y	Y
	Sarcopenia												
	Aneurysmal												
Hale, 2018	III-2	B	□	Y	U	Y	NA	N	Y	Y	Y	Y	Y
Indrakusuma, 2018	III-2	B	□	Y	U	U	NA	Y	Y	U	U	Y	Y
Newton, 2018	III-2	B	□	U	U	Y	NA	N	Y	Y	Y	Y	Y
Tanaka, 2018	III-2	B	□	U	U	Y	NA	Y	Y	Y	Y	Y	Y
	Occlusive Disease												
Addison, 2018	IV	D	□	Y	Y	Y	NA	N	Y	Y	U	Y	Y
Juszscak, 2018	III-2	B	□	Y	N	Y	NA	N	Y	Y	Y	Y	Y
Matsubara, 2015	III-2	B	-	N	U	Y	NA	N	U	U	Y	N	Y
Matsubara, 2016	III-2	B	-	U	U	Y	NA	N	U	Y	Y	N	Y
Sugai, 2018	II	B	+	Y	U	Y	NA	N	Y	Y	Y	Y	Y
	Diabetic Foot Disease												
Cheng, 2017	IV	D	□	N	Y	Y	NA	N	Y	Y	Y	Y	Y
Kim, 2018	III-2	B	-	U	N	U	NA	N	Y	Y	Y	Y	Y
	Mixed Vascular Patients												
Heard, 2018	III-2	B	-	U	U	Y	N	N	Y	U	Y	U	Y

Quality Appraisal of Articles included in the literature review: Are individuals with vascular disease at risk of poor micronutrient status?

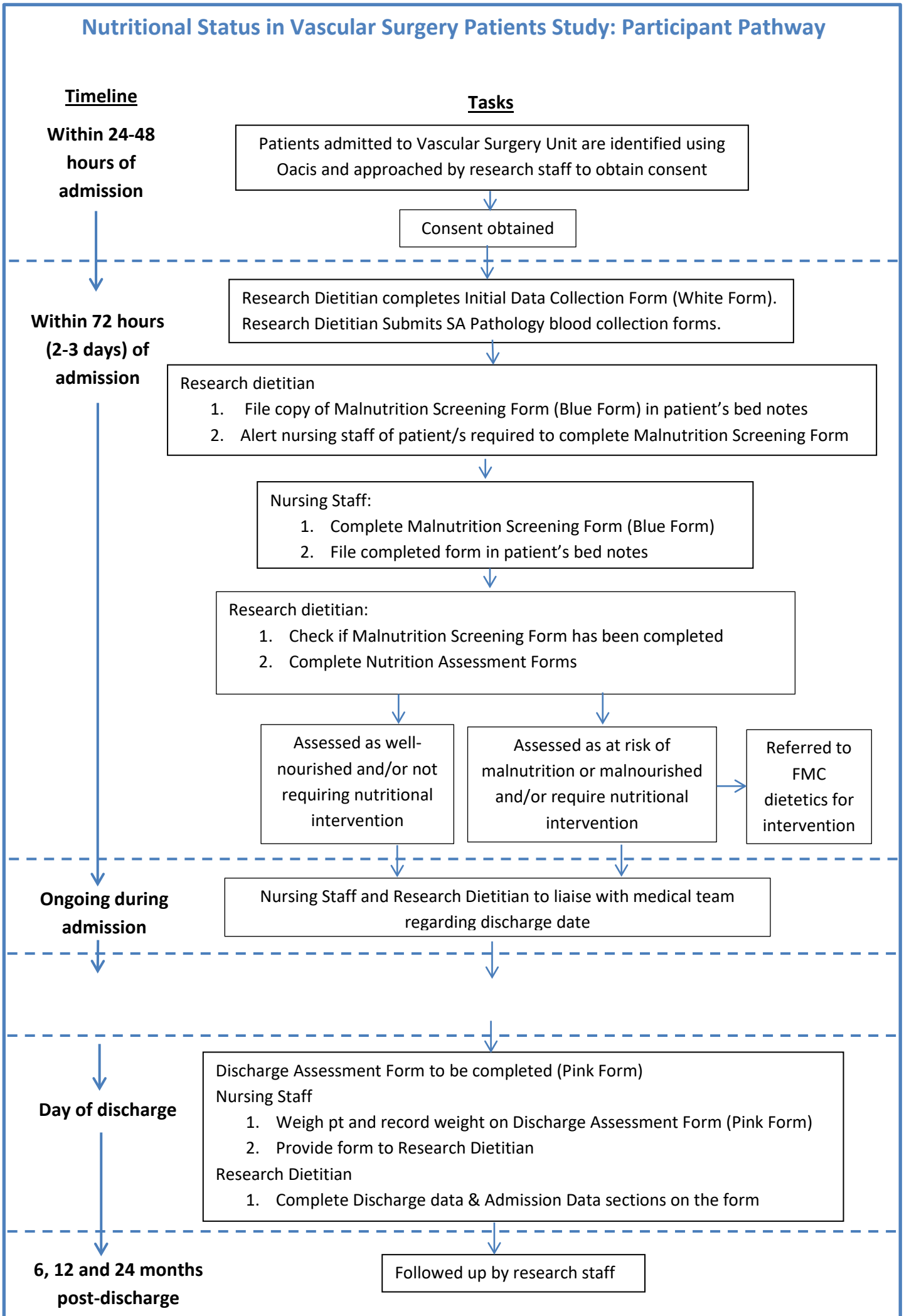
Author	NHMRC level of evidence[a]	Class of evidence[b]	Quality Rating[c]	Domains									
				1	2	3	4	5	6	7	8	9	10
	Aneurysmal Disease												
Lindqvist, 2012	IV	D	-	Y	N	Y	U	N	NA	Y	Y	U	U
Sakalihasan, 1996	IV	D	-	Y	N	U	NA	N	NA	N	Y	U	U
Warsi, 2004	IV	D	-	N	U	U	NA	N	NA	Y	N	N	Y
	Diabetic Foot Disease												
Afarideh, 2016	IV	D	+	Y	U	Y	Y	Y	NA	Y	Y	Y	Y
Bolajoko, 2017	IV	D	-	Y	N	U	NA	N	NA	Y	Y	N	Y
Caglar, 2018	IV	D	-	Y	U	N	NA	N	NA	U	N	N	Y
Feldkamp, 2018	IV	D	-	N	U	U	NA	N	NA	N	N	N	Y
Tiwari, 2013	IV	D	□	Y	U	Y	NA	N	NA	Y	U	U	Y
Wright, 2015	II	B	□	Y	U	NA	Y	N	NA	Y	Y	U	Y
Zubair, 2013	II	B	□	Y	U	Y	NA	N	NA	Y	U	Y	Y
	Venous Disease												
Agren, 1986	IV	D	-	U	U	U	N	N	NA	Y	U	U	N
Balaji & Mosely, 1995	IV	D	-	U	U	NA	NA	N	NA	N	U	U	U
Burkievcz, 2012	IV	D	-	U	U	U	NA	N	NA	Y	N	N	Y
Krejner, 2017	II	B	-	Y	U	NA	NA	N	NA	U	N	U	Y
Tobon, 2008	IV	D	-	Y	N	NA	NA	N	NA	Y	Y	Y	U
Wipke-Tevis, 1996	IV	D	-	U	N	NA	NA	N	NA	U	Y	Y	Y
	Occlusive Disease												
Bunout, 2000	IV	D	-	U	N	Y	NA	N	NA	Y	Y	U	Y
Fahrleitner, 2002	IV	D	-	Y	N	Y	NA	N	NA	Y	Y	U	U
Gaddipati, 2011	III-2	B	□	Y	U	Y	NA	N	NA	Y	Y	Y	Y
Langlois, 2001	IV	D	-	Y	N	Y	NA	N	NA	Y	Y	Y	Y
Mansoor, 2000	IV	D	-	U	N	Y	NA	N	NA	Y	Y	U	U
McDermott 2012	IV	D	□	Y	U	Y	NA	N	NA	Y	Y	Y	Y
McDermott 2014	II	B	□	Y	U	Y	U	N	NA	Y	Y	Y	Y
Vega De Ceniga, 2011	IV	D	-	Y	U	NA	NA	N	NA	N	U	N	Y
Zsori, 2013	IV	D	□	U	U	Y	NA	Y	NA	Y	Y	Y	U

Quality Appraisal of Articles included in the literature review: What malnutrition screening tools are valid and/or reliable for use in surgical patients?

Author	NHMRC level of evidence[a]	Class of evidence[b]	Quality Rating[c]	Domains									
				1	2	3	4	5	6	7	8	9	10
	Diagnostic Concordance/Agreement												
Almeida, 2012	III-2	C	□	Y	U	N	Y	U	Y	NA	Y	U	N
Badia-Tahull, 2014	III-2	C	□	Y	Y	N	Y	N	U	NA	U	U	Y
Chi, 2017	III-2	C	□	Y	Y	U	Y	U	U	NA	Y	Y	Y
Karateke, 2013	II	B	□	U	Y	U	NA	N	NA	Y	Y	U	Y
Lomivorotov, 2013	II	B	□	Y	U	U	NA	N	NA	Y	Y	U	U
Mourao, 2004	III-2	C	□	Y	Y	U	Y	N	U	NA	Y	U	Y
Van Venrooij, 2011	II	B	□	Y	N	Y	NA	N	NA	Y	Y	Y	Y
	Predictive Validity												
Shiraki, 2016	III-3	B	□	U	N	Y	NA	N	NA	Y	Y	Y	Y
Xie, 2017	III-3	B	-	U	U	Y	NA	N	NA	U	Y	Y	U

Abbreviations: [a] Level of evidence according to the NHMRC, [b] Class of evidence according to the American Dietetic Association Evidence Analysis Manual, [C] Quality rating according to the American Dietetic Association Evidence Analysis Manual Quality Appraisal Checklist, + Positive quality rating, - Negative quality rating, □ Neutral quality rating, Y – Yes the domain was adequately addressed, N – No the domain was not adequately addressed, NA – the domain was not applicable due to the study design.

Appendix 4


Nutritional Status in Vascular Surgery Patients Study: Participant Pathway
Timeline
Tasks
Within 24-48 hours of admission
Patients admitted to Vascular Surgery Unit are identified using Oacis and approached by research staff to obtain consent
Consent obtained
Within 72 hours (2-3 days) of admission
Research Dietitian completes Initial Data Collection Form (White Form).
Research Dietitian Submits SA Pathology blood collection forms.
Research dietitian
1. File copy of Malnutrition Screening Form (Blue Form) in patient's bed notes
2. Alert nursing staff of patient/s required to complete Malnutrition Screening Form
Nursing Staff:
1. Complete Malnutrition Screening Form (Blue Form)
2. File completed form in patient's bed notes
Research dietitian:
1. Check if Malnutrition Screening Form has been completed
2. Complete Nutrition Assessment Forms
Assessed as well-nourished and/or not requiring nutritional intervention
Assessed as at risk of malnutrition or malnourished and/or require nutritional intervention
Referred to FMC dietetics for intervention
Ongoing during admission
Nursing Staff and Research Dietitian to liaise with medical team regarding discharge date
Day of discharge
Discharge Assessment Form to be completed (Pink Form)
Nursing Staff
1. Weigh pt and record weight on Discharge Assessment Form (Pink Form)
2. Provide form to Research Dietitian
Research Dietitian
1. Complete Discharge data & Admission Data sections on the form
6, 12 and 24 months post-discharge
Followed up by research staff

Appendix 5

Participant Information Sheet

Non-Interventional Study - *Adult providing own consent*

Title	Are vascular surgery patients a nutritionally vulnerable group and is there a cost effective nutritional screening tool to assist in identifying the nutritionally vulnerable?
Short Title	Nutritional status in vascular surgery patients.
Protocol Number	*258.14*
Coordinating Principal Investigator/ Principal Investigator	A/Prof Michelle Miller, MNutDiet, PhD, APD,
Associate Investigator(s)	Ms Jolene Thomas, Dr Billingsly Kaambwa and Professor Ian Spark
Location	Nutrition and Dietetics, Flinders University and Vascular Surgery Unit Flinders Medical Centre

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, **Nutritional status in vascular surgery patients**. This is because you have been admitted to the Vascular Surgery Unit at Flinders Medical Centre. During this project we will be looking at how common malnutrition is in vascular surgery patients and how malnutrition may affect medical complications and health outcomes. We will also be looking at which is the best method of screening vascular patients for malnutrition when they come into hospital and the health care costs involved in this process.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want to take part in the research but in summary researchers will be asking participants a series of questions regarding their quality of life and nutritional health and will conduct a physical examination, blood test and a Dual energy Xray Absorptiometry (DEXA) scan to determine your nutritional status while you are in hospital. We will then contact you after you are discharged to repeat some of the questions and to ask questions about your vascular health, complications and use of health care services. Further details are outlined later in this brochure.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your doctor in hospital..

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to the tests and research that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Malnutrition is a common issue amongst hospital patients, and there is evidence that this may also be the case in vascular surgery patients. Poor nutritional health can have detrimental effects on overall health including increased risk of hospitalization and longer stays, infections and post-operative complications. While we suspect that malnutrition is an issue in vascular surgery patients, the difficulty is in identifying malnutrition early in admission to enable early and effective nutrition support. The aims of this study are to describe the nutritional health of vascular surgery patients at Flinders Medical Centre and to determine how common malnutrition is in vascular surgery patients. In addition to this, we aim to determine the best method for identifying malnutrition and also the effect of nutritional health on health outcomes and health care costs. It is envisaged that the results of this study will lead to the establishment of routine nutrition screening in vascular surgery patients at FMC and will provide valuable evidence for future research into optimising the nutritional health of vascular surgery patients. This study forms part of the work towards Ms Jolene Thomas (the investigator) obtaining a PhD.

3 What does participation in this research involve?

Within 24-48 hours of being admitted to the vascular surgery unit at FMC, you will be approached by the researchers to take part in this study. The researcher will describe the study and your involvement and if you agree to participate, you will be asked to sign a consent form. Following consent, research staff will access your medical records to collect information regarding your medical history, medications and current medical issues, information regarding your living situation and your age and gender.

The researcher will then ask you a series of questions regarding your nutritional health, including recent food intake, weight history and appetite. You will also be weighed and have your height measured. This visit should not take longer than 15 minutes. A 10ml blood sample from a vein in your arm will be used to measure your micro-nutrient stores. There is a potential for slight discomfort during the blood collection and a small amount of bruising afterwards but there should not be any further complications from this procedure. This will take about 5 minutes and will be collected by trained SouthPath staff.

You will be visited for a second time of approximately 40 minutes duration, during your admission by the research dietitian (Jolene Thomas or Jenni Suen). During this visit, the dietitian will assess your nutritional status using the Patient-Generated Subjective Global Assessment (PG-SGA). The PG-SGA consists of 4 questions regarding symptoms that may affect your eating, your weight history, activity and function and the types of food you are able to eat. The other part of the PG-SGA is a physical examination by the dietitian who will assess your muscle and fat stores on your limbs, face and upper back. You will also be asked a series of 5 questions regarding your quality of life. During this visit, the research dietitian will also collect the following measurements

- Your **hand grip strength**. This is measured using an apparatus called a dynomamometer where you are required to hold the apparatus in your dominant hand (unless affected by disease or disability) and squeeze the handle. This measure will be done 3 times so an average measure can be obtained.
- Your **walking speed**. This will be calculated by measuring the time it takes for you to walk a distance of 2.4m over a flat surface. We will ask you to repeat this test another two times.
- To measure your muscle mass and fat mass, **dual-energy xray absorptiometry** (DEXA) and **upper arm measurements** will be collected. The circumference of your upper arm will be measured using a tape measure. The skin fold at the back of your upper arm (Triceps Skin Fold) will be measured using a skinfold caliper. Your muscle and fat mass will also be measured by a single body scan known as a dual x-ray absorptiometry (DEXA). You will be required to lie on your back for approximately 10 minutes while the scan is being carried out. The image produced by the scan will allow researchers to determine your fat mass and fat-free mass which are important in assessing your nutritional health.
- In order for researchers to assess your food and beverage intake, you will be asked to keep the tray slips from your meal trays and to record on them the amount (nil, ¼, ½, ¾, all) that you consumed of each item over 3 days. This information will then be used by research staff to calculate your nutritional intake. This should take you no longer than 15 minutes per day for a total of 3 days.

If you are assessed as being malnourished or are deemed to be at risk of malnutrition, the research dietitian will refer you to the Flinders Medical Centre dietitians for nutrition support and education.

On the day you are discharged from hospital, you will have your weight measured on weigh scales (this will take about 2 minutes) and researchers will access your medical records to obtain details of your hospital stay.

You will be contacted via telephone by research staff at 6,12 and 24 months after your discharge so that we can obtain information regarding further hospital visits or stays since commencing in the study, medical/health complications, changes in place of residence, and changes in body weight. You will also be asked the 5 questions regarding your quality of life on each of these occasions. All of these questions will allow researchers to perform statistics to determine the impact of your nutritional health on health outcomes. It is estimated that the phone call will take up to a maximum of 10 minutes.

At the conclusion of your participation in the study, we will utilise data provided to us by the Medicare Benefits Scheme (MBS) and the Pharmaceutical Benefits Scheme (PBS) regarding your health care service usage and your medication usage. This information will be incorporated into the statistics to determine the impact of nutritional health on health outcomes and overall health care costs.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids researchers or participants jumping to conclusions.

There are no costs associated with participating in this research project, nor will any payment be involved.

4 What do I have to do?

You are not required to make any special changes or alterations to your lifestyle to participate in this study. You are able to continue with your usual medications, diet and physical activity. Your involvement does not preclude you from receiving medical care or from donating blood. If you agree to be involved in another study during the 2 years of follow up we would appreciate you contacting us to provide us with the details of the research so that we can make the necessary adjustments to our research data.

5 Other relevant information about the research project

It is anticipated that approximately 320 patients will take part in the project overall which is being run only at Flinders Medical Centre and involves researchers based at Flinders Medical Centre and Flinders University.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Vascular Surgery Unit or Flinders Medical Centre.

7 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however possible benefits may include a full nutrition assessment and early identification of nutritional issues if they are present. This will then allow early nutrition input from the Flinders Medical Centre dietitian. It is envisaged that the results of this study will allow the vascular surgery department at FMC to implement a routine nutrition screening process to assist in ensuring future patients with malnutrition are identified quickly so that nutritional support can be provided early in their admission.

8 What are the possible risks and disadvantages of taking part?

There are minimal risks and disadvantages associated with participating in this study. Listed below are the possible situations where you may feel slight discomfort.

1. Having the blood sample taken may cause some discomfort, bruising, minor infection or bleeding at the site. If this happens, it can be easily treated
2. The measuring of your triceps skin fold involves the use of a skin calliper that may cause slight discomfort for approximately 3 seconds when the calliper compresses

the skin. The likelihood of major discomfort is minimal as researchers are trained in the use of the skin callipers.

3. You are required to lie still on your back when the DEXA scan is being conducted for approximately 10 minutes. All efforts will be made to make you as comfortable as possible however, if it is causing too much discomfort, the scan can be stopped.

This research project involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 0.02mSv which is 100 times lower than the annual background dose. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk if there is one, is expected to be minimal.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms.

9 What will happen to my test samples?

A small 10ml blood sample will be collected as part of this study in order to determine the levels of micronutrients, inflammatory markers, iron, haemoglobin, proteins and electrolytes in your blood. This blood test is part of routine care and not collected solely for this study. The sample will be used for this purpose only and any unused blood sample will be discarded as per usual hospital laboratory procedures.

10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research team will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, the research team will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, the research team might consider it to be in your best interests to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

Whilst you are participating in this research project, all treatments, including medications that you are receiving as part of your ongoing care will continue,

12 What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw.

If you do withdraw your consent during the research project, the research team will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to

comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include insufficient resources or unforseen adverse events.

14 What happens when the research project ends?

On completion of the study, the results will be published in peer-review journals and/or presented at scientific meetings of relevance. They will also form part of the PhD thesis for Ms Jolene Thomas. The outcomes from the study will be made available on the Flinders University Nutrition and Dietetics web page (http://www.flinders.edu.au/sohs/sites/nutrition-and-dietetics/)

Part 2 How is the research project being conducted?

15 What will happen to information about me?

By signing the consent form you consent to the relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential and will be restricted to the use of the immediate group of researchers involved in the study. The data will be stored on site at Flinders University in secure storage for 7 years and electronic data will be stored on the secure shared drive of the Discipline of Nutrition and Dietetics, Flinders University for up to 15 years. The data may be used in the future for other studies that emanate from this study. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection for the purpose of verifying the procedures and the data. This review may be done by the relevant authorities, the institution relevant to this Participant Information Sheet, Flinders University and Flinders Medical Centre, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant research personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All data will be de-identified and presented as group data and hence individual data will not be able to be identified

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or South Australian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

16 Complaints and compensation You may feel some distress from participation in this study. If this occurs you may withdraw from this study if you wish and your care will not be affected in any way. By participating in this study you do not give up any of your legal rights.

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

As there is no intervention in this study and no pharmacological drug is being tested in this research project, there are negligible chances of any adverse effects. In case of an unexpected adverse effect, compensation may be provided in accordance with the law.

17 Who is organising and funding the research?

This research project is being conducted by Flinders University Nutrition and Dietetics and the Flinders Medical Centre Vascular Surgery Department.

18 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC).
This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher (Ms Jolene Thomas) on 0450 522 213 or any of the following people:

Clinical contact person

Name	*Professor Ian Spark*
Position	*[Head of Vascular Surgery*
Telephone	82045445
Email	*Ian.Spark@health.sa.gov.au*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Research Ethics Office
Telephone	82046453
Email	Research.ethics@health.sa.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Southern Adelaide Clinical Human Research Ethics Committee
HREC Executive Officer	Petrina Kasperski
Telephone	8204 6453
Email	petrina.kasperski@health.sa.gov.au

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Bev Stewart-Campbell
Position	Manager and Research Governance Officer
Telephone	8204 4507
Email	bev.stewart-campbell@health.sa.gov.au

Consent Form - *Adult providing own consent*

Title	Are vascular surgery patients a nutritionally vulnerable group and is there a cost effective nutritional screening tool to assist in identifying the nutritionally vulnerable?
Short Title	Nutritional status in Vascular Surgery Patients
Protocol Number	258.14
Coordinating Principal Investigator/ Principal Investigator	Associate Professor Michelle Miller
Associate Investigator(s)	Ms Jolene Thomas, Dr Billingsly Kaambwa & Prof Ian Spark
Location	Vascular Surgery Unit, Flinders Medical Centre

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purpose, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my current or future health care.

I understand that I will be given a signed copy of this document to keep.

I understand that, if I decide to discontinue the research project treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature

Form for Withdrawal of Participation - *Adult providing own consent*

Title	*Are vascular surgery patients a nutritionally vulnerable group and is there a cost effective nutritional screening tool to assist in identifying the nutritionally vulnerable?*
Short Title	*Nutritional status in Vascular Surgery Patients*
Protocol Number	*258.14*
Coordinating Principal Investigator/ Principal Investigator	*Associate Professor Michelle Miller*
Associate Investigator(s)	*Ms Jolene Thomas, Dr Billlingsly Kaambwa and Professor Ian Spark.*
Location	*Vascular Surgery Unit, Flinders Medical Centre*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *Flinders Medical Centre*

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Appendix 6 **Initial Data Collection Form**

Participant ID: _____ Participant MRN: _____

Today's Date: _____/_____/_____ Day of current admission: Day 1 2 3 4 5

Name: _____ (M / F) DOB: _____/_____/_____

Date of Admission: _____/_____/_____ Reason for Admission: _____

MHx:		
□ Hyperlipidaemia	□ Hypertension	
□ Cancer Site:_____	□ Not active □ Active	□ Past and current Tx **(Note dates, site/s, duration of Tx)** Surgery:_____ Chemotherapy: _____ Radiotherapy: _____ Hematopoietic cell transplant:_____ Bone marrow transplant : _____

Does the patient have any of the following active illnesses/conditions or treatments? *(Please tick all which apply)*			
□ Hip fracture	□ Liver Disease	□ COPD	□ Blood malignancies
□ Renal Disease	□ Diabetes	□ Cancer	□ Major abdominal surgery
□ Head injury	□ Received a bone marrow transplant		□ Stroke □ Pneumonia

Medications: (refer to reverse side for reference)	
□ Hypolipidaemic agents:_____	□ Diuretics _____
□ Anti-hypertensive: _____	□ Antibiotics: _____
□ Anti-arrhythmics:_____	□ Anti-thrombotic/ anticoagulants: _____
□ OHAs: _____	□ Insulin: _____
□ Other relevant medications: _____	

Type of Vascular patient:	□ Aneurysmal	□ Occlusive: Stage:	□ Venous
(refer to reverse side for occlusive stages)	□ Diabetic Foot Ulcers	□ Other: _____	

Living Situation:

□ Home alone □ Home with _____

□ Residential Aged Care Facility/ Nursing Home: High level care **OR** Low level care *(please circle)*

□ Other: _____

Medications:

Hypolipidaemic agents	Atrovastatin calcium (Lipotor) Cholestyramine resin (Questran Lite), Colestipol hydrochloride (Colestid Granules for Oral suspension), Ezetimbe (Ezetrol) Fluvastatin sodium (Lescol Capsules, Lescol XL)	Fenofibrate (Lipidil) Gemifibrozil (Lopid) Pravastatin sodium (Pravachol), Rosuvastain calcium (Crestor) Simvastatin (Zocor)
Diuretics	Amiloride hydrocholoride (Kaluril) Bumetanide (Burinex) Chlorthalidone (Chlorthalidone), Ethacrynic acid (Edecrin)	Eplerenone (Inspra) Frusemide (Lasix) Hydrochlorothiazide (Dithiazide) Spironolactone (Aldactone)
Anti-hypertensive	Amplodipine (Exforge, Norvasc) Candesartan cilexetil (Atacand) Captopril (Capoten) Clonidine hydrochloride (Catapres) Diltiazem hydrochloride (Cardizem CD) Diazoxide (DBL Diazoxide Injection BP) Enalapril maleate (Renitec) Eprosartan mesylate (Teveten) Felodipine (Plendil ER, Triasyn) Fosinopril sodium (Monoplus, Monopril), Minoxidil (Loniten) Hydralazine hydrochloride (Alphapress, Apresoline), Indapamide (Natrilix) Irbesartan (Avopro) Labetalol hydrochloride (Trandate) Lecanidipine hydrochloride (Zanidip)	Lisinopril dehydrate (Zestril) Losartan potassium (Cozaar) Olmesartan (Olmetec, Sevikar) Moxonidine (Physiotens), Perindopril (Coveram, Coversyl) Prazosin (Minipress) Quinapril hydrochloride (Accupril) Nifedipine (Adalat 10, Adalat 20, Adalat Oros) Methyldopa (Aldomet) Ramipril (Tritace) Sodium nitroprusside dehydrate (DBL Sodium Nitroprusside for injection BP) Telmisartan (Micardis), Telmisartan (Twynsta) Trandolapril (Gopten Valsartan hydrochlorothiazide (Co-Diovan) Verapamil (Isoptin)
Antibiotics (Anti-bacterial)	Aminoglycosides (Amikin, Nebcin, Paromomcyin) Cephalosprins Erythromycin Flagyl (metronidazole: amoebicide)	Metronidazole (IV) Methicilin Quinolones Tetracyclines
Anti-arrhythmics	Adenosine (Adenocor) Amiodarone hydrochloride (Cordarone X) Disopyramide (Rythmodan), Flecainide acetate (Tambocor)	Lignocaine hydrochloride (Xylocard) Sotalol hydrochloride (Sotacor) Verapamil hydrochloride (Isoptin Injection)
Anti-thrombotic/ Anticoagulants	Abcixmab rmc (ReoPro) Apixaban (Eliquis) Bivalirudin (Angiomax) Clopidogrel (DuoCover, Iscover) Cilostazol (Pletal) Dabigtran etexilate (Pradaxa) Dalteparin sodium (Fragmin) Danaparoid sodium (Orgaran) Dipyridamole (Persantin, Persantin SR) Dipyridamole aspirin (Asasntin SR)	Enoxaparin sodium (Clexane and Clexane Forte), Eptifibatide (Integrilin) Fondaparinux sodium (Arixtra) Lepirudin (Refludan) Prasugrel hydrochloride (Effient) Rivaroxaban (Xarelto) Ticagrelor (Brillnta) Ticlopidine hydrochloride (Tilodene) Tirofiban hydrochloride (Aggrastat) Warfarin sodium (Coumadin, Marevan)
OHAs	Acarbose (Glucobay) Acetohexamide Chloropropamide Gliclazide (Diamicron, Glyade, Nidem) Glipizide (Melizide, Minidiab), Glimepiride (Amaryl)	Glisoxepide Metformin (Diabex, Diaformin, Glucomet, Glucophage) Migitol (Glyset) Tolbutamide Voglibose
Insulin	Actrapid, Humalog (Lispro) Humulin Hypurin neutral Hypurin Isophane Protophane	Monotard Mixtard (20/80 or 30/70 or 50/50) Novorapid Repaglinide (Meglitinide, Novonorm) Ultratard

Occlusive Stages

Stage 0: Stage 1-3: Claudicant Stage 4: Rest Pain Stage 5-6: Tissue Loss

Nutrition Assessment Form

Participant ID: _____Participant MRN: _____ Today's Date: ___/____/___

Day of current admission: Day 1 2 3 4 5

Anthropometric (derived from Malnutrition Screening Form- Blue Form)

Height: _____(m)___ _____(m^2) BMI: _____(kg/m^2)

Biochemistry: Date: ___/____/___

Na (mmol/L)	
K (mmol/L)	
Cl (mmol/L)	
Cr (mmol/L)	
Albumin (g/L)	
Pre-Albumin (mg/dL)	
CRP (mg/L)	

Iron studies	
Fe (µmol/L)	
Transferrin (µmol/L)	
% Transferrin saturation (%)	
Ferritin (µg/L)	

Lipid Studies	
Total cholesterol	
HDL	
LDL	
Triglycerides	

Vitamin A (µmol/L)	
Vitamin E (µmol/L)	
Vitamin C (µmol/L)	
Vitamin D (nmol/L)	
Vitamin B12 (ng/L)	
Folate (µg/L)	
Homocysteine	

Trace elements	
Zinc (µmol/L)	
Selenium (____)	
Copper (µmol/L)	
Calcium (mmol/L)	
Magnesium (mmol/L)	
Chromium (____)	

Upper arm measurements

Attempt	**1**	**2**	**3**	**Average**
MUAC (cm)				
TSF (mm)				
Use average to calculate:				
MAMC (cm)				
cAMA (cm^2)				

MAMC (cm) = MUAC(cm) – (0.3142 x TSF (mm))

cAMA (cm^2) =

Women: $\frac{[\text{MUAC (cm)} - (3.142 \times \text{TSF (cm)})]^2}{12.56} - 6.5$

Men: $\frac{[\text{MUAC (cm)} - (3.142 \times \text{TSF (cm)})]^2}{12.56} - 10.0$

Hand Grip Strength ☐ **Not collected: Reason:_____**

Dominant hand used? ☐ YES ☐ NO: Reason_____

Attempt	**1**	**2**	**3**	
Kilograms				

Walking Speed ☐ **Not collected: Reason:_____**

Attempt	**1**	**2**	**3**	**Average**
Seconds				
Metres/sec				

DEXA

☐ Done ☐ Print out attached ☐ Not done**:** Reason_____

Nutrition Requirements	**3 Day Food Intake**
Energy Schofield equation used: _____ EER: _____kJ/day Protein Equation used: _____ EPR: _____ g/day Fluid Equation used: _____ EFR: _____ ml/day	☐ Collected ☐ Not collected: Reason:_____ ☐ Completed food intake analysis & attached print out

Appendix 7

Malnutrition Screening Form

Affix patient sticker here

Participant ID: _____ Today's Date: ___/____/___

Box 1: Anthropometric data:

Weight: _____ (kg) Time taken to weigh pt: _____(mins)

Ulna length: _____ (cm) ☐ Left arm ☐ Right arm: Reason for use_____

Wt loss without trying in last 3-6 months (*please tick answer)* ☐ YES ☐ NO ☐ UNSURE

If YES, how much (kg)? *(please circle)* 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 >15

OR ☐ UNSURE

Box 2: Mobility ***(please tick answer)***

☐ Bed or chair bound ☐ Able to get out of chair/bed but doesn't go out ☐ Goes out

Box 3: Food intake and Appetite: ***(please tick answers)***

1. Has food intake declined over the past 3 months? ☐ YES ☐ NO

(If no, proceed to Question 2)

Has food intake declined due to:

☐ Loss of appetite: Has loss of appetite been: ☐ Severe ☐ Moderate ☐ Minimal

☐ Digestive problems (e.g. constipation, diarrhoea, IBS, food intolerance)

☐ Chewing or swallowing problems (e.g. loose fitting dentures, dysphagia)

2. Has food intake declined in the previous week? ☐ YES ☐ NO

(If no, proceed Box 4)

Food intake in the previous week is approximately:

☐ 50-75% of normal ☐ 25-50% of normal ☐ <25% of normal

Box 4: Presence of disease/illness:

(ask patient the following questions or self-complete based on knowledge of patient)

1. Has the patient suffered psychological stress or acute disease in past 3 months? YES NO

Appendix 8

Ulna length (cm)

1. Ask patient to place <u>left hand</u> to touch their right shoulder.
   Please see figure below.

   <u>Exceptions:</u>
   If patient is unable to move their left arm (e.g. fractured or amputated left arm), please use right arm.
   .
2. Find the prominent bone of the wrist (styloid process) and
   the point of the elbow (olecranon process).
   Please see figure below.

3. Using a steel metal tape measure, measure the length between these two points (from the middle of the prominent bone of the wrist to the point of the elbow).
   Please see figure below.

4. Record the length in centimetres on the Malnutrition Screening Form

Image removed due to copyright restriction

Appendix 8

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Label

History

1. Weight: (see table 1 Worksheet)

Current weight_____kg

Weight **1 month** ago_____kg
OR (if 1 month data not available)
Weight **6 months** ago_____kg

During the past **2 weeks** has your weight:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

*Add score from above **with** Table 1 score* = ☐

2. Food Intake: In the **past month** I would rate my food intake (compared to my normal food intake) as:

☐ **A**. unchanged (0)
☐ **B**. more than usual (0)
☐ **C**. less than usual (1)

If C: I am now taking:
☐ normal food but less than normal in amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)^
☐ very little of anything (4)
☐ only tube feeds or only nutrition by vein (TPN) (0)#

Use highest score only = ☐

3. Symptoms: In the past **2 weeks** have you had any of the following problems which have kept you from eating:

☐ No problems eating (0)
☐ No appetite, just did not feel like eating (3)
☐ Nausea (1)
☐ Vomiting (3)
☐ Constipation (1)
☐ Diarrhoea (3)
☐ Mouth sores (2)
☐ Things taste funny or have no taste (1)
☐ Smells bother me (1)
☐ Problems swallowing (2)
☐ Feels full quickly (1)
☐ Dry mouth (1)
☐ Pain, where? (3) _____
☐ Other e.g. depression, money or dental problems (1)

_____
_____ *Additive Score* = ☐

4. Activities & Function:
Over the **past month** would you describe your activity level as:
☐ **A**. Normal, no limitations (0)
☐ **B**. Somewhat limited
☐ **C**.Little activity

If **B** would you describe it as:
☐ Not my normal self, but able to be up and about with fairly normal activities for **more than half** the day (1)
☐ Or not feeling up to most things, but in bed or sit in a chair for **less than h**alf the day (2)

If **C** would you describe it as:
☐ Pretty much bedridden, rarely out of bed, or do you do little activity and spend **most of the day** in bed or sitting in a chair(3)

Use highest score only = ☐

Additive Score of Boxes 1-4 ☐ **A**

5. Diagnoses & Disease in Relation to Nutritional Requirements
(see Table 2) Numerical Score from Table 2 ☐ **B**

6. Metabolic Demand
(see Table 3) Numerical Score from Table 3 ☐ **C**

7. Physical Examination
(see Table 4) Numerical Score from Table 4 ☐ **D**

Global Assessment (see Table 5)
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total numerical score of boxes A+B+C+D ☐

Dietitian Initials **Date**

Adapted from Scored Patient-Generated Subjective Global Assessment (PG-SGA), FD Ottery, 2000
Acknowledgement to the Society for Nutritional Oncology Adjuvant Therapy (NOAT)
& the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association

Tables & Worksheets for PG-SGA Scoring

Table 1 – Scoring Weight (wt) Loss

Only use wt loss over 6 months if wt from 1 month is unavailable

Wt loss in 1 month	Wt loss in 6 months	Points
≥ 10%	≥ 20%	4
5 - 9.9%	10 -19.9%	3
3 - 4.9%	6 - 9.9%	2
2 - 2.9%	2 – 5.9%	1
0 - 1.9%	0 – 1.9%	0

Table 1 Score (Use highest score only) ☐

Table 2 – Diagnoses & Disease

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of pressure (decubitus) ulcer, open wound, or fistula	1
Presence of trauma	1
Age greater than 65	1

Table 2 Score (additive) ☐

Table 3 – Metabolic Demand. Circle as relevant; steroid use is chronic (ie. not stat doses)

Stress	None (0 point)	Low (1 point)	Moderate (2 points)	High (3 points)
Fever	no fever	> 37.2 & < 38.2	≥ 38.2 & < 38.9	≥ 38.9
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Steroids	no steroids	low dose < 10mg prednisone equivalents/day	moderate dose ≥ 10mg & ≤ 30mg prednisone equivalents/day	high dose ≥ 30mg prednisone equivalents/day

Steroid Equivalents

No steroids	Low Dose Steroids 10mg Prednisone equivalents	Moderate Dose Steroids 20mg Prednisone equivalents	High Dose Steroids 30mg Prednisone equivalents
No Steroid medications listed in subsequent boxes	10mg Prednisolone 50mg Cortisone 40mg hydrocortisone 8mg methylprednisolone 1.5mg dexamethasone	20mg Prednisolone 100mg Cortisone 80mg hydrocortisone 16mg methylprednisolone 3mg dexamethasone	30mg Prednisolone 150mg Cortisone 120mg hydrocortisone 24mg methylprednisolone 4.5mg dexamethasone

Table 3 Score = Fever + Fever duration + Steroids (additive) ☐

Table 4 – Physical Examination. (Overall deficit)

- Ratings are used to assess degree of defecit, circle as relevent
- Weighting on score: muscle status group > fat stores group > fluid status group

	Degree of deficit rating	Nil 0	Mild 1+	Moderate 2+	Severe 3+
Muscle Status	Temples (temporalis muscle)	0	1+	2+	3+
	Clavicles (pectoralis & deltoids)	0	1+	2+	3+
	Shoulders (deltoids)	0	1+	2+	3+
	Interosseous muscles	0	1+	2+	3+
	Scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
	Thigh (quadriceps)	0	1+	2+	3+
	Calf (gastrocnemius)	0	1+	2+	3+
	Overall muscle status rating	**0**	**1+**	**2+**	**3+**
Fat Stores	Orbital fat pads	0	1+	2+	3+
	Triceps skin fold	0	1+	2+	3+
	Fat overlying lower ribs	0	1+	2+	3+
	Overall fat stores rating	**0**	**1+**	**2+**	**3+**
Fluid Status	Ankle oedema	0	1+	2+	3+
	Sacral oedema	0	1+	2+	3+
	Ascites	0	1+	2+	3+
	Overall fluid status rating	**0**	**1+**	**2+**	**3+**

Table 4 score (Overall rating, use above weighting for groups) ☐

Table 5 – PG-SGA Global Assessment Categories

Category	Stage A Well Nourished	Stage B Moderately malnourished or Suspected malnutrition	Stage C Severely malnourished
Weight	No recent weight loss or Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months. No weight stabilisation or wt gain	>5% wt loss within 1 month (or >10% in 6 months). No weight stabilisation or wt gain
Nutrient Intake	No deficit or sig. recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None or Sig. recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit or sig. recent improvement	Moderate functional deficit or recent deterioration	Severe functional deficit or recent significant deterioration
Physical Exam	No deficit or chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (eg. Severe loss of SQ tissues, possible oedema)

Global PG-SGA rating (A, B, or C) ☐

Appendix 9: EQ5D5L

Participant ID:_____ Date: ___/___/___ Assessor Name:_____

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems with walking around ❑

I have slight problems with walking around ❑

I have moderate problems with walking around ❑

I have severe problems with walking around ❑

I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑

I have slight problems with washing or dressing myself ❑

I have moderate problems with washing or dressing myself ❑

I have severe problems with washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

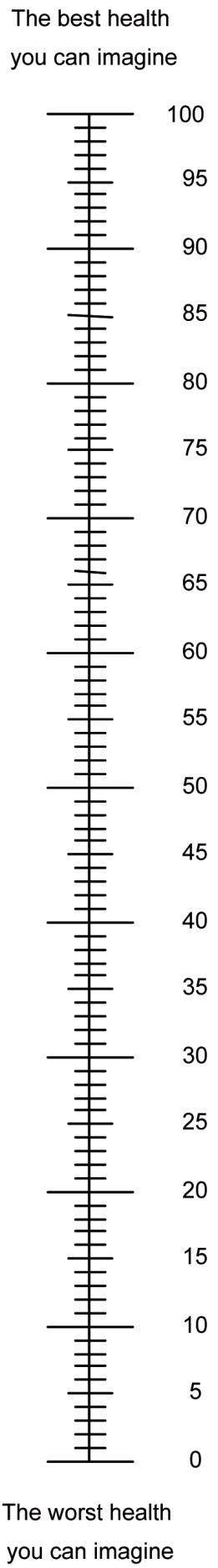
I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

Adapted from EuroQol Group, 2009, EQ-5D-5L Health Questionnaire-English version for Australia, Netherlands

Appendix 9: EQ5D5L

- We would like to know how good or bad your health is TODAY
- This scale is numbered from 0 to 100
- 100 means the BEST health you can imagine
- 0 means the WORST health you can imagine
- Mark an X on the scale to indicate how your health is TODAY
- Now, please write the number you marked in the box below



Appendix 10 Discharge Assessment Form

Participant ID: _____ Participant MRN: _____ Today's Date: ___/____/___

Anthropometric Data

Wt _____ (kg) BMI: _____(kg/m^2) Date that weight was obtained: ___/___/___

Discharge Data

Date of discharge:_____/_____/_____ LOS:_____(days)

Discharge destination: _____

Is this destination different to prior to admission? YES NO

Admissions Data

1. Did any of the following events/complications occur during admission?

(Tick and specify the event that occurred)

☐ Death - Date of death:_____ Reason for death:_____

☐ Infection ☐ Arterial/vascular stenosis ☐ Ulcer development/deterioration

☐ Surgeries/procedures

Date of surgery/procedure	Name of surgery/procedure

☐ Cardiovascular event

Date of cardiovascular event	Name of ardiovascular eent

2. Was the patient referred for nutritional input during admission? YES NO

Time from referral to dietetic input: _____(hrs) Referral reason:_____

Type of dietetic input: _____

Participant ID:_____ Date: ___/___/___ Assessor Name:_____

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems with walking around ❑
I have slight problems with walking around ❑
I have moderate problems with walking around ❑
I have severe problems with walking around ❑
I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑
I have slight problems with washing or dressing myself ❑
I have moderate problems with washing or dressing myself ❑
I have severe problems with washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

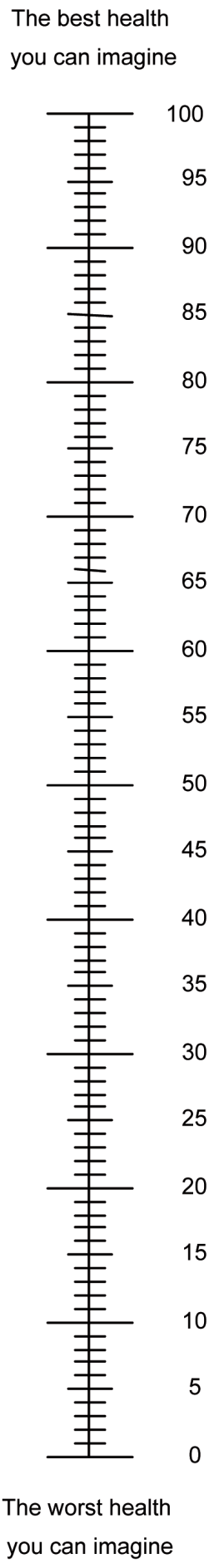
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Adapted from EuroQol Group, 2009, EQ-5D-5L Health Questionnaire-English version for Australia, Netherlands

- We would like to know how good or bad your health is TODAY
- This scale is numbered from 0 to 100
- 100 means the BEST health you can imagine
- 0 means the WORST health you can imagine
- Mark an X on the scale to indicate how your health is TODAY
- Now, please write the number you marked in the box below



12 Months Post Discharge Form

Participant ID: _____ Participant MRN: _____ Prospective 12 month date: _____

*** * * CHECK MORTALITY ON OACIS OR EPAS BEFORE CALLING PARTICIPANT * * ***

(If participant has passed away, proceed to 'Death' section on 'Event/Date/Details of the event' table below)

Date of phone call: ____/____/____

Anthropometric

Reported weight: _____kg

Ask participant:

When you left hospital, your weight was _____kg, do you think you've gained or lost weight since?

☐ gained weight ☐ lost weight ☐ maintained weight

QOL

☐ completed the attached EQ-5D-5L Questionnaire

Since discharge from hospital has the participant suffered any of the following:

Event	**Date**	**Details of the event**
Death		
Readmission to hospital		
Arterial/vascular stenosis		
Ulcer development/ deterioration		
Surgeries/procedures		
Cardiovascular event		

Data entered: Sign _____ Date _____/_____/_____

Participant ID:_____ Date: ___/___/___ Assessor Name:_____

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems with walking around ❑
I have slight problems with walking around ❑
I have moderate problems with walking around ❑
I have severe problems with walking around ❑
I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑
I have slight problems with washing or dressing myself ❑
I have moderate problems with washing or dressing myself ❑
I have severe problems with washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Adapted from EuroQol Group, 2009, EQ-5D-5L Health Questionnaire-English version for Australia, Netherlands

- We would like to know how good or bad your health is TODAY
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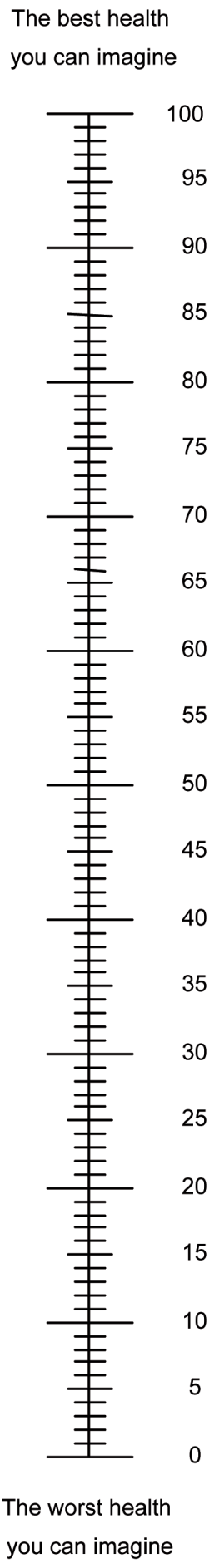
- 100 means the BEST health you can imagine
- 0 means the WORST health you can imagine
- Mark an X on the scale to indicate how your health is TODAY
- Now, please write the number you marked in the box below



Nutritional status of patients admitted to a metropolitan tertiary care vascular surgery unit

Short running title: Nutritional status of vascular surgery patients

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Running Title: Nutritional status of vascular inpatients

Abstract

Background and Objectives: Undernutrition in vascular surgery patients has a significant impact on clinical outcomes. This observational study aimed to investigate the nutritional status of a heterogeneous sample of vascular surgery inpatients and to determine the prevalence of nutritional risk, malnutrition (including nutrient deficiencies) and sarcopenia.

Methods and study design: All participants were screened for risk of malnutrition using the Malnutrition Universal Screening Tool (MUST) and assessed using the Patient-Generated Subjective Global Assessment (PG-SGA). Micronutrient status was examined via plasma/serum samples. The presence of sarcopenia was explored using an accepted algorithm incorporating gait speed, muscle mass (DEXA) and grip strength.

Results: 323 participants (69% male, mean age 67.6 ±14.1y) consented to the study.12.5% were identified as at risk of malnutrition by the MUST while 15.8% were deemed malnourished by the PG-SGA. Only 5% were diagnosed as sarcopenic. Prevalence of malnutrition was much higher when micronutrients were examined with 79% showing low vitamin C levels, 56% low vitamin D and over 40% having low zinc, vitamin B12 and folate levels. A smaller proportion were also low in selenium (19%).

Conclusions: Patients with vascular disease are a nutritionally vulnerable group. The MUST and PG-SGA did not identify the full extent of nutritional deficiencies. Further investigation is warranted to assess tool validity in this group. A number of micronutrients are crucial in these patients and hence a more comprehensive assessment that encompasses a wider range of parameters, including micronutrient status appears warranted.

Key words: vascular disease, nutritional status, micronutrient, PG-SGA, MUST.

INTRODUCTION

Vascular disease is an increasing problem with an ageing population and growing prevalence of chronic disease.[1, 2] Vascular surgery encompasses a wide range of conditions including venous disease, occlusive arterial disease, aneurysmal disease and diabetic foot infections and therefore is a heterogeneous population with varying comorbidities.

It is well understood that overweight/obesity is strongly associated with the development and progression of vascular disease including peripheral arterial disease (PAD), venous and aneurysmal disease.[3-5] However, concerning rates of malnutrition (defined as undernutrition) ranging from 61-90% [6-8] have been observed in vascular disease patients and is associated with poor clinical outcomes.[7, 9-11]

Sarcopenia is defined as the age-related loss of muscle mass and strength and has multiple contributing factors including less-than-optimal diet, bed rest or sedentary lifestyle, chronic diseases and certain drug treatments.[12] These contributing factors are common in vascular disease patients placing them at risk of sarcopenia,[12-15] which could be masked by the high prevalence of overweight and obesity in this group. Recent work has shown that a reduction in muscle mass is not limited to vascular patients with occlusive disease, with larger aortic abdominal aneurysms showing an association with a reduction in muscle mass.[16] Muscle mass and strength is crucial in the performance of activities of daily living, and in the management of vascular disease via exercise [17] hence the prevalence of sarcopenia in this population warrants further investigation.

The development of atherosclerosis and progression of vascular disease has a pro-oxidative and pro-inflammatory component which would suggest that optimal micronutrient status, particularly those micronutrients with anti-oxidative properties and/or those important in the prevention and management of wounds and ulcers is important. Micronutrient status

has been explored in vascular patients with consistent reports of suboptimal levels of vitamin D (25(OH) D), vitamin C, vitamin B12, folate and iron which worsens with disease progression.[18-21] The impact of micronutrient deficiencies are significant with higher rates of amputations observed in PAD patients with low vitamin D levels.[22] Other micronutrients such as vitamin C, vitamin A and zinc are involved in wound healing and epithelial integrity, along with immune function, hence deficiency prolongs wound healing time and contributes to reduced resistance to infection.[23]

This study aimed to investigate the nutritional status of vascular surgery inpatients and to determine and compare the prevalence of nutritional risk according to the Malnutrition Universal Screening Tool (MUST), and malnutrition (according to the Patient-Generated Subjective Global Assessment PG-SGA and also micronutrient status). The prevalence of sarcopenia was also investigated.

MATERIAL AND METHODS

Study Sample:

Participants were recruited consecutively from patients with vascular disease/conditions admitted to a metropolitan vascular surgery unit in Australia between October 2014 and August 2016. Patients admitted to the unit can undergo surgical intervention or be managed conservatively depending on their vascular condition and admitting reason. Potential participants were approached in-person by the researchers on admission to the unit where the study requirements were verbally explained and also provided in writing. If patients agreed to participate they were asked to sign a consent form prior to data collection. Participants were eligible if they were 18 years and over, able to provide informed written consent or where this wasn't appropriate, consent was able to

be obtained from the legal next of kin/guardian. Patients were excluded if admitted for day procedures only, unable to be recruited within 72 hours of admission, or were subsequently transferred to a private hospital within 72 hours. Previous participants were also excluded. Ethical approval was obtained from the Southern Adelaide Health Research and Ethics Committee (approval number 258.14) and governance approval from the participant recruitment site.

Demographic data including age, gender and vascular disease type was collected from medical records. Vascular disease types were classified as aneurysmal, peripheral arterial disease (PAD) (encompassing aorto-iliac and infra-inguinal disease), occlusive other (encompassing carotid and upper limb ischaemia), venous disease, diabetic foot infection and 'other' based on the admitting vascular surgeon's diagnosis. Those classified as other included renal access, surgical management of thoracic outlet syndrome, trauma, ulcers of mixed or unknown aetiology, admission for post-operative complications and lower limb infection not attributed to occlusive disease or diabetes.

Determination of Nutritional risk:

Malnutrition screening is conducted within the local health system using the MUST.[24] The MUST is a validated 3-item instrument to identify adults who are either malnourished or at risk of malnutrition. A score is awarded for each item; body mass index (BMI), recent weight loss and presence of acute disease with an overall score of 1 indicating low risk of malnutrition and ≥2 indicating high risk. The MUST is completed by nursing staff on admission and those with a score of ≥2 are referred to a dietitian for a full assessment.

Within 24 hours of consent being obtained, vascular surgery nursing staff

conducted a questionnaire with participants incorporating questions from the MUST. Body weight was measured using a calibrated seated weighing scales (HVL-CS Hospital Chair Scale, A&D Mercury Pty Ltd) to the nearest 0.1kg in light clothing without shoes. Ulna length was measured using a flexible non-stretch steel measurement tape to the nearest 0.5cm according to standard protocol [24] and converted to estimated height using the MUST conversion table to the nearest 1cm.[24] BMI was calculated as weight (kg) divided by the square of height (m^2) estimated from ulna length. Age-appropriate BMI cut-offs were used to classify participants as underweight, normal weight or overweight/obese for those 65 years or older (<22kg/m^2, 22-27kg/m^2, >27kg/m^2 respectively) [25] and under 65 (<18.5kg/m^2, 18.5-24.9kg/m^2, >25kg/m^2 respectively).[26] Scoring of the MUST was completed post-discharge by the research staff to allow sufficient time to pass between the assessment of nutritional status and the scoring of the screening tool to reduce bias.

Nutritional Assessment.

A full nutrition assessment using the scored PG-SGA) [27] was conducted within 72 hours of admission by a Dietitian. The PG-SGA was adapted from the Subjective Global Assessment specifically for patients with cancer [28] but has since been validated in other inpatient groups.[29-31] The scored PG-SGA is a further development of the PG-SGA incorporating a numerical score as well as providing a global rating of nutritional status. Each participant was awarded a PG-SGA score and a PG-SGA global rating of A (well nourished), B (suspected or moderately malnourished) or C (severely malnourished).

Determination of micronutrient status:

Blood samples were collected by a trained phlebotomist prior to breakfast after an overnight fast on the morning after consent was obtained. Where possible, blood samples for the research study were collected at the same time as routine blood samples for clinical care to reduce participant burden. Fasting blood samples were analysed by the hospital or state pathology service depending on the analytical test. Micronutrient status was determined as suboptimal, normal or high according to reference ranges (shown in parentheses) provided by the analysing laboratory, for iron (8-30umol/L), vitamin B12 (>260ng/L) and folate (6.5-45ug/L), vitamin A (1-3.1umol/L), vitamin C (26-85umol/L), vitamin E (12-46umol/L) vitamin D (60-160nmol/L) and the trace elements zinc (9-21umol/L) and selenium (0.8-1.64umol/L).

Identification of Sarcopenia:

Parameters used to define sarcopenia are the amount of muscle and its function measured via muscle mass, strength and physical performance.[12] Various techniques can be used to assess these parameters including dual-energy x-ray absorptiometry (DEXA) for muscle mass, handgrip strength (muscle strength) and gait speed (physical performance) which were used in this study.[12] Measurements for each parameter were converted into the relevant low/normal cut-offs and incorporated into the EWGSOP-suggested algorithm for diagnosing sarcopenia.[12] The cut-offs for each parameter are summarised in Table 1. Muscle mass was determined using the Lunar Prodigy Pro dual-energy x-ray absorptiometer (DEXA) in conjunction with Encore software version 7.5. Participants were scanned in light clothing and positioned in the supine position, feet in neutral position with hands flat by their sides. Appendicular lean soft tissue (ALST) mass was calculated as the sum of the lean soft tissue in both upper and lower limbs which was then converted to SMM (kg) according to the equation of Kim et al.[32] SMM was subsequently adjusted for height to

produce the Skeletal Muscle Index (SMI) (kg/m^2) according to the equation by Baumgartner et al.[33]

Sarcopenia was defined as SMI being less than two standard deviations below the mean of a young reference group of 229 non-hispanics as suggested by Baumgartner et al.[33]

Gait speed (metres/second) was determined using a validated a six metre walk test.[34] Participants stood with their toes positioned behind the line in non-slip footwear or bare feet depending on participant preference and medical instructions regarding footwear. Timing began with an electronic stopwatch as toes crossed the zero metre line, and ceased when toes crossed the 6 metre line. Participants walked at their usual pace and a handrail was available for the full 6 metres for safety. An average (recorded to the nearest 0.1 second) of triplicate measures was used for the determination of sarcopenia.[12]

Grip strength was measured from the dominant hand unless affected by disease or disability, using an Advanced Hand Dynomometer (Mentone Educational, Australia) with the participant standing facing forward, legs straight and feet approximately 15cm apart. If unable to stand, grip strength was collected in a seated position as this has been deemed as an appropriate alternative.[35] Participants held the dynamometer so that it did not touch the thigh and squeezed with maximum force, without swinging the arm, for three seconds. The average of triplicate measures was used in analysis. Gender specific cut-offs were adopted using data from the North West Adelaide Health Study, at two standard deviations below the mean of young adults.[36]

Statistical analysis

Analysis was conducted using SPSS for Windows version 22 (SPSS Inc, Chicago, IL). Continuous variables were assessed for normality using the Kolmogorv-Smirnov test and reported as mean (SD) or median (IQR). Sample characteristics were expressed as frequencies (n, %). Chi-square analyses to determine differences between types of vascular participants for the categorical variables gender, age categories, live in their own home, whereas Fishers Exact test was employed for the variables BMI categories, lives in aged care and lives in supported care. One-way ANOVA with Tukey post hoc test or Kruskal-Wallis test was used for continuous variables. Statistical significance was set at $p<0.05$.

RESULTS

Participant characteristics

A total of 2229 patients were admitted and screened for eligibility during the study period. Of these, 1327 were ineligible (day admissions, unable to be recruited within 72hr, previous participant), 568 declined to participate, and 12 withdrew before data collection resulting in 322 participants. Table 2 displays participant demographics. The majority of participants were male (69.3%) and over 65 years old (61.6%). Sixty-four per cent were overweight or obese. The most prevalent comorbidities across all participants were hypertension (66.9%), type 2 diabetes (51.1%) and hyperlipidaemia (45.5%).

Subgroup analysis showed some differences amongst the types of vascular disease. There was a significant difference in age across the groups with post-hoc analyses finding the participants in the aneurysmal group were significantly older ($p<0.001$) than the diabetic foot and “other” participants. Significant differences were also observed across subgroups in median BMI ($p<0.001$), BMI category ($p<0.001$), median LOS ($p=0.003$) and in the prevalence of all comorbidities except for smoking status.

Table 3 displays the range of parameters measuring nutritional status and/or nutritional risk. According to the PG-SGA, 15.5-20% of participants were moderately/suspected malnourished (PG-SGA-B) or severely malnourished (PG-SGA-C), with no differences across the groups (p=0.607). The MUST identified 12.5% of participants overall as being at risk of malnutrition with a significantly different proportion of at risk according to subgroups (p=0.024) where the PAD, occlusive other and venous groups were deemed to have a lower proportion at risk of malnutrition compared to other groups.

Micronutrient status varied however the majority of participants (78.6%) had suboptimal vitamin C levels and over half (55.6%) had low vitamin D levels (Table 3). Other nutrients of note were zinc, iron and vitamin B12 with over 40% of participants showing low levels. No significant differences were observed between the vascular types for any of the nutrients or nutrition related biochemistry.

Assessment of sarcopenia using appropriate cut-offs (Table 1) and algorithm,[12] found only 5% (n=10) to be sarcopenic with no significant difference observed between the groups.

DISCUSSION

This study found a high prevalence of nutritional deficits, particularly micronutrient deficits, in this patient group that were not recognised by the MUST or PG-SGA as neither of these tools include micronutrient status as a component of the tool. This has implications for the timely identification of those at risk and expedient nutrition intervention in a vulnerable patient group where malnutrition has a significant impact on patient outcomes.[7, 9-11]

To identify patients who warrant a comprehensive nutrition assessment, an appropriate nutrition screening tool is crucial. Currently, the MUST is used in our health care setting however the results of this study showed that only 12.5% of participants were

identified as requiring further nutrition assessment. This result is not surprising when we consider the parameters included in the MUST.[24] Given the study participants were mostly overweight/obese with minimal reporting of unintentional weight loss and while acutely unwell, they were not deemed (for the most part) critically unwell or unlikely to have no intake for 5 days they were unlikely to score highly. There are screening tools available that may be more appropriate that encompass parameters known to be prevalent in this group that affect nutritional status, such as impaired mobility, psychological stress and depression.[37-40] Exploration of the appropriateness of alternative screening tools is warranted.

The prevalence of malnutrition according to the PG-SGA was 15.5% overall which is much lower than other studies in vascular patients.[6-8] A key difference between the current study and other is the heterogeneity of our sample and the types of pathologies included. A large proportion of the previous research has been conducted in a single type of vascular disease (e.g. PAD patients only) and given the variation in pathophysiological processes of different vascular diseases, varying manifestations of symptoms and nutritional deficiencies it is not surprising that results from this pragmatic study are different to previous studies. There were 6 subgroups of participants in this study and within those groups, there was variation in the severity of disease, the presence of wounds/ulcers and whether surgical intervention occurred. Despite being managed by a vascular surgery unit, some participants (e.g. renal access patients, thoracic outlet syndrome and diabetic foot ulcers) do not have a defined cardiovascular process, which would impact on the results and make it difficult to draw comparisons with the literature.

Other potential reasons for the lower prevalence of malnutrition in this study are the different methods of identifying and assessing nutritional status and also much smaller sample sizes of 23-71 participants [6-8] compared to our large sample size. Higher rates of malnutrition were observed in studies which incorporated albumin as a measure of nutritional

status and physical examination/anthropometry however there were insufficient details to determine how the physical measures were completed or utilised in the assessment.[6, 7] The highest rate of malnutrition at 90% was observed in 32 participants all undergoing trans-tibial amputation for either gangrene or uncontrollable pain and hence had more progressive disease which may explain the higher rate of malnutrition.[8]

We observed alarming rates of micronutrient deficits between 40-78% depending on the nutrient studied. Previous literature has reported on the micronutrient status of vascular surgery patients, however these studies have again been conducted in a single type of vascular disease making it more difficult to compare to the current study. A number of studies report that low vitamin D is common in PAD patients [18, 41-43] and diabetic foot infections [44] with worsening deficits as the disease progresses, [45] and association with increased rates of amputation and CVD events.[46] Given the prevalence of suboptimal vitamin D status and the impact of limb amputation and CVD on morbidity, correcting vitamin D status is crucial. Subclinical vitamin C levels were common in our sample at 78%, substantially higher than the 14% reported by Langlois et al.[21] Suboptimal vitamin C status is of concern due to its antioxidant properties and role in wound healing which is of significance in this population.[23] Literature supports the current findings regarding vitamin B12 and iron, [20, 47, 48] and while prevalence may be lower than the current study deficits of a variety of micronutrients appear to be common in vascular surgery patients.

The difference in the rates of malnutrition according to PG-SGA and the rates of micronutrient deficits indicates that a more thorough nutritional assessment that considers malnutrition beyond the traditional weight loss is warranted.

In this study, the prevalence of sarcopenia was low at 5%. This was surprising given the proposal that adults with PAD have a decline in skeletal muscle mass or atrophy of

skeletal muscle when compared to age-matched controls,[13] particularly as the disease progresses [49] and that reduced SMM has also been observed in aneurysmal patients.[16] Muscle disuse due to pain in claudication and an increased requirement for protein and energy associated with ischaemic ulcers and vascular interventions [50, 51] is common and as well as reduced functional ability and mobility [13] which would affect gait speed. Matsubara et al [52] found that almost 44% of their CLI patients had sarcopenia when determined by skeletal muscle area assessed using computed tomography (CT), a much higher rate than observed in the present study. A possible reason for the lower than expected prevalence could relate to the cut-offs and algorithm used to diagnose sarcopenia in this study. There is no definitive method to diagnose sarcopenia, however the most common, widely accepted consensus method was utilised.[12] Also, there are no defined cut-offs for grip strength, gait speed and SMI in this patient group and while the most appropriate cut-offs were used based on the literature, they are based on populations dis-similar to the population studied

This study has a number of strengths, the first of which is its large sample size encompassing a range of vascular pathologies making it more generalizable to the general vascular surgery population. A wide range of nutritional parameters, including nutritional biochemistry were collected enabling researchers to assess multiple markers of nutritional status and all assessments were conducted by professionally trained dietitians.

This study is not devoid of limitations. The heterogeneity of our sample may be a limitation in terms of being able to make comparisons to previous research where single vascular disease types have been studied in isolation. However it is reflective of the patient population that clinicians encounter and hence results of this pragmatic study are useful for clinicians working in the area. This study measured nutritional status on admission and hence any deterioration and resultant malnutrition that may have occurred during admission

was not determined. Available literature has shown that nutritional tatus affects clinical outcomes, however this was not investigated in this study. Future studies would benefit s from exploring this relationship.

Conclusions:

This study demonstrates the nutritionally vulnerability of vascular surgery patients and a clear screening process to identify and then assess these patients is warranted. Neither the MUST nor PG-SGA identified the full extent of nutritional vulnerability when micronutrient status was included. A number of micronutrients are crucial in these patients and hence a more comprehensive assessment that encompasses a wider range of parameters, including micronutrient status appears warranted.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that they have no conflicts of interest associated with this study. No funding in the form of financial grants or other sources was received to conduct this study.

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4 Table 1:

Cut-offs used for the three parameters utilised in the diagnosis of sarcopenia in 322 vascular surgery inpatients

Parameter	Cut-off		Reference
	Male	Female	
Skeletal Muscle Index (SMI) (kg/m^2)	<6.4	<5.5	Baumgartner et al, 1998
Grip Strength (kg)	<28kg	<16kg	Massy-Westropp et al , 2011
Gait Speed (m/s)	<1.0		Cruz-Jentoft et al, 2010

Table 2: Characteristics of 322 participants admitted to a vascular surgery unit

	Aneurysmal (n=35, 10.9%)	**PAD** (n=94, 29.2%)	**Occlusive other** (n=28, 8.7%)	**Venous** (n=20, 6.2%)	**DM foot infection** (n=92, 28.6%)	**Other** (n=53, 16.5%)	**Total** (n=322)	p-value
Male (n, %)	28 (80)	63 (67.0)	17 (60.7)	13 (65)	67 (72.8)	35 (64.3)	223 (69.3)	0.549
Age (median, IQR)	75.0 (60, 90)	72.5 (52.5, 92.5)	70.0 (11.86)	69.5 (49.5, 89.5)	63.0 (45,81)	68.0 (48, 88)	68.0 (48, 88)	<0.001
Age Categories (n,%)								<0.001
<65 years	2 (5.7)	31 (33.0)	11 (39.3)	7 (35)	52 (56.5)	20 (37.7)	123 (38.2)	
65 and above	33 (94.3)	63 (67.0)	17(60.7)	13 (65)	40 (43.5)	33 (62.3)	199 (61.8)	
Median BMI								
(IQR) (n=319)	26.4 (24.1,29.7)	26.4 (23.4, 28.9)	27.9 (26.2,30.9)	30.6 (24.4,35.3)	31.5 (27.4, 37.1)	28.9 (25.6,34.0)	28.2 (20.3, 35.2)	<0.001
BMI Category								
(n, %) (n=319)								<0.001
Underweight	2 (5.7)	15 (15.8)	1 (3.6)	3 (15.8)	0 (0)	7 (13.2)	28 (8.8)	
Normal	16 (45.7)	36 (37.9)	8 (28.6)	3 (15.8)	11 (12.0)	12 (22.6)	86 (26.9)	
Overweight/Obese	17 (48.6)	44 (46.3)	19 (67.9)	13 (68.4)	81 (88)	32 (60.4)	206 (64.4)	
Living situation								
(n, %)								
Lives alone	11 (31.4)	32 (33.7)	11 (39.3)	6 (30)	28 (30.4)	17 (32.1)	105 (32.6)	0.97

Lives with another person/s	24 (68.6)	54 (57.4)	17 (60.7)	12 (60)	62 (67.4)	34 (64.2)	203 (63.0)	0.78
SCF*	0	0	0	1 (5)	1 (1.1)	0	2 (0.6)	0.18
RACF#	0	8 (8.5)	0	1 (5)	1 (1.1)	2 (3.8)	12 (3.7)	0.09
Comorbidities								
(n,%)								
Hyperlipidaemia	17 (48.6)	47 (50.0)	13 (46.4)	5 (25)	48 (52.2)	18 (32.1)	146 (45.3)	0.048
Hypertension	27 (77.1)	61 (64.9)	23 (82.1)	9 (45)	67 (72.8)	30 (53.6)	215 (66.8)	0.009
Diabetes	10 (28.6)	39 (41.5)	5 (17.9)	5 (25)	92 (100)	14 (25)	164 (50.9)	<0.001
IHD	13 (37.1)	27 (28.7)	5 (17.9)	1 (5)	15 (16.3)	11 (19.6)	71 (22)	0.027
Current smoker	6 (17.1)	18 (18.9)	4 (14.3)	3 (15)	10 (10.9)	8 (14.3)	49 (15.2)	0.777
LOS^	10 (6, 16)	8 (5, 14)	6 (4,11)	4 (3, 8.75)	8.5 (6, 13)	7 (3.5, 10)	8 (1,15)	0.003
Median (IQR)								

*Supported Care Facility, #Residential care facility, ^Length of stay

Table 3. Proportion of 322 vascular surgery inpatients identified as at risk of malnutrition, malnourished or sarcopenic.

	Aneurysmal (n=35, 10.9%)	**PAD** (n=94, 29.2%)	**Occlusive other** (n=28, 8.7%)	**Venous** (n=20, 6.2%)	**DM foot infection** (n=92, 28.6%)	**Other** (n=53, 16.5%)	**Total** (n=322)	**p-value**
Nutritionally at risk								
(n,%)								
MUST (n=320)	6 (17.1%)	7 (7.4)	0	1 (5.3)	15(16.3)	11 (20.8)	40 (12.5%)	0.024
PG-SGA Rating								
(n, %)								0.607
A	28 (80)	76 (80)	27 (96.4)	16(80)	81 (88)	44 (83.0)	272 (84.2%)	
B	7 (20)	18 (18.9)	1 (3.6)	4 (20)	11 (12)	9 (17.0)	50 (15.5%)	
C	0	1 (1.1)	0	0	0	0	1 (0.3%)	
Micronutrients								
(n,%)								
Vitamin A (n=241)	10 (37)	12 (16.7)	1 (5.3)	2 (14.3)	15 (19.7)	5 (14.7)	45 (18.7%)	0.169
Vitamin C (n=243)	21 (77.8)	57 (78.1)	18 (94.7)	10 (71.4)	59 (77.6)	27 (77.1)	191 (78.6%)	0.323
Vitamin D (n=243)	12 (44.4)	43 (58.1)	10 (55.6)	8 (57.1)	49 (64.5)	14 (40)	135 (55.6)	0.389
Vitamin E (n=240)	0	0	0	0	1 (1.3)	0	1 (0.4%)	0.826
Zinc (n=244)	14 (51.9)	37 (50)	7 (36.8)	7 (50)	29 (38.2)	14 (40)	107 (43.9)	0.569
Selenium (n=244)	6 (22.2)	17 (23)	0	2 (14.3)	10 (13.2)	10 (28.6)	45 (18.4)	0.229

Iron (n=270)	17 (58.6)	40 (50.6)	12 (52.2)	3 (17.6)	31 (38.3)	22 (51.2)	124 (45.9)	0.065
Vitamin B12 (n=258)	10 (35.7)	35 (45.5)	11 (50)	8 (50)	30 (39)	18 (45)	111 (43)	0.833
Folate (n=254)	0	0	0	0	1 (1.3)	0 (0)	1 (0.4)	0.951
Sarcopenic* (n,%)	1 (3.8)	6 (10.3)	0	1 (7.1)	2 (3.4)	0	10 (5)	0.386

*only calculated for those aged 65 years and over (n=199; aneurysmal, n=33; PAD, n=63; occlusive other, n=17; venous, n=13; DM foot infection, n=40; other, n=33)

AN EVALUATION OF THE VALIDITY OF NUTRITION SCREENING AND ASSESSMENT TOOLS IN PATIENTS ADMITTED TO A VASCULAR SURGERY UNIT

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Abstract

Vascular surgery patients are nutritionally vulnerable. Various malnutrition screening and assessment tools are available however none were developed or validated in vascular patients. This study aimed to: (1) investigate the validity of four commonly administered malnutrition screening tools (Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF)) and an assessment tool the Patient- Generated Subjective Global Assessment, (PG-SGA) compared against a comprehensive Dietitian's assessment and (2) evaluate the ability of the instruments to predict outcomes. Vascular inpatients were screened using the four malnutrition screening tools and assessed using the PG-SGA. Each was assessed by a Dietitian incorporating nutritional biochemistry, anthropometry and changes in dietary intake. Diagnostic accuracy, consistency and predictive ability were determined. Three hundred and twenty two (69.3% male) patients participated, with 75% having at least one parameter indicating nutritional deficits. No instrument achieved the a-priori levels for sensitivity (14.9-52.5%). Neither tool predicted EQ-5D-5L score. All tools except the MNA-SF were associated with length of stay, however the direction varied with increased risk of malnutrition on the MUST and NRS-2002 being associated with shorter LOS (p=0.029 and 0.045) and the reverse with the MST and PG-SGA (p=0.005 and <0.001). The NRS-2002 was associated with increased risk of complications (p=0.039). The MST, NRS-2002 and PG-SGA were predictive of discharge to an institution (p= 0.004, 0.005 and 0.003). The tools studied were unable to identify the high prevalence of undernutrition hence vascular disease-specific screening and/or assessment tools are warranted.

Introduction

Malnutrition, specifically undernutrition, refers to deficiencies or imbalances in the intake of energy and/or nutrients which can lead to weight loss, muscle wasting and micronutrient deficiencies or insufficiencies.[1] In vascular surgery patients, studies have reported rates of malnutrition as high as 60-90% based on a variety of assessment methods and tools.[2-4] Previous work by the authors revealed that 16% of patients admitted to a tertiary acute care vascular surgery unit were malnourished according to the Patient-Generated Subjective Global Assessment (PG-SGA).[5]

The identification and management of malnutrition in patients admitted to a vascular surgery unit is critical due to its reported association with poorer clinical outcomes. [6-8] Despite these consequences and the prevalence observed, malnutrition across clinical specialties remains under-recognised despite the availability of a number of validated malnutrition screening tools.

A malnutrition screening tool should be quick and simple to administer and able to be completed by an individual with minimal training or by the patients themselves. A variety of tools exist with commonly used ones being the Malnutrition Screening Tool (MST),[9] Malnutrition Universal Screening Tool (MUST),[10] the Nutrition Risk Screen -2002 (NRS-2002)[11] and the Mini-Nutritional Assessment – Short Form (MNA-SF).[12] A detailed description of each of these tools is available elsewhere,[9-12] but in summary, each tool consists of a number of items (2 to 6) pertaining to nutritional parameters known to be associated with malnutrition, with a weighted scoring system for each item and a defined cut-off score to indicate possible malnutrition, warranting further investigation by a Dietitian. It is well recognised that malnutrition screening tools need to be validated for the population in which they are to be administered to expedite nutrition assessment and interventions where indicated and allow resources to be used efficiently.[13] All four tools mentioned have been validated across a number of patient populations[14-20] and in a variety of settings.[17, 21-24]

In some settings a standardised approach to nutrition assessment is undertaken using a validated nutrition assessment tool. A commonly used tool is the scored Patient-Generated Subjective Global Assessment (PG-SGA), which awards patients with a score and a global rating of nutritional status. A detailed description of the PG-SGA can be found elsewhere.[25] While originally developed in cancer patients[26] the PG-SGA has since been validated in a number of patient groups[27-29] with high levels of sensitivity (92-100% and specificity (84-96.7%).

To date, neither malnutrition screening tools or the PG-SGA have been validated specifically in patients with vascular disease, a group characterised by a heterogeneous aetiology of disease and

presence of complex comorbidities that are growing in prevalence. Hence it is critical that we investigate methods to identify those who are nutritionally vulnerable to optimise their nutritional health and overall clinical outcomes. Therefore, the aims of this study were to (1) investigate the validity of the four commonly adopted malnutrition screening tools (the MST, MUST, NRS-2002 and the MNA-SF), and a commonly used nutritional assessment tool (PG-SGA) when compared against a dietitians clinical assessment in inpatients admitted to a vascular surgery unit and (2) evaluate the ability of the malnutrition screening tools and the PG-SGA to predict clinical outcomes, namely length of hospital stay, in-hospital complications, quality of life and discharge destination in the same population.

Methods

Study Sample

Participants were recruited consecutively from the Southern Adelaide Health Local Network (SAHLN) Vascular Surgery Unit, Adelaide Australia. Participants were aged 18 years and over and were able to provide informed written consent or where this was not appropriate, consent was obtained from the participant's legal next of kin/guardian. Participants were excluded if they presented to the emergency department without admission to the Vascular Surgery Unit or were subsequently transferred to a private hospital, or if they were admitted for day procedures only. Those who were admitted to the vascular unit were excluded if they were unable to be recruited within 72 hours of admission. Participants recruited to the study during previous admissions were also excluded. This study received ethical approval from the Southern Adelaide Health Research and Ethics Committee (approval number 258.14) and governance approval from the Flinders Medical Centre.

Data collection

Data were collected between October 2014 and August 2016. All demographic data and admission/discharge details were collected by the research team. Nutrition screening was completed by nursing staff on the vascular surgery unit within 24 hours of recruitment. Where this was not possible, a member of the research team completed the screening. Nutrition assessment was completed by the research Accredited Practising Dietitian at the bedside within 72 hours of admission to the ward, accompanied by blood test results relating to nutrient biochemistry.

Demographic data were collected from the medical records and included age, gender, and type

of vascular disease. Vascular disease types were classified according to surgeon diagnosis as aneurysmal, peripheral arterial disease (PAD) (encompassing aorto-iliac and infra-inguinal disease), occlusive other (encompassing carotid and upper limb ischaemia), venous, diabetic foot infection and other. Those classified as other included renal access, surgical management of thoracic outlet syndrome, trauma, ulcers of mixed or unknown aetiology, admission for post-operative complications and lower limb infection not attributed to occlusive disease or diabetes.

Malnutrition Screening

Data required for completion of the four malnutrition screening tools (MST, MUST, NRS-2002 and MNA-SF) were completed on entry to the study. This included the collection of body weight, using a calibrated weigh chair (HVL-CS Hospital Chair Scale, A&D Mercury Pty Ltd) in light clothing and recorded to the nearest 0.1kg, and ulna length to allow for the estimation of height (BAPEN). Following discharge, the research dietitian scored each of the four screening tools. Participants were classified as 'at risk of malnutrition' for each tool separately if they scored 2 or more on the MST or MUST, 3 or more on the NRS-2002, and 11 or less on the MNA-SF.[9-12]

Assessment of Nutritional Status.

Nutritional status was assessed by an Accredited Practicing Dietitian (APD) within 72 hours of admission during an in-person consultation, using the scored Patient Generated Subjective Global Assessment (PG-SGA)[25] with each participant being awarded a PG-SGA score and a PG-SGA global rating of A (well nourished), B (suspected or moderately malnourished) or C (severely malnourished).

Comprehensive Dietetic Assessment of Nutritional Status

The dietitian's assessment was conducted retrospectively using all data collected during the data collection as described above inclusive of nutritional biochemistry. Fasting blood samples were collected by a phlebotomist and analysed by the hospital or state pathology service depending on the analytical test. Blood samples were analysed and determined as low, normal or high based on the reference ranges (shown in parentheses) provided by the analysing laboratory, for Iron (8-30umol/L), vitamin B12 (>260mg/L) and folate (6.5-45ug/L), vitamin A (1-3.1umol/L), vitamin C (26-85umol/L), vitamin E (12-46umol/L) and vitamin D (60-160nmol/L) and the trace elements zinc (9-21umol/L) and selenium (0.8-1.64umol/L).

A participant was determined to be malnourished if they displayed a deficiency in any of the

145 micronutrients according to the following guidelines, vitamin C ≤ 0.29mg/dl,[30] vitamin B12 <
146 200mg/l,[31] folate < 3ug/l,[31] zinc <9.0umol/l, selenium <0.7umol/l,[32] vitamin A <1umol/l[31] or
147 vitamin D <60nmol/L or any of the following characteristics underweight (BMI of <22kgm^2 for
148 those aged 65 years or more[33] and <18.5kgm^2 for those aged under 65 years[34]), PG-SGA score ≥
149 9,[25] PG-SGA global rating B or C,[26] or Iron-deficiency anaemia (Ferritin<15ug/L plus
150 Haemoglobin <130g/l for males and <120g/L for females).[35]
151
152 *Ability of the screening and assessment tools to predict clinical outcomes*
153 Admission complications and discharge destination were collected from the medical records
154 following discharge to enable the evaluation of the ability of the screening tools to predict clinical
155 outcomes. Admission complications included infections, cardiovascular events, unplanned surgery
156 or procedures, deterioration or development of an ulcer or wound and vascular restenosis/acute
157 occlusion and acute renal failure.

158 Health-related quality of life (HRQoL) is commonly examined in the literature when
159 investigating clinical outcomes and in this study was included as an outcome in the predictive
160 validity analyses. In this study, HRQoL was assessed using the EuroQoL 5 Dimensions 5
161 Levels (EQ-5D-5L)[36] which includes five questions related to mobility, self-care, usual
162 activities, pain/discomfort and anxiety/depression with five levels of impairment recognised in
163 each domain: no, slight, moderate, severe and extreme problems in the relevant dimension of
164 health. Using these responses, an EQ-5D-5L utility value was created using a valuation
165 algorithm.[37] EQ-5D-5L utility values have a range of -0.624 to 1: the maximum score of 1
166 representing perfect health, a score of 0 representing death while scores less than 0 represent
167 health states that are worse than death.[38-40]

168 *Statistical Analysis*

169 The calculation of sample size was based on determining the precision of the expected
170 sensitivity and specificity of the proposed screening tools.[9, 12] A prevalence of malnutrition
171 of 61% was determined from a prospective, observational, audit of vascular surgery patients
172 in an elective setting.[2] A total sample size of 322 participants would need to be recruited
173 to obtain 197 participants with malnutrition (prevalence of the malnutrition is 61%). The
174 sample size calculation allows a point estimate of 85% sensitivity and specificity to be
175 measured with a precision of +/- 5% with 95% confidence. The sample size calculation was
176 also based on investigating the effect of nutritional status on complications and health care
177 outcomes. Although several outcomes have been addressed, patient's mortality was chosen to

justify the power and sample size calculation. Using a hierarchical cox regression model on a 3 year follow-up study of vascular patients with lower limb ulcers, Miller et al[41] demonstrated that those patients with BMI <30 kg/m^2 were 4.6 times more likely to die than those with BMI ≥30 kg/m^2 (95% confidence interval [CI]: 1.04-20.4; *P* 0.04). As the confidence interval was so wide, we used a risk of death at the lower end of the confidence interval to detect a large sample size. A two-sided log rank test with an overall sample size of 266 subjects (133 in the BMI < 30 kg/m2 group and 133 in the BMI ≥30 kg/m2 group) achieves 90.0% power at a 0.05 significance level to detect a hazard ratio of 1.50. The Power Analysis & Sample Size Software (PASS) was used to calculate the sample size.[42]

Statistical analysis was conducted using SPSS for Windows version 25 (SPSS Inc, Chicago, IL) and Stata version 14.0 (StataCorp LLC, College Station, TX). Significance was set at the P<0.05 level. Continuous variables were assessed for normality using the Shapiro Wilk test and reported as mean (standard deviation - SD). If not normally distributed, the median (interquartile range - IQR) is reported. Sample characteristics are expressed as frequencies (n, %). Contingent on the normality tests, the Independent Samples T-test or Mann-Whitney U Test were used for testing differences across two groups for continuous variables.

To determine the concurrent validity of the five tools (four screening tools and the PG-SGA), measures of diagnostic accuracy were determined. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were determined against the results of the dietitian's clinical assessment (the reference standard). In the reference standard, respondents were classified as either 'malnourished' or 'not malnourished'. To facilitate comparison to the reference standard and in keeping with clinical practice, two levels of risk were considered for each screening tool namely 'at risk' (aggregating participants with high or moderate risk of malnutrition) and 'not at risk'. Similarly, the PG-SGA global rating was classified into 'malnourished' and 'not malnourished' with ratings B (moderately, suspected malnourished) and C (severely malnourished) aggregated into one group (malnourished) as is common practice in similar literature.[16, 43, 44] A-priori values of ≥80% for sensitivity and ≥60% for specificity were used to indicate a valid instrument.[14] The dichotomous forms of each tool were used in all subsequent analyses to investigate validity in keeping with clinical practice where malnutrition screening tools have a defined cut-off to determine if a patient is 'at risk' or 'not at risk' of malnutrition. The diagnostic consistency between the five tools against the dietitians assessment was assessed by kappa (k) statistic.[45] The value of k varies from 0 to 1 with values <0.2 indicating poor, 0.21-0.4 fair, 0.41-

0.6 moderate, 0.61-0.8 substantial and >0.8 as almost perfect concordance. Negative kappa values indicates that the number of agreements observed is fewer than would be expected by chance indicating poor consistency overall.[46]

The ability of the five tools to predict clinical and HRQoL outcomes was tested using multivariate regression analysis. In all regressions, dichotomous screening and assessment tool variables (at risk or malnutrition/malnourished or not at risk/well-nourished) were entered as independent variables with age, gender, disease type and smoking status included as potential cofounders. To predict continuous dependent variables or outcomes (length of stay and EQ-5D-5L scores), generalised linear models (GLM) were fitted. To identify an appropriate family for the GLM, a modified Park Test was conducted following standard procedures.[47] For GLM models where the LOS was the dependent variable, coefficients of predicted dependent values in the modified park test indicated that the Poisson (for models including the MST and MUST) and Inverse Gaussian (for models incorporating the NRS2002, MNA-SF and PG-SGA) family of GLM were appropriate for analysis. The OLS regression model was appropriate for all models where the EQ-5D-5L Index was the dependent variable. To predict binary outcomes (1 = return to prior residence or to an institution such as residential aged care, rehabilitation or another hospital, 0 = other discharge destination and; 1 = nosocomial complications, 0 = no complications), binary regression models were fitted.

Results

A total of 2229 patients were admitted to the vascular surgery ward during the study period all of whom were screened for study eligibility. Of these, 1327 (59.5%) were ineligible, 568 (25.5%) did not wish to participate, and 12 (0.5%) participants withdrew before data collection resulting in 322 participants (14.4%). Table 1 displays the participant demographics. The majority of study participants were male (69.3%) and over 65 years old (61.6%). Nearly all (95.7%) lived independently, either alone or with another person/s with the majority (82.1%) returning to their pre-admission residence on discharge. Twenty-one percent of participants had at least one in-hospital complication and the median (IQR) hospital length of stay was 8 (5, 12) days. Median (IQR) quality of life score was 0.72 (0.46, 0.82).

Table 2 shows the results of the malnutrition screening using the four screening tools, micronutrient status and the proportion of participants assessed as malnourished by the PG-SGA and by the dietitian's clinical assessment. The malnutrition screening tools showed variable results ranging from 12.5% at risk of malnutrition according to the MUST up to 47.5% with the MNA-SF.

According to the PG-SGA, 15.8% of participants were assessed as either moderately/suspected malnourished (PG-SGA B) or severely malnourished (PG-SGA C). Suboptimal micronutrient status was prevalent with greater than 40% having suboptimal iron, zinc or vitamin B12 levels, 55.6% showed low vitamin D levels, and approximately 18% were low in selenium or vitamin A. Prevalence of suboptimal vitamin C was the greatest with 78.6% classified as having suboptimal levels and 57.2% being vitamin C deficient. The dietitian's assessment of nutritional status revealed that 75.5% of study participants had at least one nutritional parameter indicating that intervention may be warranted.

Table 2 Number and proportion of vascular surgery participants at risk of malnutrition according to the four screening tools and those assessed as malnourished according to the PG-SGA, and the dietitian's clinical assessment.

Validity of the screening and assessment tools

A higher prevalence of malnutrition (75.5% overall) was observed as a result of the dietitian's clinical assessment when compared to the PG-SGA results (Table 2). Concurrent validity and agreement of the malnutrition screening tools and the PG-SGA against the dietitian's clinical assessment is displayed in Table 3. Overall, while the MNA-SF performed best, none of the four screening tools or the PG-SGA achieved the a-priori levels for Sn and Sp and all showed poor NPV. Negative kappa values were observed between all four malnutrition screening tools and PG-SGA when compared to the dietitian's assessment indicating poor diagnostic consistency between the dietitian's clinical assessment and the tools (Table 3).

Results of the regression analyses are displayed in Tables 4 and 5. A significant association was observed between LOS and four tools (the MST, MUST, NRS-2002 and PG-SGA). However, the direction of the relationship differed. The MST and PG-SGA had positive associations (Coefficient (SE) 0.1061 (0.0376), p=0.005 and 5.02 (1.33), p<0.001 respectively) indicating that those at risk of malnutrition or already malnourished had a longer LOS while the reverse was true for the MUST (-0.00006 (0.00003), p=0.029) and NRS-2002 (-0.004 (0.002), p=0.045). No significant association was observed between LOS and MNA-SF. Associations were also observed between LOS and disease type and age in some of the models (Table 4). No significant associations were observed in the models for EQ-5D-5L Index indicating no association between the predictor variables and HRQoL. Results of the logistic regression analyses are shown in Table 5. MST, NRS-2002 and PG-SGA all showed a significant association with discharge destination when all confounders were

with participants at risk of malnutrition or already malnourished b eing at least 2.3 times more likely to be discharged to another institution (OR(SE), 2.36 (0.71), p=0.004, 2.38(0.74) p=0.005 and 2.91 (1.03), p=0.003 respectively). There were no other significant associations identified with discharge destination. When in-hospital complications were examined, only NRS-2002 had a significant association with at risk participants being 1.85 (0.56) (OR(SE)) times more likely to have complications when confounders were controlled for.

Discussion

This is the first study to explore the validity of commonly used malnutrition screening tools as well as a nutrition assessment tool (PG-SGA) exclusively in vascular surgery patients. The MNA-SF achieved a better concurrent validity than the other screening tools when compared to the clinical dietitians assessment however none of the four malnutrition screening tools or the PGSGA exhibited optimal concurrent validity as they did not achieve the a-priori acceptable levels and had low negative predictive values indicating that all underestimated the presence of malnutrition in the participants. There was poor diagnostic consistency between each of the screening tools and the PG-SGA when compared with the dietitian's assessment according to Kappa values.

Previous studies that have explored the validity of malnutrition screening tools have varied depending on the patient group in which the tools have been administered and the comparator/reference standard used. The MUST displayed excellent agreement (k 0.783) with the Subjective Global Assessment (SGA) in fifty medical inpatients (aged <65 years).[16] However in the current study, the MUST did not perform adequately (k -0.117, Sn 14.9%, Sp 94.9%) which was similar to findings in renal inpatients when compared to the SGA (Sn 53.8%, Sp 78.3%).[48] Variable results have also been found with the MST, NRS-2002 and the MNA-SF with good validity in some settings[17] and suboptimal[22, 48, 49] validity in others. The variable results lend support to the notion that there is no "one size fits all" approach to malnutrition screening.

The investigation of the ability of the tools to predict short-term clinical outcomes yielded variable results. The NRS-2002 showed the best predictive ability, with significant associations observed with discharge destination, in-hospital complications and hospital LOS indicating poorer outcomes in those classified as at risk of malnutrition.

Existing literature that has looked at the ability of the MUST, MST, NRS-2002 and MNA-SF to predict outcomes has also reported variable results, depending on the population studied, sample

size and setting. Wang et al[50] found the NRS-2002 to be predictive of LOS, non-infectious complications and higher cost and mortality in Chinese GI patients whilst Raslan et al[51] found that the NRS-2002 performed better than the MUST and MNA-SF despite it identifying the lowest proportion of nutritional risk out of the three tools studied. Both of these studies were conducted in acute care patients. However when the NRS-2002, MNA-SF and MUST were studied in nursing home residents, the MNA-SF demonstrated the better predictive ability.[44] The authors postulated this was due to the inclusion of functional, cognitive and psychological parameters in the MNA-SF. The MNA-SF has been studied more extensively, particularly in the older age groups, showing that it is associated with increased risk of discharge to institutional care[52] and longer LOS in geriatric rehabilitation[52, 53] and also long-term mortality.[50] However these results were contradicted by Marshall et al[28] who found that the MNA-SF was not able to detect a significant difference in similar outcomes in their sample of geriatric rehabilitation patients. In younger populations, the results are not clear cut. The MNA-SF was found to be strongly associated with mortality in younger Ugandan adults,[54] whereas a trend towards longer LOS and increased likelihood of readmission was observed in younger rehabilitation patients but the results failed to reach significance as the study was likely underpowered.[55] In the current study, the MST was predictive of discharge destination and LOS. Similar to the other screening tools, the literature is variable with the MST being predictive of LOS in acute care patients[9] but not in renal patients[48] and not predictive of any clinical outcomes in patients undergoing geriatric rehabilitation.[22] The variable results in the current study and also in existing literature highlight furtherthat no one screening tool is suitable for use across a range of population groups and selected tools need to be valid for the population for which it is intended.

The NRS-2002 is the only screening tool to have been examined in vascular patients to date. De Waele et al[2] found that the NRS-2002 did not result in any false positives, however the presence of false negatives was not mentioned, which was found to be high in the present study. Participants were limited to elective surgery patients and those needing urgent surgery and/or limb amputations were excluded whereas our sample included all surgery types, and both elective and emergency patients making it a more representative sample of a routinely heterogeneous acute vascular surgery unit.

The suboptimal performance of the malnutrition screening tools and the PG-SGA is likely related to the parameters included in each of these tools, which are of less relevance to vascular surgery patients. Malnutrition screening tools traditionally focus on weight and/or BMI status, unintentional weight loss and reduced appetite/oral intake. The NRS-2002 also accounts for disease

severity and age while the MNA-SF incorporates parameters known to impact on nutritional status that may be more relevant to this patient group; suboptimal mobility,[56] increased psychological stress and depression.[57-59] The participants in this study were mostly overweight or obese with minimal reporting of unintentional weight loss hence they would not score highly on the tools that focus solely on these parameters. The MNA-SF identified the highest proportion of 'at risk' participants likely due to the inclusion of broader parameters.

Overall, the four malnutrition screening tools and the PG-SGA performed poorly as they do not account for micronutrient status which we found to be a key nutritional issue in the participants of this study. Incorporating micronutrient status into the clinical dietitian's assessment provides a more comprehensive determination of nutritional status and this study has demonstrated that malnutrition screening tools or assessment tools that neglect this important area will likely be inadequate for implementation in a vascular surgery setting.

Micronutrients are crucial in this patient group for wound healing,[60] and vascular health[61] hence ensuring adequate micronutrient status is critical to ensure optimal perioperative and long-term outcomes. The malnutrition screening tools that are currently available in existing literature do not include biochemical assessment of micronutrients as this contravenes the premise that a screening tool should be quick and simple to administer by any trained person or the patient themselves due to the requirement for additional resources and time rendering it more costly, not quick, nor simple. A cost analysis would be important to support or refute the inclusion of nutritional biochemistry within a screening tool. It is important to consider the strengths and limitations of this study to enable us to draw conclusions. This study is the first of its kind to investigate a range of screening tools in the vascular surgery population. It has a large sample size of 322 participants that are heterogeneous and therefore representative of the spectrum of vascular disease likely to be encountered in a vascular surgery unit. Nutrition assessment bias was minimised by having an Accredited Practising Dietitian (APD) conduct the PG-SGA who was not involved in the screening process and all measurements were conducted by a trained APD. Nursing staff that conducted the nutrition screening were trained via in-service education sessions and individual support by research team members.

While the study has many strengths, it is not devoid of limitations. The clinical dietitian's assessment was completed retrospectively utilising information collected via the screening and nutrition assessment processes, hencethe dietitian was not able to clarify information with individual participants and this may have influenced the assessment results. However this is not relevant to the biochemistry results and hence the impact on results is likely to be minimal. When

investigating the validity of the tools, participants at medium and high risk of malnutrition according to the MNA-SF, MUST and the PG-SGA were merged for analysis so the relationship between the different levels of risk or malnutrition with clinical outcomes could not be explored. Due to the small proportion of severely malnourished participants in this sample, it is unlikely that any statistically significant relationships would have been observed.

In conclusion, vascular surgery patients are complex with a range of pathologies influenced by nutrition. This study found a high prevalence of malnutrition secondary to suboptimal micronutrient status that was not identified by the four malnutrition screening tools investigated or the PG-SGA indicating that the development of vascular disease-specific screening and assessment tools that encompass additional parameters of relevance such as micronutrients and mobility measures are warranted to ensure that those at nutritional risk receive appropriate nutritional care to optimise patient and clinical outcomes.

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551 concern in peripheral arterial disease. Journal of the American Medical Directors
552 Association.**11**,308-11.
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557 Table 1: Participant Characteristics of 322 vascular surgery patients participating in a validation study
558 of malnutrition screening and assessment tools
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Characteristic	N (%) unless indicated
Male	223 (69.3)
Age (mean, SD)	67.6 (14.14)
Age Categories	
<65 years	123 (38.2)
65 and above	199 (61.8)
Weight (kg)	
(Med/IQR)	85.5 (59.9, 111.1)
Median BMI	
(IQR) (n=320)	28.2 (20.3, 36.1)
Pre-admission living situation	
Lives alone	105 (32.6)
Lives with another person/s	203 (63.4)
SCF	2 (0.6)
RACF	12 (3.7)
EQ-5D-5L Score (Med/IQR)	0.72 (0.36, 1.08)
Proportion with noso-comial complications	69 (21.4)
Discharge Destination	
Return to prior living	260 (82.0)
D/c to institutional care	57 (18.0)
LOS (Med/IQR)	8 (1, 15)

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568 Table 2 Number and proportion of vascular surgery participants at risk of malnutrition according to the four
569 screening tools and those assessed as malnourished according to the PG-SGA, and the dietitian's clinical
570 assessment.
571

Nutritional Parameter	**Proportion of participants (n=322)**
Nutritionally at risk	
MST	93 (28.8%)
MUST (n=320)	40 (12.5%)
NRS-2002	79 (24.5%)
MNA-SF (n=320)	152 (47.5%)
PG-SGA Rating	
A (well nourished)	272 (84.2%)
B (moderately/suspected malnutrition)	50 (15.5%)
C (Severely malnourished)	1 (0.3%)
Dietitians assessment	244 (75.5)

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Appendix 12: Accepter pre-print of publication arising from chapter 5

Table 3: Concurrent validity of four commonly used screening tools and the PGSGA against the clinical dietitian's assessment of malnutrition in 322 vascular surgery patients

	MST	MUST	NRS-2002	MNA-SF	PG-SGA
Sensitivity (Sn)	32.8	14.9	29.9	52.5	20.9
Specificity (Sp)	83.5	94.9	96.1	67.9	100
Positive Predictive Value (PPV)	86.0	90.0	92.4	83.6	100
Negative Predictive Value (NPA)	28.7	26.4	29.9	31.5	29
Kappa (k)	-0.154	-0.117	-0.223	-0.155	-0.237

Desirable cut-offs:

Sn ≥80, Sp ≥60,

k <0.2 poor agreement, 0.21-0.4 fair agreement, 0.41-0.6 moderate agreement, 0.61-0.8 substantial agreement, >0.8 excellent agreement

Table 4 Generalised Linear Model (GLM) results

	Dependent variable = Length of Stay (LOS)									
	Model inc MST[a]		**Model inc MUST[a]**		**Model inc NRS2002[b]**		**Model inc MNASF[b]**		**Model inc PGSGA[b]**	
Predictors	Coefficient (SEM)[d]	P value	Coefficient (SEM) [d]	P value	Coefficient (SEM) [d]	P value	Coefficient (SEM) [d]	P value	Coefficient (SEM) [d]	P value
MST	0.1061 (0.0376)	0.005	-		-		-		-	
MUST	-		-0.00006 (0.00003)	0.029	-		-		-	
NRS-2002	-		-		-0.004 (0.002)	0.045	-		-	
MNA-SF	-		-		-		0.00001 (8.08e-6)	0.183	-	
PG-SGA	-		-		-		-		5.02 (1.33)	<0.001
Gender	0.0087 (0.0385)	0.821	0.004 (0.038)	0.913	-0.0003 (0.002)	0.889	-0.0003(0.002)	0.875	0.28 (1.04)	0.785
Smoker	0.012 (0.052)	0.819	0.0096 (0.052)	0.852	-0.0004 (0.003)	0.890	-0.0002(0.003)	0.936	0.22 (1.39)	0.874
Age	0.004 (0.001)	0.004	0.0041 (0.001)	0.003	6.00E-05(0.0001)	0.378	-0.00009 (0.00007)	0.230	0.02 (0.04)	0.636
Venous	-0.22 (0.11)	0.05	-0.203 (0.11)	0.065	0.009 (0.008)	0.301	0.007 (0.008)	0.372	-2.51 (2.49)	0.313
Aneurysmal	0.335 (0.08)	<0.0001	0.351 (0.083)	<0.0001	-0.007 (0.005)	0.155	-0.008 (0.005)	0.113	2.76 (2.18)	0.206
PAD	0.256 (0.07)	<0.0001	0.26 (0.073)	<0.001	-0.006 (0.005)	0.211	-0.006 (0.005)	0.191	1.63 (1.84)	0.173
DM limb	0.32 (0.07)	<0.001	0.324 (0.074)	<0.001	-0.007 (0.004)	0.127	-0.007 (0.005)	0.114	2.53 (1.85)	0.173

Other vascular	0.150 (0.08)	0.06	0.170 (0.08)	0.033	-0.004 (0.005)	0.442	-0.004 (0.005)	0.398	0.60 (1.99)	0.763
Constant	1.79 (0.123)	<0.001	1.82 (0.123)	<0.001	0.02 (0.007)	0.003	0.021 (0.007)	0.002	6.62 (3.14)	0.036
	Dependent variable = EQ-5D-5L Index									
	Model inc MST[d]		**Model inc MUST[d]**		**Model inc NRS2002[d]**		**Model inc MNASF[d]**		**Model inc PGSGA[d]**	
Predictors	Coefficient (SEM)[c]	P value	Coefficient (SEM)[c]	P value	Coefficient (SEM)[c]	P value	Coefficient (SEM)[c]	P value	Coefficient (SEM)[c]	P value
MST	54.15 (87.10)	0.535	-		-		-		-	
MUST	-		0.0005 (0.047)	0.992	-		-		-	
NRS2002	-		-		70.40 (91.95)	0.444	-		-	
MNASF	-		-		-		-0.0005 (0.057)	0.994	-	
PGSGA	-		-		-		-		-85.1 (110.2)	0.441
Gender	-58.23 (86.30)	0.50	-60.69 (86.26)	0.482	-56.96 (86.31)	0.510	-60.61 (86.66)	0.485	-65.15 (86.37)	0.451
Age	3.51 (3.04)	0.249	3.52 (3.04)	0.249	3.35 (3.05)	0.273	3.52 (3.06)	0.251	3.88 (3.07)	0.208
Smoker	198.93 (115.09)	0.085	199.13 (115.20)	0.085	200.46 (115.06)	0.082	199.08 (115.36)	0.085	197.32 (115.07)	0.087
Venous	14.11 (206.11)	0.945	8.599 (207.13)	0.967	9.28 (205.87)	0.964	9.03 (208.01)	0.965	23.79 (206.77)	0.908
Aneurysmal	-24.50 (180.8)	0.892	-15.95 (180.35)	0.930	-24.69 (180.54)	0.891	-15.83 (181.64)	0.931	-3.33 (180.91)	0.985
PAD	79.95 (151.75)	0.599	82.01 (151.80)	0.589	78.48 (151.73)	0.605	82.09 (152.05)	0.590	95.96 (152.72)	0.530
DM limb	129.40 (153.40)	0.400	132.10 (153.43)	0.390	129.67 (153.32)	0.398	132.12 (153.68)	0.391	141.92 (153.81)	0.357
Other vascular	14.03 (164.76)	0.932	15.81 (165.63)	0.924	15.54 (164.68)	0.925	16.07 (165.43)	0.923	29.13 (165.56)	0.860
Constant	-247.99 (261.45)	0.344	-233.460 (260.75)	0.371	-239.19 (260.44)	0.359	-233.85 (262.36)	0.373	-252.48 (261.48)	0.335

[a] GLM model family for LOS model that included results of the malnutrition screening tool (MST) and malnutrition Universal Screening Tool (MUST) assessments (both coded as 1 = at risk and 0 = not at risk) was Poisson and link was log;

[b] GLM model family for LOS model that included results of the Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF) assessments (both coded as 1 = at risk and 0 = not at risk) was Inverse Gaussian and link was power $^{-2}$;

[c] SEM = Standard Error of the Mean

d Regression model for EQ-5D-5L model that included results of the Nutrition Risk Screen -2002 (NRS-2002) and the Mini-Nutritional Assessment – Short Form (MNA-SF) assessments (both coded as 1 = at risk and 0 = not at risk) was ordinary least squares (OLS).

Table 5: Binary Logistic Regressions results

	Dependent variable = Discharge Destination									
	Model inc MST		**Model inc MUST**		**Model inc NRS2002**		**Model inc MNASF**		**Model inc PGSGA**	
Predictors	OR (SE)[a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value
MST	2.36 (0.71)	0.004	-		-		-		-	
MUST	-		0.58 (0.30)	0.295	-		-		-	
NRS-2002	-		-		2.38 (0.74)	0.005	-		-	
MNASF	-		-		-		1.0 (0.003)	0.821	-	
PGSGA	-		-		-		-		2.91 (1.03)	0.003
Gender	0.98 (0.31)	0.937	0.89 (0.28)	0.698	0.96 (0.30)	0.90	0.94 (0.29)	0.843	0.98 (0.31)	0.953
Age	1.00 (0.01)	0.710	1.00 (0.01)	0.774	1.00 (0.01)	0.90	1.01 (0.01)	0.641	1.00 (0.01)	0.943
Smoker	0.53 (0.26)	0.194	0.55 (0.27)	0.215	0.55 (0.27)	0.22	0.55 (0.27)	0.217	0.54 (0.27)	0.211
Venous	0.44 (0.39)	0.356	0.45 (0.40)	0.363	0.41 (0.37)	0.32	0.44 (0.39)	0.349	0.31 (0.28)	0.196
Aneurysmal	0.40 (0.29)	0.206	0.52 (0.38)	0.369	0.41 (0.3)	0.22	0.49 (0.35)	0.313	0.37 (0.27)	0.176
PAD	1.19 (0.63)	0.748	1.26 (0.66)	0.655	1.17 (0.62)	0.76	1.21 (0.63)	0.714	1.00 (0.53)	0.999
DM limb	0.80 (0.44)	0.684	0.91 (0.50)	0.863	0.82 (0.45)	0.72	0.85 (0.46)	0.759	0.72 (0.40)	0.552
Other vascular	0.84 (0.50)	0.771	1.02 (0.60)	0.974	0.87 (0.52)	0.82	0.90 (0.52)	0.853	0.71 (0.42)	0.559
Constant	0.17 (0.17)	0.067	0.25 (0.24)	0.147	0.22 (0.20)	0.10	0.21 (0.2)	0.10	0.30 (0.28)	0.200
	Dependent variable = In-hospital Complications									
	Model inc MST		**Model inc MUST**		**Model inc NRS2002**		**Model inc MNASF**		**Model inc PGSGA**	
Predictors	OR (SE)[a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value	OR (SE) [a]	P value
MST	0.64 (0.20)	0.159	-		-		-		-	-
MUST	-		0.87 (0.38)	0.754	-		-		-	
NRS2002	-		-		1.85 (0.56)	0.039	-		-	

MNASF	-		-		-		1.00 (0.14)	0.945	-	
PGSGA	-		-		-		-		1.72 (0.61)	0.128
Gender	0.98 (0.30)	0.951	0.99 (0.30)	0.970	1.03 (0.31)	0.916	1.02 (0.31)	0.956	1.02 (0.31)	0.932
Age	1.00 (0.01)	0.965	1.00 (0.01)	0.956	0.99 (0.01)	0.825	1.00 (0.01)	0.973	1.00 (0.01)	0.778
Smoker	1.19 (0.46)	0.654	1.17 (0.45)	0.678	1.21 (0.47)	0.626	1.18 (0.46)	0.673	1.20 (0.46)	0.642
Venous	0.39 (0.34)	0.282	0.43 (0.38)	0.340	0.40 (0.35)	0.300	0.43 (0.38)	0.337	0.36 (0.32)	0.253
Aneurysmal	1.36 (0.83)	0.618	1.30 (0.80)	0.670	1.17 (0.72)	0.796	1.31 (0.80)	0.661	1.16 (0.71)	0.805
PAD	1.20 (0.63)	0.726	1.19 (0.62)	0.736	1.17 (0.72)	0.796	1.18 (0.61)	0.755	1.07 (0.56)	0.898
DM Limb	1.11 (0.59)	0.843	1.11 (0.59)	0.842	1.06 (0.56)	0.913	1.09 (0.58)	0.869	1.02 (0.54)	0.977
Other vascular	0.76 (0.45)	0.638	0.80 (0.48)	0.716	0.74 (0.44)	0.609	0.77 (0.45)	0.653	0.68 (0.40)	0.516
Constant	0.31 (0.28)	0.200	0.28 (0.26)	0.169	0.26 (0.24)	0.147	0.26 (0.24)	0.141	0.32 (0.29)	0.211

[a] OR (SEM) = Odds ratio (standard error of the mean)

Appendix 13: Definitions of the NHCDC Cost Buckets

1.1. Ward Medical Clinical Services Cost Bucket

The total inpatient related cost of medical services (salaries and wages of all medical officers including sessional payments) for each separation.

Excludes Medical Salaries & Wages reported in:

- Imaging
- Pathology
- Critical Care
- Operating rooms
- Emergency Department
- Specialist Procedure suites

Includes Medical Salaries & Wages posted in Clinical Service areas

Excludes the following other costs:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

1.2. Ward Nursing Clinical Services Cost Bucket

Include here all costs associated with nursing care in general ward areas. Exclude any nursing costs that are more strongly associated with other headings below. The total inpatient related cost of nursing (salaries and wages) for each separation.

Excludes nursing Salaries & Wages reported in:-

- Imaging
- Pathology
- Critical Care
- Operating rooms
- Emergency Department
- Specialist Procedure suites

Includes nursing Salaries & Wages posted in Clinical Service areas

Excludes:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

1.3. Non-Clinical Salaries

The only costs reported in this bucket will be Direct Other S&W for departments considered to be in a Clinical Group e.g. wards and clinics.

1.4. Pathology Cost Bucket

A part of the health care facility that performs diagnostic clinical laboratory tests for the diagnosis and treatment of patients or pathology cost provided by an external organisation.

Exclude:

- Pathology costs reported in;
  - Critical Care
  - Operating rooms
  - Emergency Departments
  - Specialist procedure suites
- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

Include:

- Medical salaries and wages reported in Pathology
- Nursing salaries and wages reported in Pathology
- Allied Health salaries and wages reported in Pathology
- Other salaries and wages reported in Pathology
- Medical surgical supplies reported in Pathology
- Pharmacy reported in Pathology
- Goods and services reported in Pathology
- Other costs reported in Pathology
- Pathology charges

1.5. Imaging Cost Bucket

A part of the health care facility where diagnostic and therapeutic images are produced under the direction of a qualified radiographer or suitably qualified technician and reported by a medical practitioner (radiologist).

Exclude:

- Imaging costs reported in;
  - Critical Care
  - Operating rooms
  - Emergency Departments
  - Specialist procedure suites
- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses

- Prostheses
- Oncosts

Include:

- Medical salaries and wages reported in Imaging
- Nursing salaries and wages reported in Imaging
- Allied Health salaries and wages reported in Imaging
- Other salaries and wages reported in Imaging
- Medical surgical supplies reported in Imaging
- Pharmacy reported in Imaging
- Goods and services reported in Imaging
- Other costs reported in Imaging

1.6. Allied Health Cost Bucket

A part of the health care facility that delivers clinical services by qualified health professionals (exclusive of medical and nurse trained personnel) who have direct patient contact and provide services listed below:

Audiology	Physiotherapy
Dietetics	Podiatry
Occupational Therapy	Social Work
Orthoptics	Speech Pathology
Orthotics	Other Allied Health
Psychology	

Exclude Allied Health Salaries & Wages reported in:-

- Critical Care
- Operating Rooms
- Imaging
- Pharmacy
- Pathology
- Emergency Departments
- Specialist Procedure suites

Exclude:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

Include:

- Allied Health Salaries & Wages reported in Clinical Service areas
- Allied Health Salaries & Wages reported in Allied Health Cost Centre
- Other Salaries & Wages reported in Allied Health Cost Centre
- Medical / Surg Supplies reported in Allied Health Cost Centre
- Goods & Services reported in Allied Health Cost Centre
- Other Costs reported in Allied Health Cost Centre

1.7. Pharmacy

A part of the health care facility associated with the provision of pharmaceuticals. This includes purchasing, production, distribution, supply and storage of drug products and clinical pharmacy services.

Excludes pharmacy costs reported in:-

- Critical Care
- Operating Rooms
- Emergency Departments
- Pathology
- Imaging
- Specialist procedure suites

Excludes:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

Includes:

- Pharmacy costs reported in Clinical Service areas
- Allied Health salaries and wages in pharmacy cost centre

- Other salaries and wages in pharmacy cost centre
- Drugs in pharmacy cost centre
- Medical surgical supplies in pharmacy cost centre
- Goods and services in pharmacy cost centre
- Other costs in pharmacy cost centre

Note: Where pharmaceuticals are an intrinsic part of the provision of services in other parts of the health agency they are reported in that cost bucket (eg drugs used to enhance imaging results are reported in imaging). Otherwise they are reported in the cost bucket labelled pharmacy.

1.8. Critical Care Cost Buckets (several)

Critical care is the combination of Intensive Care and Coronary Care units.

An intensive care unit (ICU) is a designated ward of a hospital which is specially staffed and equipped to provide observation, care and treatment to patients with actual or potential life threatening illnesses, injuries or complications from which recovery is possible.

The ICU provides special expertise and facilities for the support of vital functions and utilises the skills of medical, nursing and other staff trained and qualified in the management of these problems.

Critical Care **excludes:**

- high dependency units
- special care nurseries
- intensive nursing units
- step down units

Contains the following cost centres:

- Adult Intensive Care Units
- Neonatal Intensive Care Units
- Paediatric Intensive Care Units

Coronary Care Units defined as follows:

Nature of Facility
A Coronary Care Unit must be a separate and self contained facility in the hospital capable of providing basic multi-system and advanced cardiac life support.

Care Process
A CCU must be capable of providing invasive cardiac monitoring for a period of several days.

Clinical Standards and Staffing Requirements
A Coronary Care unit must substantially conform to appropriate guidelines of the ACHS.

Other Critical Care

Exclude:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

Include:

- Medical salaries and wages reported in critical care
- Nursing salaries and wages reported in critical care
- Allied Health salaries and wages reported in critical care
- Other salaries and wages reported in critical care
- Medical surgical supplies reported in critical care
- Pharmacy reported in critical care
- Goods and services reported in critical care
- Pathology **provided and reported** in critical care
- Imaging **provided and reported** in critical care
- Other costs reported in critical care

1.9. Operating Rooms (OR) Cost Bucket

A part of the health care facility functioning under sterile conditions where significant surgical procedures are carried out under the direction of suitably qualified medical practitioners.

The operating room must be equipped to deliver general anaesthesia and conform to the College of Anaesthetists and Faculty of Intensive Care standards.

Exclude:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

Include:

- Medical salaries and wages reported in operating rooms
- Nursing salaries and wages reported in operating rooms
- Allied Health salaries and wages reported in operating rooms

- Other salaries and wages reported in operating rooms
- Medical surgical supplies reported in operating rooms
- Pharmacy reported in operating rooms
- Goods and services reported in operating rooms
- Pathology **provided and reported** in operating rooms
- Imaging **provided and reported** in operating rooms
- Other costs reported in operating rooms

1.10. Specialised Procedures Suites (SPS) Cost Bucket

A part of the health care facility designed and equipped specifically to provide an environment where diagnostic and therapeutic procedures can be performed under the direction of suitably qualified medical practitioners.

These areas **do not** conform to the requirements of the Operating Room definition.

Excludes general-purpose ward/procedure rooms.

Exclude:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts

Include:

- Medical salaries and wages reported in SPS
- Nursing salaries and wages reported in SPS
- Allied Health salaries and wages reported in SPS

- Other salaries and wages reported in SPS
- Medical surgical supplies reported in SPS
- Pharmacy reported in SPS
- Goods and services reported in SPS
- Pathology **provided and reported** in SPS
- Imaging **provided and reported** in SPS
- Other costs reported in SPS

1.11. Emergency Department Cost Bucket

A part of the health care facility designed and equipped specifically to provide an environment where patients presenting in an unscheduled manner can be triaged, assessed and treated.

This would include a capability to provide complex, multi-system life support (including mechanical ventilation and invasive cardiovascular monitoring) for a limited period of time.

These areas conform to the requirements of the ACHS trauma guidelines.

Exclude:

- Depreciation & Amortisation
- LSL & Annual Leave Revaluation
- Bad Debt Expenses
- Interest & Other Financial Expenses
- Prostheses
- Oncosts
- EECU costs

Include:

- Medical salaries & wages reported in emergency department
- Nursing salaries & wages reported in emergency department
- Allied Health salaries & wages reported in emergency department
- Other salaries & wages reported in emergency department
- Medical surgical supplies reported in emergency department
- Pharmacy reported in emergency department
- Goods & services reported in emergency department
- Pathology **provided and reported** in emergency department
- Imaging **provided and reported** in emergency department
- Other costs reported in emergency department

1.12. Ward Supplies - Goods, Supplies & Services Buckets

Comprises, For Clinical service (Wards/clinics) only:
3 cost buckets-

Bucket -Direct Goods & services
Bucket- Medical and surgical supplies
Bucket- Ward/clinic Overheads (Indirect G&S and Indirect or allocated Other S&W)

Exclude:

Goods, Supplies and Services to allied health, critical care, emergency department, imaging, pathology, operating room and pharmacy.

1.13. Prostheses

The costs of prostheses used for each separation. This will include prostheses appearing on hospital accounts. Include prostheses reported in:

Allied Health
Operating Rooms
Critical care
Emergency Departments
Specialist Procedure suites
Clinical Service areas

1.14. Depreciation & amortisation

As defined in the Department of Health Common Chart of Accounts

1.15. Oncosts

Includes:

- Superannuation
- Termination payments
- Lump Sum payments
- Fringe Benefits Tax
- Long Service Leave
- Payroll Tax
- Workers compensation

Excludes items paid as part of a salary package such as:

- Salaries and wages
- Sick and Annual Leave
- Leave loadings paid
- Allowances such as motor vehicle, rent, uniform, regional allowances etc.

1.16. Hotel Services

The Hotel Services bucket is a grouping of the following overheads type services:

- Cleaning Services
- Linen & Laundry Services
- Food Services (patients)
- General Hotel Services
- Porters and Orderlies

The majority of these items are allocated as overheads, although ‘Direct’ payments should be included. eg. cleaning re-charges to each ward.