MALNUTRITION IN OLDER GENERAL MEDICAL INPATIENTS: IDENTIFICATION, PREVALENCE AND BENEFITS OF EARLY NUTRITIONAL INTERVENTION

by

Dr Yogesh Sharma

MBBS; MD; FRACP

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College of Nursing and Health Sciences

Flinders University, Adelaide, South Australia

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TABLE OF ABBREVIATIONS

AFA Arm fat area

AMA Arm muscle area

AMI Acute myocardial infarction

AMU Acute medical unit

ASPEN American society of parenteral and enteral nutrition

BMI Body mass index

CCK Cholecystokinin

CEA Cost effectiveness analysis

CEAC Cost effectiveness acceptability curve

CEP Cost effectiveness plane

CGA Comprehensive geriatric assessment

CHF Congestive heart failure

CI Confidence interval

COPD Chronic obstructive pulmonary disease

CT Computed tomography

CUA Cost utility analysis

DRG Diagnosis related group

DRM Disease related malnutrition

DXA Dual-energy x-ray absorptiometry

ED Emergency department

EQ5D 5L European quality of life questionnaire 5 dimension 5 level

ESPEN European society of parental and enteral nutrition

FMC Flinders Medical Centre

GDS Geriatric depression scale

GNRI Geriatric nutrition risk index

GP General practitioner

HAP Hospital acquired pneumonia

HGS Handgrip strength

HRQoL Health related quality of life

ICD-10-AM International classification of diseases tenth revision Australian modification

ICER Incremental cost effectiveness ratio

ICU Intensive care unit

IL Interleukin

IQR Inter quartile range

LASA Longitudinal Ageing Study Amsterdam

LOS Length of hospital stay

MAMC Mid arm muscle circumference

MBS Medicare benefit schedule

MET Medical emergency response team

MIA Malnutrition inflammation atherosclerosis

MNA Mini nutrition assessment

MNA-SF Mini nutrition assessment short form

MUAC Mid upper arm circumference

MUST Malnutrition universal screening tool

n-3 PUFA n-3 Long-chain polyunsaturated fatty acids

NRI Nutrition risk index

NRS Nutrition risk screening

NSW New South Wales

ONS Oral nutrition supplements

PBAC Pharmaceutical benefits advisory committee

PBS Pharmaceutical benefits scheme

PEM Protein energy malnutrition

PEN Parenteral nutrition

PG-SGA Patient generated subjective global assessment

ProBNP pro b-type natriuretic peptide

PYY Peptide YY

QALY Quality adjusted life year

RCT Randomized controlled trial

ROC Receiver operating characteristic

SD Standard deviation

SE Standard error

SF-QoL Short form quality of life

SGA Subjective global assessment

SK test Skewness kurtosis test

TNFα Tumor necrosis factor alpha

TST Triceps skinfold thickness

UK United Kingdom

USA United States of America

VAS Visual analogue scale

WHO World health organization

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SUMMARY

Malnutrition is common in hospitalized patients and is associated with adverse clinical outcomes and is costly for the public health system. Although hospitals have established nutrition screening protocols, still patients miss nutrition screening because of unknown reasons. The malnutrition universal screening tool (MUST) is commonly used in hospitalized patients but has not been validated in older general medical patients. With an ageing population it is possible that the prevalence of malnutrition is increasing and this needs further verification. Clinicians need to be informed about the clinical consequences of malnutrition and whether malnutrition influences the risk for readmission and can be used in readmission prediction models. The clinical and economic benefits of nutrition intervention in general medical patients needs further clarification because recent research has suggested inconsistent benefits of nutrition intervention in older medical patients.

This research investigated factors responsible for a missed nutritional screening and determined the prevalence and clinical consequences of malnutrition in older general medical inpatients. In addition, a randomized controlled trial (RCT) tested clinical and economic benefits of an early and extended nutritional intervention in older medical inpatients.

This study found that over 50% of older general medical patients were malnourished and a similar number missed nutrition screening. Factors such as patients' outward appearance and location in the hospital were more likely to be associated with a

missed nutrition screening. The MUST was confirmed as a valid nutrition screening tool when compared against a reference standard in older medical patients. Malnourished patients were found to have poor clinical outcomes manifesting as a longer length of hospital stay (LOS), a higher number of nosocomial complications, higher mortality and more frequent readmissions following hospital discharge. An RCT, comparing an early and extended nutrition intervention in 148 older general medical patients over a period of 3-months, found that nutrition intervention was associated with an improvement in nutritional status and also resulted in a significant shortening of LOS in the intervention group. Economic evaluation conducted alongside the clinical trial found that nutrition intervention was cost-effective in terms of both an improvement in costs per unit improvement in nutrition score and costs per quality adjusted life years (QALY) gained and resulted in net cost savings of AU$907 per patient.

This research suggests that there are clinical and economic benefits of treating older malnourished patients. The findings of this study provide compelling evidence to clinicians to incorporate nutrition screening in their practice and for the policy makers to justify greater allocation of resources to improve the nutrition status of hospitalized patients.

SIGNED DECLARATION

I, Yogesh Sharma, declare that this thesis presents work carried out by myself and does not incorporate, without acknowledgement, any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge does not contain any material previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

Yogesh Sharma

YOGESH SHARMA

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Chapter 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Malnutrition in hospitalized older patients: a major public health issue

Healthy ageing has been regarded as one of the major challenges of the current century as the number of people aged 60 years or over has doubled since the 1980's and is forecast to increase to more than 2 billion people by 2050.[1] The number of people aged 80 years or over are predicted to quadruple in the period between 2000-2050.[2]

According to the Australian Bureau of Statistics, by 2064 there will be 9.6 million people above the age of 65 years and 1.9 million over the age of 85 years in Australia.[3] Older people are more likely to be hospitalized and data suggests that in 2013-14, 40% of all hospital separations in Australia were for people aged 65 years and over (**Figure 1)**.[4]

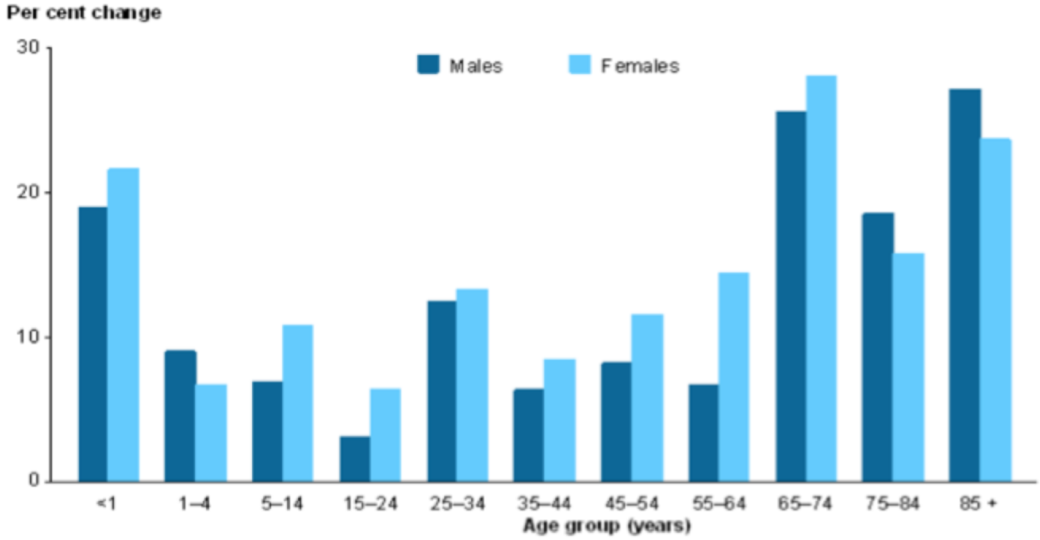

Figure 1 Percent change in hospital separations by sex and age group, 2010-11 to 2014-15

1.2 Definition of Malnutrition/Undernutrition

Malnutrition can be defined as "a state resulting from lack of intake or uptake of nutrition that leads to an altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease".[5] Malnutrition can result from starvation, disease or advanced ageing, alone or in combination.[6]

According to the American Society of Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics (Academy)[7] six criteria need to be considered for the potential diagnosis of malnutrition: i.e. low energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, fluid accumulation, and reduced hand grip strength and at least two should be fulfilled for the diagnosis of malnutrition.

Malnutrition can further be classified according to etiology as disease related malnutrition (DRM) with or without inflammation and malnutrition without disease.

1.2.1 DRM with inflammation

DRM is a special type of malnutrition caused by a concomitant disease. DRM with inflammation is a catabolic condition, including anorexia and tissue breakdown elicited by an underlying disease.[8] Advanced ageing per se may contribute to the state of inflammation.[9] In addition, inactivity and bed rest contributes to muscle catabolism during DRM with inflammation.

The concepts of chronic DRM with inflammation and cachexia are exchangeable, although cachexia is often incorrectly perceived as end stage malnutrition.

Cachexia is traditionally defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle mass with or without loss of fat mass.[10] The prominent feature of cachexia is weight loss in adults.[11] Cachexia occurs frequently in patients with end-stage organ diseases that are complicated by catabolic inflammatory responses e.g. cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease and end-stage congestive heart failure.[12]

1.2.2 DRM without inflammation

DRM without inflammation or non-cachectic malnutrition is a form of disease triggered malnutrition where inflammation is not a major contributing factor rather other factors like dysphagia, intestinal malabsorption, neurological diseases like Parkinson’s disease, amyotrophic lateral sclerosis, dementia and psychiatric illnesses like depression and anorexia nervosa are typical examples of this form of malnutrition.[13] Advanced ageing itself may lead to malnutrition by non-inflammatory mechanisms by causing anorexia called “anorexia of ageing” **(Figure 2)**.[14]

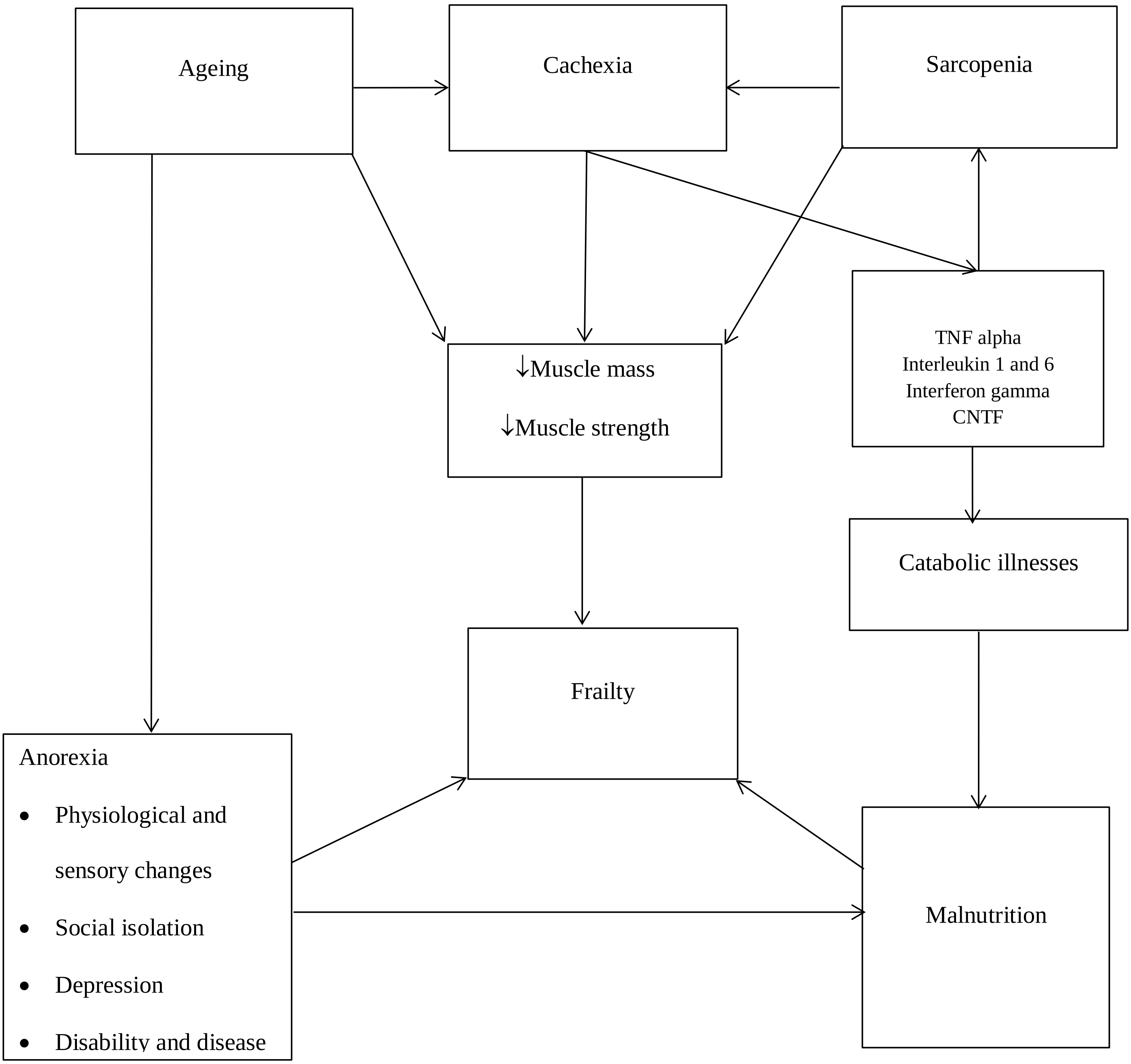

Figure 2 The geriatric syndromes and the vicious cycle leading to reduction is skeletal muscle mass and wasting. TNF, tumor necrosis factor; CNTF, ciliary neurotrophic factor.

1.3 The Geriatric syndromes

Malnutrition should be differentiated from two other related syndromes:

1.3.1 Sarcopenia

Sarcopenia is a syndrome of progressive and generalized loss of skeletal muscle mass, strength and function (performance) with a consequent risk of adverse outcomes **(Table 1)**.[15] Sarcopenia can be further classified as primary (associated as part of ageing) or secondary as a consequence of disease, activity related (e.g. disuse) or nutrition related (e.g. protein deficiency). Diagnostic criteria for sarcopenia have not been firmly established to date but recommendations of the European Working Group on Sarcopenia in Older Persons[15] suggest using an algorithm based on loss of muscle mass and strength and/or function. Muscle mass can be estimated by any validated technique such as dual energy x-ray absorptiometry (DXA) or computed tomography (CT) scanning.[16] Reduced muscle function can be measured by reduced gait speed or failure of chair standing tests and muscle strength can be determined by handgrip strength.[15]

Table 1 Differences between sarcopenia, cachexia and frailty

	Sarcopenia	**Cachexia**	**Frailty**
Definition	Muscle mass <2SD of young healthy population, decreased muscle	Weight loss >5% in 6 months	Reduced physiological reserves which increases

	Sarcopenia	Cachexia	Frailty
	function		vulnerability to adverse outcomes
Mechanism	Ageing	Pathologic	Ageing
Comorbid conditions	+/−	+++	+++
Functional limitation	++	+++	+++
Inflammation	-	++	+
Fat mass	Increased	Decreased	Increased
Protein degradation	+/−	+++	+
Resting energy expenditure	Decreased	Increased	Decreased
Anorexia	+	++	+

1.3.2 Frailty

The definition of frailty is evolving and is an emerging concept still under discussion among experts in geriatrics. Frailty is defined as a state of vulnerability and non-resilience with limited reserve capacity in major organ systems.[17] This leads to reduced capability to withstand stress such as trauma or disease and thus frailty is a risk factor for dependence and disability. Frailty is mainly associated with advanced age but can be modified by lifestyle interventions. Fried et al[18] has suggested that three out of five criteria: weight loss, exhaustion (fatigue), low physical activity, slowness (e.g. reduced gait speed) and weakness (e.g. reduced handgrip strength) be used to define frailty.

1.4 Malnutrition in older adults

Ageing is associated with changes in body structure and function and older adults experience a progressive, generalized loss of skeletal muscle and physical function with increased risk of disability, poor health related quality of life (HRQoL) and death.[19]

Data shows that older patients are at a high risk of malnutrition than others and reasons for poor nutritional status in this group are multifactorial and include physiological, social and psychological factors which affect food intake and weight and this is further exacerbated by underlying medical illness **(Table 2)**.[20-22]

Ageing is associated with a decline in senses of smell and taste and reduced salivary secretions which decreases flavor of food and hence reduction in food intake.[23 24] Hormonal factors include a reduced sensitivity to ghrelin or the " hunger hormone" and increased cholecystokinin (CCK) which is a prototype satiety hormone and peptide YY (PYY) both of which convey anorexigenic signals to the hypothalamus.[25 26] Similarly increased leptin and insulin levels play an important role in anorexia of ageing.[27] Ageing is associated with altered gut motility and delayed gastric emptying, which contributes to post prandial satiety.[25 28] Moreover, chronic low grade inflammation accompanies ageing with increased circulating levels of interleukin (IL) 1, IL6 and tumor necrosis factor alpha (TNF α) which are known to suppress appetite and delay gastric emptying and thus contribute to the anorexia of ageing.[29 30]

Table 2 Factors that increase risk of malnutrition in older people (adapted from Sonya Brownie Why are elderly individuals at risk of nutritional deficiency International Journal of Nursing March 2006)

Determinant of nutrition deficiency	Consequence
Physiological changes	
Changes in body composition	Reduced metabolic rate
Reduced lean body mass	Reduced energy requirements
Increased fat stores	Increased truncal obesity
Reduced cellular capacity to store water	Dehydration
Changes in gastrointestinal tract	
Decline in oral health-dental loss, poorly fitting dentures, gingivitis	Reduction in food intake
Reduced gastrointestinal motility	Reduced nutrient absorption, anorexia
Changes in sensory function	
Diminished taste and smell sensation	Anorexia, inappropriate food choices
Changes in fluid and electrolyte regulation	
Reduced glomerular filtration rate, reduced renal flow and altered thirst sensation	Dehydration
Chronic diseases	
Stroke	Chemosensory impairment
Cancers	Increased metabolic rate
Arthritis and osteoporosis	Anorexia

Determinant of nutrition deficiency	Consequence
Visual impairment	Loss of dexterity and coordination
Dementia	Difficulty with food preparation
Depression	
Polypharmacy	Impaired taste
	Altered absorption, utilization and excretion of essential nutrients
Psychosocial determinants	Inability to self-feed
Social isolation	Reduced food security
Reduced mobility and lack of transport	Inappropriate food choices
Financial constraints	

1.5 Prevalence of Malnutrition in hospitalized patients

Malnutrition is widely prevalent in hospitalized elderly with reported rates of between 30-80% depending upon the type of settings whether medical or surgical patients and depending upon the criteria used to diagnose malnutrition **(Table 3)**. Cereda et al[31] in their meta-analysis involving 66 studies in hospitalized patients over the age of 60 years and using mini nutritional assessment (MNA) tool found that the prevalence of malnutrition was 22% (95% CI 18.9 – 25.2) and 45.6 % (95% CI 42.7 – 48.6) were at risk of malnutrition. They highlighted that one tool may not be suitable to diagnose malnutrition in all settings and future research should also focus on the identification of factors which can affect the prevalence of malnutrition. Rahman et al[32] in their study in an acute care hospital in Canada using Malnutrition Universal Screening tool found that 45% of elderly patients with a mean age of 71 years were malnourished. McWhirter et al[21] found that prevalence of malnutrition was 40% at the time of admission to an acute teaching hospital and out of these, fewer than 50% had any documentation of their nutritional status in the case-notes. Alvarez-Hernandez et al[33] in their PREDyCES study in Spanish hospitals found that 1 in 4 patients admitted to hospital were malnourished and multivariate analysis showed that age, gender, diabetes, dysphagia and polypharmacy were the main factors associated with malnutrition. Lazarus et al[34] in their study found that prevalence of malnutrition was 42.3% in New South Wales hospitals and there was poor documentation of malnutrition and only 1 out of 137 malnourished patients had any documentation of that fact and only 15.3% were referred for nutrition intervention. They found that missed diagnosis of malnutrition had cost their hospital AU$634516 for that year under a care payment system.

Thomas et al[35] in their study found that prevalence of malnutrition was 53% in an acute assessment unit using the patient generated subjective global assessment (PG-SGA) tool and was associated with prolonged LOS. Given the short LOS in an acute assessment unit they emphasized the need for outpatient and domiciliary dietetic intervention and follow-up.

Charlton et al[36] in their retrospective analysis of 2076 patients from two sub-acute hospitals in NSW, Australia found that 30% patients were malnourished and 53% were at risk of malnutrition. LOS was higher in malnourished patients and hazard rate of death in the malnourished patients was 3.41 times the rate in the well-nourished group. Discharge to a higher level of residential care was 33.1%, 16.9% and 4.9% for malnourished, at-risk and well-nourished patients, respectively; $P \leq 0.001$

Marshall et al[37] in their study have reported the prevalence of malnutrition to be 53% using the PG-SGA tool (class B and class C) in rural rehabilitation patients in Australia. In their study they found that the PG-SGA score and ratings performed consistently well when compared to the International Classification of Diseases Tenth Revision Australian Modification (ICD-10-AM) classification of protein-energy malnutrition.[38]

Although the above studies suggest a high prevalence of malnutrition in hospitalized patients, limited studies have been conducted in older general medical patients in the Australian health care settings. A study confirming this finding in the general medical patients may help convince and increase awareness of this problem among the general physicians taking care of these patients.

Table 3 Prevalence of protein energy malnutrition

Author & Country	**N subjects**	**Age, y (Mean ±SD)**	**Criteria to define PEM**	**Prevalence**
McWhirter et al., 1994[21], UK	500	range 16 – 64	BMI	BMI ≤20 – 36%,
Braunschweig et al., 1999[39], US	404	53.7 (SE 0.82)	SGA	55%
Correia et al., 2003[40], Brazil	709	50.6 (17.3)	SGA	31.8%

Author & Country	N subjects	Age, y (Mean ±SD)	Criteria to define PEM	Prevalence
Thomas et al., 2007[35], Australia	64	79.9	PG-SGA	53%
Singh et al., 2006[41], Canada	69	66	SGA	69%
Pirlich et al., 2006[42], Germany	1886	62.2 (17.4)	SGA, AMA, AFA	SGA-27.4%; AMA <10th percentile-11.3%, AFA <10th centile-17.1%
Buurman et al., 2012[43], The Netherlands	639	78.2 (7.8)	CGA	52%
Alvarez-Hernandez et al., 2012[33], Spain	1718	range 18 - 85	NRS 2002	23.7%
Holyday et al., 2012[44], Australia	143	83.5 (SE 0.8)	MNA	83%
Dent et al., 2014[45], Australia	172	85.2 (6.4)	MNA and GNRI	MNA-31%, GNRI-48%
Baek et al., 2015[46], Korea	141	73.5 (5.2)	MNA, MNA-SF, GNRI, MUST, NRS 2002	MNA-65.9%, MNA-SF-72.3%, GNRI-60.3%,

Author & Country	**N subjects**	**Age, y (Mean ±SD)**	**Criteria to define PEM**	**Prevalence**
				MUST-36.2%, NRS 2002-56%
Rahman et al., 2015[32], Canada	315	71	MUST	45%
Bonetti et al., 2017[47], Italy	1066	76.8 (7.8)	MNA	22%

SD, standard deviation; y, years; PEM, protein energy malnutrition; UK, United Kingdom; BMI, body mass index; SE, standard error; US, United States; SGA, subjective global assessment; PG-SGA, patient generated subjective global assessment; AMA, arm muscle area; AFA, arm fat area; CGA, comprehensive geriatric assessment; NRS 2002, nutritional risk screening 2002; MNA, mini nutritional assessment; GNRI, geriatric nutritional risk index; MNA-SF, mini nutritional assessment short form; MUST, malnutrition universal screening tool

1.6 Changes in nutritional state during hospital admission

The prevalence of malnutrition in the community is 5-10%[48] and when these patients are admitted to a hospital they are at a risk of further nutritional decline due to a number of factors including lack of awareness of malnutrition among health professionals, anorexia due to acute illness, “nil per oral” orders, polypharmacy, dislike for hospital food and catabolic effects of illness **(Figure 3)**.[49 50] The stress of medical illness or treatment such as surgery increases nutritional demands which may not be met in the presence of anorexia and this eventually leads to weight loss.[51] Data suggests that weight loss in healthy volunteers is associated with apathy, depression and loss of motivation to recover.[52]

The factors associated with decreased nutritional intake in hospitalized patients are complex and even patients with a good appetite may not eat well due to factors like meals being placed outside reach,[22] inability to handle cutlery,[23] poor dentition[32] and frequent interruptions.[53]

McWhirter and Pennington[21] in their landmark study in hospitalized patients found that the majority of patients lose weight during a hospital stay and the greatest weight loss occurs in patients who are moderately malnourished at admission as compared to the severely malnourished who received intervention in their study. Similarly, Braunschweig et al[54] in their study using the subjective global assessment[55] tool in 404 adults ≥18 years, found that nutritional decline occurred in 38% of patients with normal nutrition status, 20% of those with moderate malnutrition and 33% with severe malnutrition at the time of admission.

Nutritional status frequently declines during hospital admission and is independently associated with detrimental outcomes and prolonged length of hospital stay (LOS).[22] Not eating while in hospital is detrimental to the patient's recovery and is indeed a multifactorial phenomenon. Patient may experience hyporexia because of disease related (e.g. cytokines) or psychological (e.g. depression, anxiety) reasons. Impaired cognitive function and dissatisfaction with hospital meals may also compromise food intake.[22 56] Furthermore, prolonged and unjustified orders for nothing by mouth may be prescribed because of diagnostic procedures and surgical interventions.[57] Factors that contribute to weight loss during hospital stay include the anorexia associated with underlying diseases, the catabolic stress of acute illness, insufficient oral intake and inappropriate management of nutritional problems.[58-60]

Malnutrition itself is, therefore associated with higher health-care costs because malnourished patients stay longer in hospitals, suffer more infectious and non-infectious nosocomial complications and have frequent hospital re-admissions and have a higher utilization of health-care resources in the community.[61] Very limited studies have looked into the nutrition status of older hospitalized general medical patients in the Australian health care settings and further research in this group will help determine the prevalence and consequences of malnutrition.

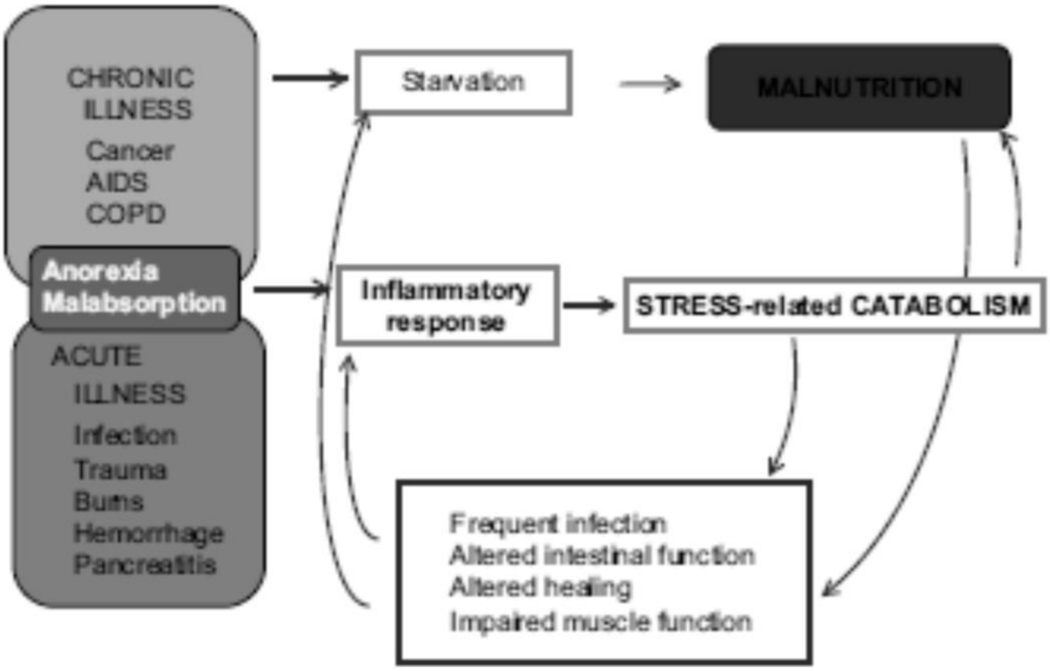

Figure 3 Vicious circle in the progression of malnutrition during acute illness adapted from Norman et al Clinical nutrition 2008[66]

1.7 Consequences of malnutrition in hospitalized patients

Malnutrition in hospitalized patients has a negative impact on their clinical outcomes and is associated with increased healthcare costs, independent of their underlying acute illness, associated co-morbidities, patient's age and socioeconomic factors.[58 62 63] In particular, malnutrition at admission is an independent predictor of subsequent hospital readmission and is associated with higher mortality after discharge.[64 65]

1.7.1 Malnutrition and LOS

Studies suggest that the average LOS is increased by 40-70% in malnourished patients as compared to the well-nourished patients **(Table 4)**.[66] Allard and colleagues in a multicenter study involving 1015 hospitalized patients with a mean age of 66 years (range 54 – 77), found that malnutrition at admission reduces the chances for discharge on any particular day (HR 0.73; 95% CI 0.62 – 0.86) and was independently associated with a prolonged LOS.[67] Similarly Caccialanza et al[58] in their study in 1274 ambulatory patients with a mean age of 60 years admitted to hospital for medical or surgical treatment found a longer LOS in those with a nutritional risk index (NRI) score of less than 97.5 (RR 1.64; 95% CI 1.31 – 2.06) and a significant association was found with in-hospital starvation of three or more days (RR 1.14; 95% CI 1.01 – 1.28). Lim et al in their study in a tertiary hospital in Singapore used the SGA tool to diagnose malnutrition and found that malnourished patients had longer hospital stays (6.9 ± 7.3 days vs. 4.6 ± 5.6 days, P = 0.001) and were more likely to be readmitted with 15 days of discharge (adjusted RR 1.9; 95% CI 1.1 – 3.2, P = 0.02).[62]

Table 4 Malnutrition increases length of hospital stay

Author and country	Subject n	Age y	Length of hospital stay (days)*	
			Nourished	Malnourished
Caderholm et al., 1995[68], Sweden	205	75 (range 74 – 76)	9.2	15.6
Edington et al., 2000[69], UK	850	58.5 (SD 18.3)	5.7	8.9
Correira et al., 2003[70], Latin America	9348	52.2 (range 33.8 – 70.6)	10.1	16.7
Kyle et al., 2004[71], Switzerland	652	57.3 (range 38.5 – 76.1)	11	10.2**/25.8***
Perlich et al., 2006[42], Germany	1886	62.2 (44.8 – 79.6)	11	15**/17***
Caccialanza et al., 2010[58], Italy	1274	60 (SD 16)	7	13
Lim et al., 2011[62], Singapore	818	51.9 (36.5 – 67.3)	6.9	4.6
Allard et al., 2016[67], Canada	1015	66 (range 54 – 77)	6	7**/9***

- P value significant; y, years; **Moderate malnutrition; ***Severe malnutrition

1.7.2 Malnutrition and mortality

A low body mass index (BMI) has been described as an independent predictor of shortened survival in the hospitalized older patients.[72] There is a close relationship between malnutrition and mortality not only in patients with chronic diseases like cancer[73] but also in acute care settings such as stroke and hip fracture **(Table 5)**.[74 75] Sullivan et al[64] in their study in 102 hospitalized patients found that those patients with a daily in-hospital nutrient intake of less than 50% of their total energy requirements (estimated using the Harris-Benedict equation)[76] had higher in-hospital mortality (RR 8.0; 95% CI 2.8 - 22.6) and 90-day mortality (RR 2.9; 95% CI 1.4 - 6.1). Malnourished patients admitted to the intensive care unit (ICU) have a poorer prognosis and survival.[77]

Table 5 Association between malnutrition and mortality

Author and country	Subjects	Setting	Mortality in malnourished vs. nourished
Van Wissen et al., 2016[78], The Netherlands	226	Hip fracture	In hospital mortality 27% and 1 year mortality 46% in malnourished vs. 7% and 17% in well-nourished
Buscemi et al., 2016[79], Italy	225	Medical inpatients	Malnourished patients with MNA scores <22 had higher mortality at 2 years (HR 1.85; 95% CI 1.22 – 2.81, P = 0.004)
Dizdar et al., 2015[80], Turkey	68	Infectious diseases	Malnourished patients with NRS score >3 had higher mortality due to infection (OR 2.92; 95% CI 1.43 – 5.97, P = 0.003)
Huang et al., 2016[81], China	1772	Geriatric patients with Coronary artery disease	At 27 months follow-up 22.8% mortality in malnourished patients vs. 9.8% in nourished group (HR 2.71; 95% CI 2.07 – 3.55, P < 0.001)
Gomes et al., 2016[82], UK	543	Stroke unit	At 6 months after stroke 42% mortality in patients at high risk of malnutrition vs. 6% in low risk group (HR 9.2; 95% CI 5.6 – 15.3, P < 0.001)

MNA, mini nutrition assessment; HR, hazard ratio; CI, confidence interval; NRS, nutrition risk screening

1.7.3 Malnutrition and morbidity

Malnutrition significantly prolongs convalescence following disease, surgery or trauma.[66] Studies suggest that the inflammatory process associated with acute illness is prolonged with impaired proliferation of fibroblasts with reduced collagen synthesis and neoangiogenesis and this increases the risk of pressure ulcers[83] and poor wound healing in surgical patients.[84-86] The degree of malnutrition correlates with the risk of infectious and non-infectious complications, in particular hospitalized malnourished patients are at a very high risk of developing nosocomial infections like pneumonia.[87 88] Schneider et al in their study in 1637 hospitalized patients found that the risk of nosocomial infections was 7.6% in moderately malnourished patients, 14.6% in severely malnourished patients as compared to 4.4% in non-malnourished patients.[88] Impaired nutrition status has been associated with respiratory muscle weakness[89] which impairs ventilatory drive and this prolongs ventilation duration and increases the need for reintubation with resultant prolonged ICU stay.[90-92]

Functional impairment is a well-known consequence of malnutrition due to skeletal muscle dysfunction and this contributes to falls, deconditioning and resultant prolonged LOS. Vivanti et al[93] in their study in hospitalized older patients with a mean age of 71 years found that the risk of falls was 42% in those severely malnourished as compared to 29% in well-nourished patients (OR 1.49; CI 0.8 – 2.7, $P < 0.20$) however their results did not reach statistical significance due to lack of study power. Marshal et al in their meta-analysis involving 1020 older patients ≥65 years, admitted in rehabilitation units concluded that malnutrition played a negative role on functional recovery and quality of life following discharge to the community.[94] In addition, their meta-analysis suggested that malnutrition is a significant factor for a patient to be admitted to a higher level of care or acute care than be discharged to the community.[95]

Various studies have found that malnutrition has an independent association with poor HRQoL.[96-99] A Swedish study involving 1402 patients in the age range of 60-96 years found that malnutrition was significantly associated with poor HRQoL, both in physical (OR 2.31; 95% CI 1.18 – 4.52) and mental (OR 2.34; 95% CI 1.22 – 4.47) dimensions. The correlation of malnutrition with HRQoL in the older subjects can be direct, as lower energy intake may influence subjective perception of well-being, or it could be indirect, by decreasing functional ability.

Malnutrition is regarded as one of the major factors contributing to unplanned readmissions in elderly patients. Jeejeebhoy et al[100] in their prospective study involving 1022 patients recruited from 18 acute care hospitals in Canada found that severe malnutrition was an independent predictor of 30-day readmission (OR 2.12; 95% CI 1.24 – 3.93). Lim et al[101] in their study in older patients found that those malnourished at admission were at 1.4 times higher risk of readmission after 90 days and 6 months of discharge but this significance diminished after the results were controlled for age, gender, ethnicity and diagnosis-related group (DRG). Ulltang et al in their study involving 153 patients admitted acutely with a mean age of 62 years found that those screened as at risk of malnutrition had over three times the odds of being readmitted to hospital within 90 days, compared with those screened not at risk.[102]

Bermejo et al[103] in their study in 145 hospitalized heart failure patients with a mean age of 69.6 years, found that proBNP (pro b-type natriuretic peptide) levels were directly correlated with nutritional status and malnutrition seems to be a mediator of disease progression and a determinant of poor prognosis. With a mean follow-up of 326 days, they found 27 (19%) had a hospitalization for heart failure and 61 (42.1%) were re-admitted for other reasons.

Although above studies indicate that malnutrition is associated with poor clinical outcomes in hospitalized patients, but still there is no convincing evidence that nutrition intervention is beneficial in medical inpatients as suggested by the findings of a recent meta-analysis.[104] A randomized controlled trial (RCT) investigating the effects of nutrition intervention study on clinical outcomes may help clarify this issue.

1.7.4 Economic implications associated with malnutrition

Due to longer LOS, need for more intensive treatment and higher unplanned readmission, malnutrition has undeniably also become a major economic issue. A study in the Netherlands found that the total additional costs of managing patients with disease related malnutrition were to €1.9 billion in 2011.[105] In Germany, UK and Ireland the annual costs of malnutrition on a national level have been calculated as €9 billion (2006), £15 billion (2007) and £1.5 billion (2009) respectively.[105-107] Robinson et al[108] demonstrated that patients with an impaired nutritional status on admission experienced 30% increase of hospital stay with an associated doubling of costs, even though the patients had similar severity of illness. A South American study[40] in 709 hospitalized patients found that malnutrition increased total costs by more than 300%

due to higher complications and longer LOS, they calculated that the mean daily costs of managing malnourished patient was US$228 as compared to US$153 for well-nourished patients. A Spanish study PREDyCES[109] found that the costs of managing patients who were at risk of malnutrition at hospital admission were significantly higher than the costs for those not at risk (€8590 ± 6127 vs. €7085 ± 5625, P = 0.015) and extrapolation of these results to national level found that the potential cost of hospital malnutrition in Spain was to the extent of €1.143 billion per year. In addition, Elia[110] found that after discharge malnourished patients have higher utilization of outpatient services with more frequent visits to their general practitioners as well as increased risk of residential care placement. After application of these costs, they calculated that the public expenditure of DRM in the UK was to the extent of £7.3 billion in 2003. Malnutrition may also indirectly increase healthcare costs by way of the casemix funding system, as exists in Australia and other countries around the world.[111] Under casemix based funding, hospitals are reimbursed for the patient admission based on diagnosis related group (DRG; Australian Refined Diagnosis Related Groups) assigned to the patient.[112] Malnutrition, when documented as a co-morbidity often results in a higher DRG classification and hence has the potential to attract greater hospital reimbursement.[113] A missed diagnosis and documentation of malnutrition thus generates less hospital revenue. Rowell and Jackson[114] in their study in Australian public hospitals found that a recorded diagnosis of malnutrition adds AU$1,745 per admission even after controlling for the underlying medical condition and treatment administered and estimated that in 2003-2004 the total cost of malnutrition to their hospital to be at least AU$10.7 million.

Milte et al[115] in their systematic review involving 16 economic evaluation studies have highlighted that only a small number of published studies have targeted economic benefits of protein and energy supplementation in older adults and the quality of published studies is variable. They suggested that there is a need for inclusion of high quality comprehensive economic evaluations alongside studies of clinical effectiveness to demonstrate the cost-effectiveness of nutrition intervention for the treatment of malnutrition.

1.8 Diagnosis of malnutrition often missed in hospitalized patients

Despite the high prevalence of malnutrition, malnourished patients are often discharged undiagnosed from acute care.[116] Part of the problem is that malnutrition does not have any specific signs and symptoms and weight loss is a very non-specific sign which could be due to underlying disease. Moreover, clinicians are not very familiar with the problem. To obtain BMI, good measurements of height and weight are necessary, using regularly calibrated equipment and some training for the staff. This should not be costly or onerous but neither of these conditions is commonly met in most hospital wards.[116] Jeznach-Steinhagen[117] found that only 43.4% patients were ever weighed during hospital admission whereas McWhirter and Pennington[21] found only 23% patients had been weighed at admission and information concerning any change in appetite and body weight was recorded in fewer than 50% of the admissions.

Kellet et al[113] found that although the prevalence of malnutrition in their study was up to 53%, only 0.9–5.4% of patients were coded as malnourished. There was a resultant loss of revenue of AU$8,536,200 per annum to their hospital. Middleton et al[118] in their study in older hospitalized patients found that 64% of the malnourished patients had not been identified during their hospital stay. There were a greater number of moderately malnourished patients who missed diagnosis as compared to severely malnourished. Studies have suggested that, in a busy clinical environment, some guesswork is used by the clinicians and patients who appear well-nourished may miss nutrition screening due to the false belief that they are unlikely to be malnourished. Agarwal et al[119] in the Australasian Nutrition Care Day Survey 2010 which involved 56 hospitals in Australia and New Zealand found an overall poor level of adherence to the recommended nutrition guidelines for weighing, screening and rescreening of patients during their hospital admission. Sullivan et al[50] in their study in older patients admitted to Veterans hospital, found inadequate screening for protein-energy malnutrition with the resultant missed opportunity to diagnose malnutrition. Therefore, support and nutrition therapy were underutilized and ineffectually managed. Studies suggest that simple nutrition parameters like weight may not be done during hospital admission.

It is not entirely clear what factors lead to a missed diagnosis of malnutrition in hospitalized patients. It is possible that some of the factors may relate to patients' logistics after admission to the hospital (e.g. location away from the home ward) and others may relate to availability of equipment (e.g. lack of properly calibrated weighing scales) or staff workload (e.g. reduced workforce on night shifts or during weekends or holidays). Although hospitals have established nutritional screening protocols, clinicians' adherence to these protocols and the exact nutrition screening rate needs ongoing verification to confirm that nutrition screening is up to the expected standards. So far, very few studies have investigated factors which lead to a missed diagnosis of malnutrition in hospitalized patients. Identification of these factors may pave the way for future targeted interventions which may help improve hospitals' performance in terms of improved nutrition screening. Moreover, there is a need for ongoing studies to check the prevalence rate of hospital malnutrition. It is possible that the prevalence of hospital malnutrition may change over time with the changing population dynamics as life expectancy is lengthening.[120] Nutrition screening early during the hospital admission gains further significance, as recent years have witnessed a reduction in LOS due to an increasing emphasis on medical ambulatory care and the hospital at home services.[121] It is possible that a shortening of LOS may lead to even a greater chance of nutrition screening being missed, unless it is performed early during hospital admission.

1.9 Screening of Malnutrition in current times

Due to the high prevalence of malnutrition, experts[122-124] now recommend nutrition screening of all patients at the time of hospital admission and refer patients identified at high nutrition risk for further assessment by an expert. In the last couple of decades a number of nutritional screening and assessments tools have been developed to obtain an indication of a patient's nutritional status. The terms "nutrition screening" and "nutrition assessment" are often used interchangeably in both the literature and clinical practice.[125] These terms may be confusing for physicians who may not understand the distinction and may think that the purpose of the tool is simply to identify malnourished patients. Moreover, tools which have been developed for nutrition screening have also been used as reference standards for comparison and validity testing.[126]

Understanding the differences between the tools is pivotal to ensure best clinical practice in the management of malnutrition, and may diminish some of the reported barriers to nutrition screening, such as lack of time and inadequate knowledge about nutrition.[127] Malnutrition screening is a quick and easy procedure using valid malnutrition screening tools, to identify patients who are malnourished or at risk of malnutrition and may benefit from intervention by a dietitian or an expert clinician.[128] Malnutrition screening tools are often designed in a questionnaire format addressing risk factors for malnutrition (e.g. anorexia or functional limitations) and indicators of malnutrition (e.g. recent unintentional weight loss) and are commonly administered by the nursing staff.[129] The commonly used malnutrition screening tools include: malnutrition screening tool (MST), MUST, short nutritional assessment questionnaire (SNAQ) and MNA-SF.[130-133] Malnutrition screening must be differentiated from nutritional assessment which is an in-depth, specific and detailed evaluation of nutrition status often performed by a trained dietitian.[129] The SGA, PG-SGA and MNA are commonly used nutrition assessment tools and in the absence of gold standard to diagnose malnutrition, these assessment tools has been used as reference standards in validation studies of malnutrition screening tools.[134-136]

No study has validated MUST against a reference standard like PG-SGA in general medical patients with multiple co-morbid illnesses. General physicians need convincing evidence that MUST has a good sensitivity and specificity in detecting malnutrition among general medical polymorbid patients. A study validating MUST against a reference standard in this subgroup of hospitalized patients can clarify this issue.

1.9.1 MUST

MUST was initially developed for use in the community by a multi-disciplinary group of health professionals and patients to detect both undernutrition and obesity in adults of different ages and diagnoses.[126] This tool includes assessment of a BMI score, a weight loss score, and an acute disease score.[137] It includes three parameters rating them as 0, 1 or 2 as follows: BMI >20 kg/m^2 = 0; 18.5 - 20.0 kg/m^2 = 1; <18.5 kg/m^2 = 2; acute disease: absent = 0; present = 2. Overall risk of malnutrition is established after addition of all points allocated, as follows: 0 = low risk; 1 = medium risk; 2 = high risk.[131] MUST has been designed to identify the need for nutritional treatment as well as establishing nutritional risk on the basis of knowledge about the association between impaired nutritional status and impaired function.[126 129 138] The MUST has been documented to have a high degree of reliability (low inter-observer variation) with a k = 0.88 - 1.00.[129] The use of this tool was later extended to other health care settings, including hospitalized patients, where again it has been found to have excellent inter-rater reliability with other tools, and predictive validity (LOS, mortality in elderly wards, and discharge destination in orthopedic patients).[125]

Velasco et al compared MUST with a more complex reference assessment tool, the SGA[55] and found a good agreement between these two tools (k = 0.635) and suggested the use of MUST for nutrition screening on admission to the hospital.[139] Poulia et al in their multicenter study involving 1146 patients found that MUST had a better correlation than NRS 2002 when compared to the ESPEN new diagnostic criteria for malnutrition for both outpatient (k = 0.777, P < 0.001 vs. k = 0.256, P = 0.001) and hospitalized patients (k=0.843, P < 0.001 vs. k = 0.228, P < 0.001).[140]. Various international nutrition societies; e.g. the European Society for Clinical Nutrition and Metabolism advises the use of MUST for older adults.[125]

Studies suggest that MUST score at admission can predict LOS. Kyle et al in their study in all newly admitted patients found that patients who had a high risk MUST score was associated with longer LOS (OR 3.1; 95% CI 2.1 – 4.7) whereas medium risk did not.[141] In the study by Amaral in patients with cancer, those with a higher MUST score stayed longer in hospital than those with a low score, adjusted for sex and age (OR 3.24; 95% CI 1.5 – 7.0).[142]. Stratton et al in their study in geriatric patients (mean age 85, SD 5.5) found that the LOS increased progressively with malnutrition risk category as determined by MUST (low risk, median LOS 15 days (95% CI 11 – 19), medium risk, median LOS 24 days (95% CI 16 – 32), high risk. 28 days (95% CI 21 – 35), P = 0.02).[143]

Koifman et al in their study involving newly admitted medical patients with a mean age of 67.6 years found that a MUST score of 2 or more (high risk) was an independent predictor of in-hospital mortality (19.3% vs. 3.2%, P < 0.001).[144] Raslan and colleagues compared MUST with NRS-2002 and mini nutritional assessment short form (MNA-SF) and found that it has a fair predictive validity for death, LOS and complications, with areas under the receiver operative characteristic (ROC) curve for all outcome measures of around 0.6 which was better than MNA-SF but inferior to NRS.[145]

MUST showed fair to good criterion or construct validity in several studies when applied to adult hospital patients but performance of MUST for screening malnutrition in older patients remains to be confirmed.[146] Cascio et al[147] in their systematic review compared the efficacy of five nutrition screening tools (MUST, MNA-short form, NRS, MST and GNRI) and found similar effectiveness in identifying patients at risk of malnutrition but emphasized that there has been limited research in the use of MUST in hospitalized older patients. This review suggested that future studies should focus on applying nutrition screening tools in older hospitalized patients and results should be compared using identical parameters such as age, acute condition and age-related comorbidities. Power et al[148] in their review involving 15 studies testing the validity of MUST against various reference standard tools, suggests that although MUST is a practical tool and has been widely accepted by the healthcare professionals for assessing malnutrition in the general adult population, its use in older adults across all healthcare settings remains uncertain.

A study comparing the validity of MUST against a reference standard in older hospitalized general medical patients may help fill this gap in literature.

1.9.2 SGA and PG-SGA

There is no gold standard reference assessment tool (comprehensive nutrition assessment by a registered dietitian is close to 'gold standard') for diagnosis of malnutrition[149] but experts[133 150] recommend that patients who are identified as at risk of malnutrition on nutrition screening should undergo further assessment to confirm the diagnosis of malnutrition by using one of the valid assessment tools.

SGA[55] is a method of nutritional assessment based on a medical history and physical examination, whereby each patient is classified as well-nourished (SGA A) or suspected of being malnourished (SGA B), or severely malnourished (SGA C).[134] SGA has been validated against objective nutrition parameters (% weight loss, BMI) measures of morbidity (survival, LOS), and quality of life and has a high degree of inter-rater reliability.[134 151] A further development of SGA is the PG-SGA, which incorporates score as well as global assessment.[135 152] The scored PG-SGA includes seven components for assessment: weight, food intake, nutrition impact symptoms, activities and function, medical condition, metabolic stress, and physical examination.[94 135] The questions regarding short-term weight loss and nutrition impact symptoms increase the PG-SGA's sensitivity to changes in nutrition status over a short period of time. The scored PG-SGA not only provides a global rating of nutrition status for a nutritional diagnosis but also provides a continuous numerical score for intervention triage.[153 154] Typical scores range from 0 to 35 with a higher score reflecting a greater risk of malnutrition. It has been demonstrated to be a valid method of nutrition assessment in a number of patient groups.[135 155-157] The PG-SGA score correlates with objective nutrition parameters [158], HRQoL, morbidity (survival, LOS), it has a high degree of inter-rater reproducibility and a high sensitivity and specificity when compared with other validated nutrition assessment tools **(Table 6)**.[135 155 157 158] Marshall et al[159] used the PG-SGA in a study involving older rehabilitation patients with a mean age of 79.1 (SD 7.3) years and found that both PG-SGA scores and ratings performed consistently well when compared to the ICD-10-

AM[38] criteria for classification of malnutrition. The ICD-10-AM classification is determined using BMI, weight history, dietary intake and a physical assessment of fat and/or muscle wasting and these criteria are used in Australian hospitals to provide casemix funding reimbursements.[113]

The continuous scoring system of the PG-SGA allows prioritization of patients requiring more urgent treatment and thus may facilitate more effective use of resources.[135] The PG-SGA score places people into triage categories indicating the need for nutrition or medical intervention: 0-1 points (category 1, no intervention required), 2-3 points (category 2, patient and family education required), 4-8 points (category 3, requires intervention by a dietitian), ≥9 points (critical need for symptom management and/or nutrition intervention).[160] In older subjects, however, the PG-SGA scores ≥7 have been found to identify malnutrition with a critical need for nutritional intervention.[94]

The PG-SGA score can be used as an objective measure to demonstrate the outcome in nutritional intervention studies **(Table 6).**[156] SGA has limitations, as it classifies patients into categorical groupings, and it is often difficult to demonstrate a change in nutritional status on the basis of SGA and it lacks sensitivity to detect improvements in nutritional status observed over a short period of time e.g. during hospital admission.[135] On the other hand, by performing serial measurements, the change in the PG-SGA score may be used to demonstrate subtle changes in nutritional status. Isenring et al[156] in their study in cancer patients receiving radiotherapy, demonstrated that a PG-SGA score of nine was required to move one SGA category. They highlighted that a patient assessed at weekly intervals may be classified as moderately malnourished on both occasions, however the PG-SGA score may reflect clinically important changes.

Mulasi et al[161] in their study in head and neck cancer patients found that higher PG-SGA scores (individuals at higher risk of malnutrition) directly correlated with bioelectric impedance analysis parameters suggestive of loss of muscle mass.

Table 6 Validity of PG-SGA in diagnosis of malnutrition

Author and country	No of patients	Setting	Comparison/Validity
Mulasi et al., 2016[161], USA	19	Head and neck cancer patients, mean age 59	Good agreement between ASPEN consensus criteria and PG-SGA sensitivity 94% and specificity 43%
Marshall et al., 2015[94], Australia	57	Rehabilitation patients, mean age 79.1 (7.3)	Using ICD-10-AM classification of malnutrition as reference PG-SGA score (sensitivity 92%, specificity 84%)
Kim et al., 2013[162], South Korea	35	Stroke patients, age range 60-89	Significant correlation between PG-SGA and MNA scores ($r = 0.651$, $P < 0.01$)
Laky et al., 2008[163], Australia	194	Gynecological cancer patients, mean age 58.5 (14.4)	Significant correlation of PG-SGA scores with albumin, Triceps skinfold thickness (TST) and total body

Author and country	No of patients	Setting	Comparison/Validity
			potassium to predict malnutrition
Desbrow et al., 2005[157], Australia	60	Hemodialysis patients, age range 63.9 ± 16.2	PG-SGA score ≥ 9 has sensitivity of 83% and specificity 92% to predict SGA class, significant correlations of PG-SGA score with serum albumin and percent weight loss over previous 6 months

PG-SGA, patient generated subjective global assessment; ASPEN, American society for parenteral and enteral nutrition; ICD-10-AM, international statistical classification of diseases 10th revision Australian modification; MNA; mini nutritional assessment; SGA, subjective global assessment

1.10 Malnutrition and HRQoL

The worldwide increasing older population has higher expectations of ‘the good life’ within society. At the same time, due to limited resources, there has been a push to reduce public expenditure and provide quality care and this has generated international interest in measurement of quality of life in this group.[164]

Medical care is no longer evaluated solely by traditional biomedical indicators and there is now a focus to have a broader concept of patient outcomes such as HRQoL.[165 166] The World Health Organization (WHO)[167] defines quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns. Health contributes to quality of life, and the actual impact of health and disease on quality of life is known as HRQoL. HRQoL is one dimension of a broader concept of quality of life and is defined in relation to optimum levels of mental, physical and social functioning; it includes relationships as well as perceptions of health, fitness, life satisfaction, and well-being.[168]. It has been proposed that assessment of quality of life, as a health outcome in older people, should include physical functioning and symptoms, emotional, behavioral, cognitive and intellectual functioning, energy and vitality; all combining to reflect HRQoL. Assessment of quality of life is now recognized as a clinically relevant outcome measure when evaluating new treatment strategies in patient populations including the older patient.[169 170]

The impact of nutrition on HRQoL has not been well documented, however there are several studies that have observed poorer HRQoL outcomes in malnourished patients when compared with well-nourished patients.[171-173] Rasheed and Woods[174] in their meta-analysis of 27 studies found that malnutrition is associated with poorer quality of life in older people (OR 2.85; 95% CI 2.20 – 3.70, $P < 0.001$). Investigations suggest that the strongest association of nutritional risk is with impaired physical functioning in the elderly followed by sensory abilities.[175 176] These findings may be attributed to the fact that physical issues are salient for elderly patients, as they may interfere with several important daily activities, including eating. The physical domains of quality of life includes pain perception, fatigue, mobility and sensory abilities (sight, touch, smell and taste); all of which can affect the nutritional status of older patients. In addition the decline of physiological function with ageing[177], which is itself exacerbated by underlying illnesses[178], interferes with the patient's ability to follow a balanced diet and thus can lead to a further decline of nutritional status.[179]

Interventions designed to improve nutritional status can lead to significant improvements in quality of life; both physical ($P = 0.002$) and mental ($P < 0.001$) components.[174] The assessment of HRQoL using patient-reported outcome measures has evolved greatly over the last decade.[180 181] One measure, the EuroQoL (EQ-5D), was developed jointly by a group of European-based researchers with the intent of constructing a simple, self-administered instrument that provided a composite index score representing the preference for a given health state.[182] The EuroQol group designed the new instrument to be quick and easy to be used alongside other measures of health status. This instrument provides both a health profile and an index for individuals or groups that allow clinical and economic evaluation of medical interventions.[183] Cardiovascular medicine and oncology are two areas where the EQ-5D has been used quite often, but new studies in musculoskeletal, respiratory, and gastrointestinal diseases have included the EQ-5D as a generic questionnaire.[180 184] Furthermore, the EQ-5D is one of a handful of measures recommended for use in cost-effectiveness analyses by the Washington panel on cost-effectiveness in health and medicine.[185]

The EQ-5D-5L questionnaire comprises of five single item dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[186] Using these responses, the EQ-5D-5L is able to distinguish between 3,125 states of health. A UK-specific algorithm developed using time-trade-off techniques can be used to convert the EQ-5D 5L health description into a valuation ranging from -0.281 to 1[187]. Scores less than 0 represent health states that are worse than death.[182] The EQ-5D-5L has been validated in different clinical populations.[188] Studies have shown that EQ-5D-5L has content and face validity and is expected to have better discriminative capacity, to detect changes in health state and sensitivity as compared to EQ-5D-3L with smaller ceiling effects.[189].

Very few studies have measured HRQoL according to the nutritional status of patients hospitalized in Australia and there is a need to test EuroQol in Australian health care settings.[190] Furthermore, there is a need to include HRQoL as an outcome measure in the nutrition intervention studies, as recent meta-analyses have highlighted that a major deficiency of the existing nutrition intervention trials is the lack of outcome measures which may be relevant to patients.[104 191] The effect of a nutrition intervention on HRQoL in older hospitalized patients may be difficult to assess, as a range of other factors (e.g. the effect of acute hospitalization, chronic co-morbidities and functional status) may also influence HRQoL.[192-195] Moreover, HRQoL often improves after hospital discharge due to recovery from acute illness.[196] Moreover, nutrition intervention studies so far have shed little light on the duration of intervention that will be required to improve clinical outcomes including HRQoL.[51] It has been suggested however that, after initiating nutrition intervention, the temporal pattern that usually follows is: first improvement in nutrition parameters like weight, then improved muscle function and lastly HRQoL.[197] From this information it seems obvious that any nutrition intervention limited only for the period of hospitalization will not sufficiently impact patients' HRQoL and that clinical trials of sufficient longer duration will be needed to determine whether nutrition intervention is really an effective strategy in improving HRQoL of older patients.

1.11 Treatment of malnutrition

Screening for undernutrition is useless and unethical if this is not accompanied by an effective nutritional intervention care plan. It is expected that adequate nutritional intervention prevents a further decline of nutritional status and may have a positive influence on disease outcomes compared to no treatment. RCTs providing "no" versus "adequate" nutritional intervention can answer this question but experts have expressed fears that these kinds of study protocols will not receive ethical approval.[146] Several studies **(Table 7)** have found beneficial effects of nutritional therapy in the malnourished inpatient population. A recent meta-analysis focusing on nutritional support in medical inpatients found that nutritional support was associated with increased intake of energy and protein and an increase in body weight,[104] however, there was a little effect on clinical outcomes including mortality, hospital acquired infections and functional outcome. The only significant impact of nutritional intervention, found in this meta-analysis, was on the reduction in the risk of non-elective readmissions which were significantly lower among the intervention patients. This meta-analysis found that the number of patients who needed to be treated for preventing one readmission was 23 (95% CI 16 – 52). This meta-analysis also found that LOS stay was shorter in the intervention group, but only in the subgroup of patients who were malnourished at the time of hospital admission.

Nutritional support in the form of oral nutrition (either dietary modification or use of oral nutritional supplements (ONS)) and enteral (tube) nutrition feeding is one of the most common interventions used in medicine.[104] However, there is a lack of comprehensive research data demonstrating beneficial effects of such interventions on clinical outcomes in the general medical inpatient population. This paucity might explain why there is no standard nutritional algorithm for use in general medical inpatients with multiple co-morbidities. Most guidelines from the ASPEN and the ESPEN have focused on specific medical disciplines (e.g. patients with cancer, sepsis etc.) or organ systems (e.g. chronic kidney disease, COPD and wound healing) but give little guidance on the nutritional management of general medical patients with multiple co-morbid illnesses. The lack of guidelines is mostly due to a lack of comprehensive clinical trials demonstrating any beneficial effects of nutrition intervention in the general medical inpatient population. As a consequence, general physicians caring for medical inpatients with multiple comorbidities have insufficient evidence for optimal use of nutritional therapy. More importantly, data from critical care have suggested that although malnutrition is independently associated with worse clinical outcomes for ICU patients,[198] provision of nutritional therapy early during ICU admission can negatively affect clinical outcomes.[199 200] During the acute phase of an illness, there is a higher catabolism with increased energy requirements. To match the resultant increase in the resting energy expenditure, the body mobilizes substrates from muscle and fat, which are used in the liver to produce glucose by gluconeogenesis. During this phase, exogenous provision of calories may not inhibit ongoing gluconeogenesis and therefore excessive nutrition during acute illness can induce an occult overfeeding state which may adversely interact with autophagy.[200] Autophagy is currently considered as an important housekeeping process, which helps in clearing intracellular organisms and macromolecular damage, including damaged organelles and protein aggregates. Evidence in the last two decades has demonstrated a protective role of autophagy in various diseases and it may help in recovery of function in critical illness.[201 202] Autophagy can be activated by inflammation, hypoxia/ischemia, oxidative stress, mitochondrial damage and nutritional deprivation.[203] On the other hand, provision of nutrition may suppress autophagy and this has been hypothesized to be one of the reasons that may explain the harmful effects of early parenteral nutrition (PEN) in critically ill patients. However, other research[204-206] demonstrated benefits from individually optimized energy supplementation with early parenteral feeding in severely ill patients admitted into the ICU for which enteral nutrition alone was insufficient. These contradictory findings from critical care trials[206 207] could be partially explained by the differences in time points when feeding was initiated but they also demand further studies which focus on clinical outcomes. Also, there is a lack of cost-benefit data for the use of nutritional intervention in medical inpatients because costs may still outweigh clinical benefits. Bounoure et al[123] found that there is a lack of well-designed high quality clinical trials suggesting benefits of nutritional intervention in general medical patients. The specific clinical trials that have so far been carried out in organ specific diseases have shown inconsistent results but suggest that nutritional therapy should be considered in malnourished medical inpatients in an effort to improve nutrition related outcomes. The authors suggest that more studies are needed to better understand the effects of nutritional intervention on clinical outcomes in general medical inpatients.

Milne et al[51] in their meta-analysis of protein and energy supplementation in older patients at risk of malnutrition included sixty-two trials with 10,187 patients. They found beneficial effects of nutritional supplementation on weight and mortality in undernourished patients (RR 0.79; 95% CI 0.64 – 0.97) but no significant difference in LOS. The authors found that intervention time was too short (majority of studies had intervention duration <35 days) to have a realistic chance of detecting differences in morbidity, functional status or quality of life and suggested that future trials need to have sufficient statistical power, length of follow-up, properly concealed allocation, blinding and be performed with an intention-to-treat analysis. They also suggested that trials should focus on primary outcomes of relevance to patients such as improvement in function and HRQoL measures.

Table 7 Nutrition intervention studies

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
Deutz et al., 2015[65], US	Hospitalized elderly patients with CHF, Acute myocardial infarction, pneumonia and COPD, n = 652	Standard of care plus 2 servings of ONS containing beta-hydroxy-beta methylbutrate (HMB) with 350 kcal, 20gm protein, 11gm fat, 160U Vitamin D and micronutrients vs. placebo	3 months	No difference in 90 day readmission rate but mortality was significantly lower in supplemented group (4.8% vs. 9.7%; 95% CI 0.27 – 0.90, P = 0.018)
Munk et al., 2014[208], Denmark	Hospitalized oncology, orthopedic and urology patients, n = 84	Protein-enriched dishes supplemented to standard food service vs. hospital diet	Hospital stay	Significantly more intervention patients achieved ≥ 75% of protein requirements but not energy requirements, no difference in muscle function or LOS between

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
				two groups
Holyday et al., 2012[44], Australia	Geriatric inpatients, n = 143	Food fortification and nutrition supplements vs. individual diet fortification on request	Hospital stay	Significant reduction in LOS in malnourished intervention patients (19.5 ± 3 days vs. 10.6 ± 1.6 days, P = 0.013), no difference in readmissions at 1, 3 and 6 months post discharge
Neelemaat et al., 2012[197], The Netherlands	Hospitalized malnourished elderly, 210	Energy and protein enriched diet and ONS, Vitamin D3 400U daily, Calcium 500mg daily, telephone counseling vs. usual care	3 months	No significant improvement in QoL measured by EQ5D and physical activities but significant improvement in functional limitations in intervention

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
				group
Feldblum et al., 2011[209], Israel	Hospitalized adults ≥ 65 years at nutritional risk, n = 259	Individual nutritional treatment, 237ml containing 12.6 gm of fat, 13 gm protein and 47.3 gm carbohydrates (total 360 kcal) in addition to food fortification vs. routine care	6 months	Significant improvement in nutritional status measured by MNA (3.01 ± 2.65 vs. 1.81 ± 2.97, P = 0.004) and lower mortality (3.8% vs. 11.8%, P = 0.04) in the intervention group
Somanchi et al., 2011[210], USA	Malnourished elderly patients, n = 400	Nutrition screening and clinical care plan initiated by nurse manager vs. usual hospital screening and nutritional counseling on demand	Hospital stay	Significant reduction in LOS (6.1 ± 5.3 vs. 8.7 ± 11.7, days, P < 0.05) with nutritional intervention with significant cost savings
Starke et al.,	Malnourished	Individual	Hospital stay	Intervention

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
2011[211], Switzerland	elderly patients, n = 134	nutritional care with food fortification with maltodextrin, rapeseed oil, protein powder, snacks and oral nutritional supplements vs. standard nutritional care		patients maintained body weight at discharge (0 (2.9) vs. -1.4 (3.2), $P < 0.001$) and improved plasma ascorbic acid levels (46.7 (26.7) micromole/L vs. 34.1 (24.2) micromole/L, $P = 0.008$) with significant reduction in complications (4/66 vs. 8/66, $P = 0.035$), antibiotic use (1/66 vs. 8/66, $P = 0.03$) and 6 month readmissions (14/64 vs. 28/61,

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
				P = 0.02)
Rufenacht et al., 2009[212], Switzerland	Malnourished elderly medical inpatients, n = 53	Individual nutritional counseling and intervention (NT group) vs. hospital diet plus ONS (ONS group)	10-15 days	No significant difference in energy and protein intake between two groups QoL improved in both groups at discharge but significant further improvement was noted at 2 months only in NT group
Hickson et al., 2004[213], UK	592	Focused nutritional care by health care assistants vs. usual care	Hospital stay	No difference in LOS, anthropometric measures, mortality or functional status but significantly less use of intravenous

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
				antibiotics in intervention patients (1.0 (1-2) vs. 2.0 (1-2), P = 0.02)
Vermeeran et al., 2004[214], The Netherlands	COPD patients with acute exacerbation, n = 56	Oral nutritional supplement 125ml 3 times daily at 2.38MJ/day, consisting of 20% protein, 20% fat and 60% carbohydrate vs. placebo	Hospital stay	Significant increase in energy (16% vs. placebo) and protein intake (38% vs. placebo) in the intervention group but no additional improvements in lung function or muscle strength
Gazzotti et al., 2003[215], Belgium	Hospitalized geriatric patients, n = 80	Intervention patients received 2 oral nutritional supplements with 500 kcal and 21 gm protein/day with	2 months	Control patients lost significant weight (1.23 ± 2.5, vs. 0.28 ± 3.8, P = 0.01) and MNA scores significantly

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
		standard diet vs. standard diet alone		higher in supplemented group (23.5 ± 3.9 vs. 20.8 ± 3.58, P = 0.004)
Roberts et al., 2003[216], UK	Hospitalized geriatric patients, n = 381	Intervention patients received 120 ml oral sip-feed supplement 3 times daily with 22.5 gm protein, 2260 kJ energy/day	Hospital stay	Total energy intake increased significantly in intervention patients (5898 kJ/d vs. 4563 kJ/d, 95% CI 557 – 2331, P = 0.001)
Potter et al., 2001[217], UK	Hospitalized geriatric patients, n = 381	Intervention patients received 120 ml oral sip-feed supplement 3 times daily with 22.5 gm protein, 2260 kJ energy/day	Hospital stay	Severely malnourished patients had significant improvement in mortality in (5/34 vs. 14/49, P < 0.05 and improved function (17/25 vs. 11/28, P <

Author and Country	Clinical Setting and sample size	Intervention used	Duration of intervention	Clinical outcome
				0.04)
Vlaming et al., 2001[218], UK	549	Intervention patients received 400 ml of oral sip feed supplement providing 600 kcal/day, 25 gm protein, 80.8 gm carbohydrates, 19.6 gm fat and multivitamins along with hospital food vs. placebo	Hospital stay	Longer LOS in intervention patients 2.8 days (95% CI -0.8 – 6.3)

1.12 Cost-effectiveness of nutrition intervention

Health care costs are expected to increase with the ageing population.[219] In the current era of budget constraints there is a growing pressure on the decision makers to obtain the maximum possible benefits and judiciously allocate the available resources.[220]

There is no controversy to the fact that malnutrition is associated with an increase in health-care costs as malnourished patients stay longer in hospitals, are more likely to be discharged to a residential care facility, utilize more health care resources in the community and are more likely to have unplanned readmissions.[221-223] Mitchell and Porter[224] in their systematic review on the cost-effectiveness of identifying and treating malnutrition in hospitalized patients found that interventions demonstrated a positive effect on clinical outcomes and cost-effectiveness, however, due to the limited number of studies, there is an uncertainty regarding the treatment effect **(Table 8)**.

There is a paucity of economic evidence in treating malnutrition and this has also been proposed as the main reason for the failure of uptake of evidence-based nutritional guidelines in clinical settings.[225]. The authors suggested that, to bridge this evidence gap, the inclusion of economic considerations should be a routine part of future malnutrition research.

Three recent meta-analyses have also suggested that nutrition intervention has economic benefits in hospitalized patients.[115 226 227] However, the authors have also indicated that their findings need further verification in different age groups and in different health-care settings. This is due to the fact that the majority of the studies included in these meta-analyses have been conducted in Europe. Despite the growing body of evidence of the economic impact of malnutrition and evidence that nutritional intervention is clinically beneficial, still limited health economic evaluations have been conducted in Australian health care settings. Holyday et al[44] determined the costs of nutrition intervention in geriatric malnourished patients in Australia, however this study did not determine cost-effectiveness or cost-utility analyses (CUA) and thus quality adjusted life years (QALY) were not determined. The QALY is regarded as the preferred cost-effectiveness outcome, as it measures not only the quantity but also the quality of life lived.[228] As for other research interventions, it is recommended that QALY be measured for the health assessment of medical nutrition interventions.[229]

Table 8 Nutrition intervention cost-effectiveness studies

Author and Country	**Clinical setting and population**	**Study design and type of economic evaluation**	**Intervention and Comparator**	**Results**
Giraldo et al., 2015[230], Spain	Hospitalized malnourished patients >55 y, n = 227	Cohort study with cost-effectiveness analysis	Early nutrition therapy (ENT) vs. delayed nutrition therapy (DNT)	Costs per patient discharged alive was US$10,261 in ENT vs. US$15,553 in DNT group ($P = 0.04$).
Holyday et al., 2012[44], Australia	Hospitalized geriatric patients >80 y, n = 143	Randomized controlled trial, Costs of hospitalization according to DRG, dietitian consultation and ONS were determined	Early individualized Malnutrition care plan (MCP) vs. usual care	Reduced hospitalization costs in the intervention group (total cost savings AU$63,360)
Nuijten et al., 2012[231], Germany	Malnourished patients ≥18 y in community and nursing homes, n = 193,078	Health economic evaluation	Use of ONS (2 × 200ml/d for 3 months) vs. no use of ONS	The extra costs of ONS (€ 534) are offset by a reduction of hospitalization costs (€768) leading to cost savings of €234-€257 per patients Total cost savings = €604-€662 million.
Freijer et al., 2012[232], The Netherlands	Older>65 y patients in residential and home care, n = 720,223	Health economic evaluation using decision tree model Cost-benefit analysis combined with	Use of ONS (2 × 200ml/d for 3 months) vs. no use of ONS	The use of ONS leads to cost saving of €12,986 million. Additional costs of ONS (€57 million) are more than balanced by reduction of total

Author and Country	Clinical setting and population	Study design and type of economic evaluation	Intervention and Comparator	Results
		budget impact analysis		costs of DRM due to a reduction of rehospitalization (€70 million)
Neelmaat et al., 2012[233], The Netherlands	Older hospitalized patients ≥60 y with DRM, n = 210	Randomized controlled trial, Cost-utility and cost-effectiveness analysis	Standardized nutritional intervention including ONS (2 × 200ml/d) during hospital stay and for 3 months post-discharge	ICER for QALY: €26,962; ICER for physical activities: €4,470; ICER for functional limitations: -€618. The intervention is cost-effective for functional limitations.
Wyers et al., 2012[234], The Netherlands	Patients ≥55 y with hip fracture admitted for surgery, n = 152	Multicentre randomized controlled trial, Cost-utility and cost-effectiveness analysis	Dietary counseling and ONS (2 × 200ml/d) during hospital stay and for 3 months post-discharge vs. usual care	ICER for total societal costs was €241/kg weight gain (high probability of being cost-effective) and €36,943/QALY (low probability of being cost-effective; except in those younger than 75 y).
Norman et al., 2011[235], Germany	Patients ≥ 18 y with DRM suffering from benign	Randomized controlled study, Cost-utility analysis	Use of ONS (3 × 200ml/d) along with dietary counseling for 3	ICER for additional QALY: €9497 (low price ONS) and €12,099(high price ONS), deemed cost-effective

Author and Country	Clinical setting and population	Study design and type of economic evaluation	Intervention and Comparator	Results
	gastrointestinal disease, n = 120		months after hospital discharge vs. dietary counseling alone	according to international thresholds (<€50,000/QALY): probability between 89.9% and 91.5%.
Freijer et al., 2010[236], The Netherlands	Virtual cohort of patients ≥ 18 y with DRM undergoing abdominal surgery, n = 160,283	Health economic evaluation using decision tree model Cost-benefit analysis related malnutrition in different care	Use of ONS (2 × 200ml/d for 8.5 d before and after surgery vs. no use of ONS	Use of ONS reduces costs by 7.6% per patient and hospitalization costs reduce by 8.3% with an annual cost saving of €40.4 million based on 160,283 abdominal surgery procedures per year.
Kruizenga et al., 2005[237], The Netherlands	Hospitalized malnourished patients both medical and surgical > 55 y, n = 588	A controlled trial, cost-effectiveness analysis	Use of additional 600 kcal and 12g protein in intervention patients vs. usual care	The incremental costs of a one day reduction in LOS is €76 and deemed cost-effective as cost of staying in hospital is €476.
Rypkema et al., 2003[238], The Netherlands	Patients >60 y with DRM admitted to geriatric wards, n = 298	Prospective controlled trial, Cost-effectiveness analysis	Early multidisciplinary intervention including screening and nutritional intervention	Lower costs per patient: €7516 vs. €7908. Total net cost difference of €80 to €110 per patient. ICER total costs: -€392/Kg weight gained with maximum willingness to pay of €530/Kg weight gained.

Author and Country	Clinical setting and population	Study design and type of economic evaluation	Intervention and Comparator	Results
			including use of ONS vs. standard care during hospital stay	

DRG, diagnosis related group; ONS, oral nutrition supplements; DRM, disease related malnutrition; ICER, incremental cost effectiveness ratio; QALY, Quality adjusted life year

CHAPTER 2: GAPS IN MALNUTRITION RESEARCH IN GENERAL MEDICAL PATIENTS

This narrative review suggests that malnutrition is widely prevalent and is associated with poor clinical outcomes measured in terms of increased LOS, higher number of nosocomial complications, higher mortality, increased number of unplanned readmissions and a poor HRQoL in hospitalized patients. Despite this malnutrition screening rates are suboptimal and the factors responsible for missed nutrition screening are unknown. MUST is a commonly used nutrition screening tool in hospitalized patients but its validity in older general medical patients needs confirmation. General physicians need up-dating about the current prevalence and consequences of malnutrition due to changing population dynamics and an increase in the number of older patients admitted in general medical units. Finally there is a lack of high quality RCTs confirming the clinical and economic benefits of nutritional intervention in older general medical patients. There is an ongoing debate as to whether provision of excessive nutrition in critical care patients may cause harmful effects. Importantly, critical care data cannot be unconditionally transferred to general medical patients who have a lower severity of illness. This conflicting critical care data calls for further studies looking into the benefits of nutrition intervention in general medical patients. Furthermore, the paucity of high-level evidence explains the lack of strong guideline recommendations for type, caloric and protein amount and timing of nutritional therapy in medical inpatients.

Although clinical nutrition is one of the most commonly used interventions in medicine, there is no standard algorithm for its use in hospitalized general medical patients. In light of recent evidence from critically ill patients, a re-appraisal of how nutrition intervention should be used in less critically ill general medical patients is required. As with use of pharmacotherapy, the selection, timing and doses of nutrition in hospitalized patients needs evaluation, with the aim of maximizing efficacy and minimizing iatrogenic toxicity and costs.

As of today, positive effects of providing an early nutritional intervention in multimorbid general medical patients remain largely unproven.[104 239] Recent studies from critical care have found contradictory effects of aggressive early feeding and has challenged the safety of nutrition intervention approach in hospitalized medical patients.[199] Furthermore, nutritional interventions are expensive, time-consuming and sometimes not beneficial for patients (e.g. use of tube feeding for patients with dementia).[240 241] Therefore, the current approach of provision of nutrition intervention in medical inpatients needs to be re-evaluated. Previous trials have investigated the effects of nutritional interventions on selected patient outcomes (e.g. changes in body weight and nutrition specific quality of life).[242] These trials were highly heterogeneous in terms of study design, patient populations and types of interventions used. In addition, these trials lacked power to appropriately assess safety and, in aggregate, produced inconclusive results.[51] Not surprisingly, previous meta-analyses confirm that there is a lack of high quality evidence to endorse or reject nutritional support in medical inpatients.[51 239 242 243] These, meta-analyses, however, did not specifically focus on the effects of early nutritional therapy in multimorbid, hospitalized general medical patients. Moreover, these meta-analyses have suggested that a short duration of nutrition intervention (e.g. limited to the period of hospitalization) may not be sufficient to produce a discernible effect on clinical outcomes like HRQoL. These meta-analyses have suggested that there is a need for nutrition intervention studies in different patient sub-groups and the future studies should be of sufficient duration, adequately powered and should focus on specific clinical outcomes which are relevant to patients (e.g. HRQoL).[51 104]

Very limited nutrition intervention studies are available in relation to Australian health care settings and no study has so far been conducted in older general medical patients. In the current era of economic constraints, the health care providers also need firm evidence that nutrition intervention is a cost-effective strategy to justify allocation of limited resources. Clearly this whole area of medical practice will be bolstered by good evidence of the efficacy of an intervention applied to an inpatient population of complex often old patients with significant co-morbidities.

2.1 Research Questions

This thesis therefore combines a series of five interconnected studies **(Table 9)** which were designed and conducted to address the following research questions:

1. What are the factors responsible for a missed diagnosis of malnutrition in hospitalized patients?

2. What is the prevalence and clinical consequences of malnutrition in older general medical patients?

3. Is MUST a valid nutrition screening tool as compared to PG-SGA in older general medical patients?

4. What are nutritional and clinical benefits of an early and extended nutrition intervention in older general medical patients?

5. Is nutrition intervention a cost-effective strategy in older general medical patients?

These studies are now presented as separate research publications all accepted into and now published in peer-reviewed journals within the period of my enrolment for this doctoral degree.

Table 9 Studies included in this thesis

Study	Total number of participants	Design	Aims	Findings
1.	205	Prospective cross-sectional	To determine factors responsible for missed malnutrition screening in older general medical patients	100/205 (50.3%) missed MUST screening. Time of hospital admission and patients' location in hospital were found to be significant predictors of malnutrition screening
2.	205	Prospective cross-sectional	Prevalence and consequences of malnutrition in older general medical patients	Prevalence of 53.5% according to PG-SGA. Malnourished patients had significantly longer LOS, poor HRQoL and had higher mortality within 1 year of discharge
3.	297	Prospective cross-sectional	To determine whether admission nutrition status predicts readmission and death within early (0-7 days) or late period (8-180 days) following discharge	Malnutrition was a significant predictor of readmission or death in both early and late periods following hospital discharge

Study	Total number of participants	Design	Aims	Findings
4.	132	Observational study	To test validity of MUST against PG-SGA in older general medical patients	MUST had a sensitivity of 69.7% and specificity of 75.8% against PG-SGA
5.	148	RCT	To test efficacy of early and extended nutrition intervention in older hospitalized patients	Early and extended nutrition intervention improved nutrition status as determined by PG-SGA scores and reduced LOS in intervention group.
6.	148	RCT	Health economic evaluation of early and extended nutrition intervention in older hospitalized patients	Early and extended nutrition intervention was cost-effective in terms of QALYs gained and produced net per-patient cost-savings of AU$907 in the intervention group

MUST, malnutrition universal screening tool; PG-SGA, patient generated subjective global assessment; LOS, length of hospital stay; HRQoL, health related quality of life; QALYs, quality adjusted life years

CHAPTER 3: FREQUENCY OF MALNUTRITION SCREENING AND FACTORS CONTRIBUTING TO ABSENCE OF MALNUTRITION SCREENING IN OLDER HOSPITALIZED PATIENTS

This chapter is a co-authored publication accepted in 2016. Please refer to appendix 1.1 for the statement of author contributions.

Sharma Y, Miller M, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition screening in acutely unwell elderly patients. *British Journal of Nursing*.2016;25(18):1006-1014.

3.1 Abstract

3.1.1 Background

The rate of malnutrition among hospitalized older patients in Australia is 42.3%. Malnutrition is known to lead to significant adverse outcomes for the patients and increase hospital costs through increased use of resources.

3.1.2 Aim

This study assessed the frequency of malnutrition screening and investigated factors associated with a missed opportunity to identify risk and subsequent diagnosis of malnutrition.

3.1.3 Methods

A prospective cross-sectional study involving 205 general medical patients aged ≥60 years admitted acutely in a tertiary hospital over a period of one year. Patients who were not screened for risk of malnutrition were noted and all patients underwent nutritional assessment using the PG-SGA. The researchers assessed demographic data and performed univariate analysis of factors contributing to the absence of malnutrition screening.

3.1.4 Results

Ninety-nine patients (49.5%) were screened for malnutrition using the MUST and 100 (50.3%) missed initial nutritional screening (data incomplete for 6 patients). Of those screened, more were malnourished (n = 64; 61.5%) than those not screened (n = 40;

38.5%), P<0.001. There was no significant difference in screening rates over the weekends and public holidays compared with weekdays (P = 0.14). MUST screening was less likely to be performed if patients were admitted during night hours (P = 0.03) and if patients were admitted to an outlier ward location (P = 0.001).

3.1.5 Conclusion

This study indicates common associations that might explain low inpatient screening rates for malnutrition; these include apparently adequate nutritional status, after hours hospital admissions and outlier ward locations. Ensuring consistent nutrition screening with appropriate diagnosis and therapeutic interventions for patients and educational interventions for staff could pay dividends not only in terms of improved patient health but also in terms of hospital financial reimbursement.

3.2 Introduction

Malnutrition is defined as a state of nutrient insufficiency, as a result of inadequate nutrient intake or inability to absorb or use ingested nutrients.[244] Malnutrition is widely prevalent in hospitalized patients with reported worldwide prevalence rates of 13-78%[245] depending on the setting and whether medical or surgical inpatients-one study in Australia found that overall 42.3% of all inpatients were malnourished,[34] while 28% of adults were found to be malnourished at admission in UK.[246] Prevalence of malnutrition is even higher in the elderly population as many changes associated with ageing, for example, decrease in taste acuity and smell, deteriorating dental health and decline in physical activity may affect nutrient intake and make this group more prone to malnutrition.[247 248] Malnutrition increases risk of infections due to impaired immune response, predisposes patients to pressure ulcers, impairs wound healing, increases risks of falls and is associated with high mortality.[249-251] Complications associated with malnutrition lead to an increased LOS stay with consequent increased use of health care resources and also lead to frequent readmissions and increased risk of residential care placement; all with significant increases in healthcare costs.[222 252]

In 1974, Butterworth described malnutrition as ‘skeleton in the hospital closet’ as it often goes undiagnosed and untreated.[253] The diagnosis of malnutrition is often missed in hospitals owing to a number of factors including a lack of knowledge of malnutrition among health professionals and busy clinical settings with increasing emphasis on discharging patients home early.[254] Eide et al (2015) found that there is a lack of clarity whether nutritional screening is the responsibility of the treating clinician or nurses, and a lack of understanding among health professionals of the various screening tools available further compounds the problem.[255] Given the high prevalence of malnutrition in hospitalized patients and a possibility that even patients with a normal BMI can still be malnourished[256] the ASPEN[257] has recommended screening all patients presenting to the hospital for malnutrition by using a valid screening tool like the MUST.[258] If the screening is positive, malnutrition should be confirmed by a reference assessment tool like the PG-SGA.[259]

MUST has been validated in a number of clinical settings and is commonly used in hospitals to screen patients for malnutrition.[260] The MUST includes a BMI score, a weight loss score, and an acute disease score. MUST was designed to identify the need for nutritional treatment as well as establishing nutritional risk on the basis of knowledge about the association between impaired nutritional status and impaired function.[129 138] In the absence of a gold standard to diagnose malnutrition, dietitians commonly use PG-SGA to diagnose malnutrition and initiate appropriate nutritional intervention. SGA is a method of nutritional assessment based on a medical history and physical examination, whereby each patient is classified as well-nourished (SGA A) or suspected of being malnourished (SGA B), or severely malnourished (SGA C).[134] A further development of SGA was the PG-SGA, which incorporates both nutritional score and global clinical assessment.[135] Typical scores range from 0 to 35 with a higher score reflecting a greater risk of malnutrition. It has been demonstrated to be a valid method of nutrition assessment in a number of patient groups including hospitalized patients.[156 157]

Although hospitals have established nutrition screening protocols in Australia, limited data is available on the actual nutritional screening rates of elderly hospitalized patients and the factors that prevent nutrition screening. The present study looked into the frequency of nutritional screening as well as the associated individual and environmental factors influencing nutritional screening in older patients admitted to the general medicine department of a large tertiary care hospital.

3.3 Methods

A total of 205 hospitalized patients were recruited from November 2014 to November 2015. Patients admitted to general medicine wards of Flinders Medical Centre (FMC) who were eligible for the study based on inclusion and exclusion criteria were approached and invited to participate in the study. Inclusion criteria were age 60 years or over admitted to a general medicine ward. Exclusion criteria were patients admitted purely for palliative purposes, Indigenous Australians, non-English speaking patients (in both cases due to lack of funds to seek services of an interpreter), those residing outside metropolitan Adelaide (patients in this study were a part of an intervention study, which involved a repeat visit at 3 months for another assessment-the long travel times from rural areas would have posed practical problems) and inability to obtain valid consent. Ethical approval for the study was obtained from Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) approval number 273.14.

In FMC, all patients referred from the emergency department for general medicine admission are first admitted under the acute medical unit (AMU), which has greater staff availability compared to other wards (the AMU is counted as a general medicine ward). However, if AMU beds are not available then patients may be admitted to the outlier ward locations, that are not specifically designed or designated for the type of care general medical patients require. The staff availability in the AMU is greater than other wards and the clinical needs of general medical patients are better met if they are placed in the AMU. From AMU patients are either discharged home within 48 hours and those expected to stay longer are transferred under long stay teams. Potential participants who were admitted to the AMU and general medicine department of FMC were identified and written informed consent was obtained from all participants. In the case of dementia/cognitive impairment, consent was obtained from their legal guardian.

3.4 Data Collection and Measures

Baseline data on demographics and health and medical history was obtained from medical records and case notes. The completion of MUST was verified from the case notes. If the MUST was not found, its absence was noted. Each MUST completion, or lack thereof, was also confirmed with the attending nurse. In FMC, it is a requirement that all patients who are admitted under general medicine have the MUST completed, as a part of initial nursing assessment. It is completed electronically and a printed copy is inserted in the case notes. In patients where the MUST was not completed, a member of the research team either requested the assessment nurse to perform the MUST or completed the MUST himself/herself. In those instances, the patient was categorized for this study as not having had a MUST completed. All patients were then referred to a research dietitian who was blinded to the MUST nutritional risk score and performed the PG-SGA as well as anthropometric measurements to ascertain nutritional status. The time and day of the week patient got admitted to the hospital and the time of MUST completion was recorded from the medical records. Nurses shift hours from 0800-2100 were classified as day shifts and between 2101-0759 as night shifts. Anthropometric measures included hand grip strength with a hand held dynamometer in patient's dominant hand, Mid-upper-arm Circumference (MUAC) measured at midpoint between acromion process and olecranon), TSF using calibrated Harpenden skinfold caliper on the right side, and mid-arm muscle circumference (MAMC) was determined using formula:

MAMC (cm) = MUAC- (0.3142 × TSF (mm)

3.5 Data Analysis

Data analysis was performed using STATA (version 13.1). Descriptive analysis was conducted for all the demographic variables and categorical variables expressed as proportions. Data were assessed for normality using the Skewness-Kurtosis test (sk test). Data are presented as means and standard deviation if normally distributed and medians and interquartile ranges (IQR) for non-normally distributed variables. Continuous variables were assessed for statistical significance using t test, if normally distributed and Mann Whitney U test was used for non-normally distributed variables. χ^2 statistics was used to compare categorical variables. For comparison all patients with a MUST score of zero ('low risk' on the screening tool) were classified as well-nourished and those with MUST score of 1 or more (on the screening tool, 1 is 'medium risk' and 2 or more is 'high risk'); similarly all patients with PG-SGA class A were classified as well-nourished and those in PG-SGA class B and C as malnourished, combining the two classes of ‘suspected to be malnourished’ and ‘severely malnourished’.

3.6 Results

A total 205 patients were enrolled from November 2014 to November 2015 and complete data were available for 199 patients for analysis. Of these 99 patients (49.7%) had MUST completed while 100 (50.3%) did not have this initial nutrition screening performed before researchers’ prompting. According to MUST screening (including those completed later), 114 (57.3%) patients were found to be malnourished, while PG-SGA found 106 (53.5%) patients as malnourished. Of those who initially had nutritional screening performed using MUST (i.e. before researchers’ prompting), more were malnourished (n = 64; 61.5%) than nourished and the opposite was true in the group who did not have MUST completed. Of 100 patients who missed nutrition screening by the nursing staff, 40 (40.0%) patients were confirmed to be malnourished by PG-SGA scoring.

The mean age and other demographic features were not significantly different between the two groups (MUST-screened and those without a MUST assessment **(Table 10)**. The anthropometric measures **(Table 11)** were significantly lower in patients who had the MUST completed. In other words, those patients who were thinner and who looked as if they might be malnourished were more likely to be screened. There was no significant difference in the MUST screening rate over the weekends and public holidays (26/44; 59.1%) as compared with weekdays (72/154; 46.8%), P = 0.14, **(Table 12)**. MUST screening was more commonly performed on patients admitted during day shifts than on night shift. Significantly higher numbers of patients were screened if the first ward they entered after leaving the emergency department (ED) was the AMU (85/142; 59%), as compared with those initially placed in another ward of the hospital (14/57; 23.7%, $P < 0.001$). More malnourished patients ($n = 32$; 50%) were coded at the time of discharge, if they had initial nutritional screening performed by MUST as compared to those who missed MUST screening ($n = 12$; 30%, $P = 0.04$).

Table 10 Baseline characteristics of patients depending on MUST completion

Parameter	MUST completed	MUST not completed	P-value
Patient number (%)	99 (49.7%)	100 (50.3%)	
Malnourished, n (%) (by PG-SGA assessment)	64 (61.5%)	40 (38.5%)	< 0.001
Age, median (IQR)	82 (74-87)	80.5 (71.5-86)	0.20
Sex, n (%)			
Males	41 (41.4%)	30 (30%)	0.09
Females	58 (58.6%)	70 (70%)	
Impaired cognition, n (%)	2 (2.2%)	4 (4%)	0.68
CCI, mean (SD)	2.2 (1.8)	2.5 (1.9)	0.21
Medications, mean (SD)	8.9 (4.6)	10.1 (4.4)	0.05
Patients on vitamin D/calcium supplements, n (%)	40 (54.8%)	33 (45.2%)	0.28
Principal diagnosis, n (%)			
Respiratory	34 (34.3%)	37 (37%)	0.41
Cardiovascular	17 (17.2%)	9 (9%)	
Falls	12 (12.1%)	12 (12%)	
CNS	4 (4.0%)	8 (8%)	
Miscellaneous	32 (32.3%)	34 (34%)	
Residence, n (%)			
Home	88 (89.8%)	88 (88%)	0.64
Nursing home	9 (9.2%)	12 (12%)	
Other	1 (1%)	0	
Mobility, n (%)			
Independent	46 (48.4%)	56 (55.1%)	0.77
Stick	9 (9.5%)	7 (7.1%)	
Walking frame	37 (39%)	33 (33.7%)	
Bedbound	3 (3.1%)	4 (4.1%)	

PG-SGA, patient-generated subjective global assessment; IQR, interquartile range; SD, standard deviations; CCI, Charlson comorbidity illness; MUST, malnutrition universal screening tool; SD, standard deviation; CNS, central nervous system

Table 11 Anthropometric measures of patients based on MUST completion

Parameter	MUST completed	MUST not completed	P-value
Weight, median (IQR)	56.8 (49–67)	64.9 (54.2–76)	0.0003
BMI in kg/m^2, median (IQR)	20.5 (18.6–24.3)	24.1 (20.1–27.5)	0.0008
Handgrip strength in kg, median (IQR)	16 (12–22.8)	16.5 (12–23.5)	0.78
TST in mm, median (IQR)	10.4 (6.4–17)	14.7 (10.3–19.8)	0.002
MAMC in cm, median (IQR)	21.5 (18.7–23.5)	23.3 (20.6–25.5)	0.0002
Nutrition state according to PG-SGA			
Nourished	32 (44.3)	57 (44.7)	<0.001
Malnourished	64 (51.7)	40 (52.3)	

IQR, interquartile range; BMI, body mass index; TST, triceps skinfold thickness; MAMC, midarm muscle circumference; PG-SGA, patient generated subjective global assessment

Table 12 MUST completion according to weekday, shift and location

Parameter	MUST completed n (%)	MUST not completed n (%)	P-value
Weekdays	72 (73.5%)	82 (82.0%)	0.14
Weekend and holidays	26 (26.5%)	18 (18.0%)	
Morning shift	74 (74.8%)	60 (60.0%)	0.03
Night shift	25 (25.2%)	40 (40.0%)	
AMU	85 (85.9%)	57 (57.0%)	< 0.001
Non AMU	14 (14.1%)	43 (43.0%)	
Malnutrition coding	32 (50%)	12 (30%)	0.04

MUST, malnutrition universal screening tool; AMU, acute medical unit

3.7 Discussion

The present study indicates that nutritional screening is still suboptimal in hospitalized elderly patients. Only 49.7% of patients aged over 60 years and under the care of the general medicine department of this hospital were screened for malnutrition at the time of admission, despite hospital policy that all inpatients be screened on admission to the ward.

Porter et al[261] in their study in Australian hospitals also found low nutritional screening rates with the highest rate of screening using MUST tool of only 61% and they highlighted numerous barriers including workload pressures and lack of awareness among the staff that malnutrition can be a problem in hospitals and lack of knowledge of the condition as significant factors and suggested need for nursing leadership role to establish nutrition screening culture among staff. In a study by Kelly et al[116] in a tertiary care hospital in the UK, in both acute medical and surgical inpatients over the age of 16 years, it was found that 13% of all hospitalized patients were malnourished and malnutrition diagnosis was left unidentified in 75% of the patients. The authors highlighted difficulties in obtaining accurate weight and height as one of the major factors in missed diagnosis.[116] In the UK, evidence-based clinical practice guidelines for nutritional support in adults recommend screening all patients for malnutrition, as available research indicates that early screening and treatment of malnourished patients can reduce LOS.[262] Studies suggest that hospitalization is associated with a significant decline in nutritional status due to a number of factors including catabolic effects of illness, anorexia due to polypharmacy, dislike of hospital food and ‘nil by mouth’ orders.[66 263] A missed diagnosis of malnutrition at this crucial phase will often result in patients being discharged in a significant worse nutritional state than they were at the time of hospital admission. This further emphasizes the point that clinicians cannot take chances by missing this important but often hidden diagnosis especially when more than 50% of patients are noted to be at risk of malnutrition on admission in studies conducted in both UK[143] and Australia.[264]

This study indicates that nutritional screening was more likely to be performed if the patient appeared visually malnourished. The median BMI and other nutritional parameters were significantly higher in patients who missed nutritional screening by MUST. Raja et al (2008) in their study on nutritional screening in general medical and surgical patients with age range 14-97 years, also found that to prioritize care in a busy clinical setting, some judgment is applied by nurses based on weight status and patients who 'look healthy' or obese may be excluded with a false belief that these patients are unlikely to be malnourished.[127]

This study also highlights that the physical location of patients in different wards may influence frequency of nutritional screening. Patients who were admitted to the AMU had higher MUST completion rates when compared with general medical patients admitted to other medical and surgical wards in the hospital. This may be due to more staff availability in AMU compared with the other wards. Studies suggest that placement of patients in outlier wards that do not offer specialized care may lead to suboptimal and fractured provision of care.[265 266]

The data also show that nutritional screening is more likely to occur in day shifts as compared with night shift hours (after 9 pm). The authors hypothesize that this difference could also be due to greater staff availability during day shift hours and factors such as reluctance to disturb patients during night hours.

The prevalence of malnutrition in this population (determined by PG-SGA) was 53.5%; similar to other inpatient populations.[143] The MUST tool delivers a false negative rate of around 25%.[141] This means that of the 40 malnourished patients originally undetected in this cohort due to absence of a MUST being performed, at least 30 would have been detected if all patients had had a MUST on admission to the ward. Targeted intervention to address such unrecognised yet common malnutrition (and at-risk malnutrition) might improve outcomes in the general medicine inpatient population.

Recognition of malnutrition is important not only to identify patients who need immediate intervention but also to identify those who are at risk of malnutrition and will require close monitoring for future intervention. Recognition and documentation of malnutrition is also important as it ensures that hospitals receive appropriate remuneration. As malnourished patients utilize more health resources, early recognition and targeted treatment may pay dividends in today's economically constrained environment and at least in Australia, simply identifying patients as malnourished generates significant increased reimbursements for the hospitals by the government. Rowell and Jackson in their study of hospitals in Victoria in 2003-2004 found that after controlling for the underlying condition and treatment administered, recorded diagnosis of malnutrition was estimated to add AU$1,745 per admission.[114]

3.8 Limitations

The authors acknowledge that this is a single-centre study and that there was an inability to recruit a significant number of cognitively impaired patients, mainly due to difficulty in obtaining valid consent. This study is limited to older general medical patients who typically suffer from multiple clinical problems[267] and the results may not be applicable to relatively younger sub-specialty patients with single organ involvement. A major strength of this study is that the research dietitian was blinded to the screening results and confirmed nutrition status. This study has identified new factors such as an outlier ward location and nurses' shift hours as significant determinants of nutrition screening. If future research confirms this study's findings then interventions such as discouraging patients being placed in outlier ward locations and increase availability of staff after hours can be recommended.

3.9 Conclusion

This study indicates that nutrition screening is still inadequate in hospitalized elderly patients. Other than having the anthropometric appearance of good nutrition, no patient characteristic predicted those who would miss out on screening upon admission. Placing the general medical patient in the correct ward following transfer from the ED (i.e. the AMU) improved the chances of screening but did not guarantee it. Patients admitted to the AMU or any other ward during the nightshift were less likely to be screened.

Keeping all general medical patients in a dedicated ward, rather than in different locations in the hospital, may improve nutrition screening and an effort should be made to screen night-transferred patients in the same way as daytime admissions. This might require some prior prospective work to determine whether the nutrition screening omission is cultural (i.e. ward-based or shift-based) or workload-based. The authors advocate a consistent effort on the part of health professionals to prioritize nutrition screening as a part of routine patient care and include completion rates of nutrition screening tools as benchmarks for hospitals' performance, to address this common but easily treatable condition

CHAPTER 4: PREVALENCE AND CLINICAL CONSEQUENCES OF MALNUTRITION IN OLDER GENERAL MEDICAL PATIENTS

This chapter is a co-authored publication accepted in 2016. Please refer to appendix 1.2 for the statement of author contributions.

Sharma Y, Thompson C, Shahi R, Hakendorf P, Miller M. Malnutrition in acutely unwell hospitalized patients – 'The skeletons are still rattling in the hospital closet". *The Journal of Nutrition Health and Ageing*. 2017;21(10):1210-1215. doi: 10.1007/s12603-017-0903-6.

4.1 Abstract

4.1.1 Background

Malnutrition is common in hospitalized patients with prevalence rates of up to 30% in Australian hospitals with adverse consequences for both the patients and health care services. Despite formulation of nutritional screening protocols, not all hospitalized patients get nutritional screening. Real life screening rates of hospitalized elderly patients are unknown.

4.1.2 Aim

The present study explored nutritional screening rates in acutely admitted older general medical patients admitted in a large tertiary hospital in Australia and determined how these patients fared depending upon their nutrition status.

4.1.3 Methods

A prospective cross-sectional study involving 205 general medical patients ≥60years recruited between November 2014 and November 2015. The number of patients who missed nutritional screening were noted and all patients underwent nutritional assessment by a qualified dietitian using PG-SGA and HRQoL was measured using EQ-5D-5L. A survival curve was plotted and a multivariate cox proportional hazard model was used for analyses and adjusted for confounders**.**

4.1.4 Results

Initial nutritional screening by MUST was found to be performed in only 99 (49.7%) patients. One hundred and six (53.5%) patients were confirmed as malnourished by the PG-SGA. Malnourished patients had a significantly longer LOS and a worse HRQoL as compared to the nourished patients. Mortality was significantly higher in malnourished patients at one year (23 (21.7%) vs. 4 (4.3%); $P < 0.001$) and cox proportional hazard model suggests that malnutrition significantly affects survival even after adjustment for confounders like age, sex, Charlson comorbidity index (CCI) and polypharmacy (HR 5.32; 95% CI 1.703 – 14.863; $P = 0.003$).

4.1.5 Conclusion

This study confirms that nutritional screening is still suboptimal in older hospitalized patients with adverse consequences and suggests need for review of policies for improvement in screening practices.

4.2 Introduction

Malnutrition is defined as a state of nutrient insufficiency, as a result of inadequate nutrient intake or inability to absorb or use ingested nutrients.[244 268] Malnutrition is widely prevalent in hospitalized patients with reported worldwide prevalence rates of 13-78% depending upon the type of setting.[245] In Australia, a retrospective analysis from two hospitals in New South Wales, found that 30% of patients were malnourished and 53% of patients were at risk of malnutrition.[36] Malnutrition is associated with adverse clinical outcomes, as it increases risk of infections due to impaired immune response, predisposes patients to pressure ulcers, impairs wound healing, increases risk of falls and is associated with high mortality.[249-251 269] Malnutrition also adversely impacts health care services as it is associated with increased LOS, increased utilization of health care resources, frequent readmissions and increased risk of placement with consequent increase in costs.[222 252 270 271]

Malnutrition is often described as a 'skeleton in the hospital closet' as it often goes under diagnosed and under treated.[253] Diagnosis of malnutrition is often missed in hospitals due to a number of factors including low awareness of malnutrition, busy clinical settings with increasing emphasis on discharging patients home early, lack of clarity as to whether nutritional screening is a responsibility of the treating clinician or nurses and lack of understanding of the various available screening tools.[255] Historically, diagnosis of malnutrition is made by the examining clinician based on the history of weight loss and clinical examination but given the high prevalence of malnutrition in hospitalized patients and a possibility that even patients with a normal or high BMI[272] can still be malnourished or at high risk of malnutrition, experts have now recommended screening all patients presenting to the hospital for malnutrition by using a valid screening tool like the MUST and then if the screening is positive to confirm by a reference assessment tool like the PG-SGA.

MUST has been validated in a number of clinical settings and is commonly used in hospitals to screen patients for risk of malnutrition. The MUST includes a BMI score, a weight loss score, and an acute disease score. The MUST is designed to identify need for nutritional treatment as well as establishing nutritional risk on the basis of knowledge about the association between impaired nutritional status and impaired function.[129 138 273] It has been documented to have a high degree of reliability (low inter-observer variation) with a k = 0.88-1.00.[274] SGA[55] is a method of nutritional assessment based on a medical history and physical examination, whereby each patient is classified as well-nourished (SGA A) or suspected of being malnourished (SGA B), or severely malnourished (SGA C).[134] A further development of SGA is the scored PG-SGA, which incorporates score as well as global assessment.[152] Typical scores range from 0 to 35 with a higher score reflecting a greater risk of malnutrition. It has been demonstrated to be a valid method of nutrition assessment in a number of patient groups.[156 157]

Although nutritional screening protocols have been established in hospitals, limited data is available in Australia, looking into actual nutritional screening rates of elderly hospitalized patients and how these malnourished patients fare as compared to nourished patients during their hospital journey and upon discharge from hospital. The present study looked into the nutritional screening rate and clinical outcomes associated with a dietitian-supported diagnosis of malnutrition in acutely unwell older patients admitted to a large tertiary hospital.

4.3 Methods

A total of 205 hospitalized patients were recruited from November 2014 to November 2015. These patients are participants in an RCT (registration number ACTRN1261400083362) investigating the cost effectiveness of an extended ambulatory nutritional intervention in patients who are discharged from acute care. All patients admitted to general medicine wards of FMC who were eligible for the study based on inclusion and exclusion criteria were approached and invited to participate in the study. Inclusion criteria were age ≥60 years admitted under general medicine ward and exclusion criteria were palliative patients, Indigenous, non-English speaking patients, residing outside metropolitan Adelaide and inability to obtain valid consent. Ethical approval for the study was obtained from the Southern Adelaide Human Research Ethics Committee (SA HREC) approval number 217.14.

4.3.1 Procedure

Potential participants who were admitted to the AMU and general medicine wards of FMC were identified and an information package about the study was provided and explained to the participants, and written informed consent was obtained from all participants. In case it was found that participants had dementia/cognitive impairment, then consent was obtained from their legal guardian.

4.3.2 Data Collection and Measures

Baseline data on demographics and health and medical history was obtained from medical records and case notes. The MUST score was obtained from the case notes, where available. In FMC, it is expected that all patients who are admitted under general medicine have the MUST completed, as a part of initial nursing assessment electronically and a hard copy is inserted in the case notes. Where MUST was not found in the case notes, it was taken into account and a member of the research team either asked the assessment nurse to perform MUST or completed the MUST himself/herself. All consenting patients were then referred to a research dietitian, who was blinded to the MUST nutritional risk score and performed PG-SGA as well as anthropometric measurements including hand grip strength with a hand held dynamometer in the patient's dominant hand, MUAC (measured at midpoint between acromion process and olecranon), TSF using a calibrated Harpenden skinfold caliper on the right side and MAMC was determined using the formula MAMC: MUAC - (0.3142 × TSF (mm) = in cm.

A HRQoL questionnaire using the Australian version of EQ-5D-5L was also completed to assess impact of nutritional status on quality of life. EQ-5D-5L was developed jointly by a group of European-based researchers with the intent of constructing a simple, self-administered instrument that provides a composite index score representing the preference for a given health state.[182] The EQ-5D-5L consists of two parts: the health state descriptive system and visual analogue rating scale (VAS).[275] The descriptive system records the level of self-reported problems on each of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). For each dimension the respondent is asked to choose between five options: no problem, some problem, moderate problem, extreme problem or unable to perform. Respondents then describe their own health status using a 20cm VAS with endpoints labeled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively.[183]

4.3.3 Data Analysis

Data analysis was performed using STATA (version 13.1). Descriptive analysis was conducted for all the demographic variables and categorical variables expressed as proportions. Data are presented as means, unless otherwise specified. Data were assessed for normality using the sk test. To describe patient characteristics according to malnutrition risk, comparisons were made using t test for two independent samples and rank sum (Mann Whitney U-test) if data were skewed. Proportions were compared using χ^2 statistics or Fisher's exact test. For comparison all patients with a MUST score of zero were classified as nourished and those with MUST score of ≥1 as malnourished. Similarly, all patients with PG-SGA class A were classified as nourished and PG-SGA class B and C as malnourished.

Investigating the association between malnutrition status and LOS is problematic since those who die earlier on in the follow-up period may, by definition, have a lower LOS. Therefore LOS was adjusted for in-hospital mortality. In order to account for the source of cofounding, a Cox proportional hazards model was used with death as the censoring variable and the model was adjusted for the covariates — age, gender, CCI and total number of medications. The covariate of interest is the effect of nutritional status on survival status so the survival plot displaying the cumulative survival function on a linear scale and PG-SGA category and the associated hazard ratios from the cox regression are presented. Statistical significance was defined as $P \leq 0.05$.

4.4 Results

A total 205 patients were enrolled from November 2014-November 2015 and complete data was available for 199 patients for analysis. Initial nutrition screening by MUST was found to be performed in 99 (49.7%) of patients while 100 (50.3%) missed MUST screening by nursing staff but had MUST screening subsequently performed by research staff. Ninety-two (46.5%) patients were confirmed to be well-nourished and 106 (53.5%) as malnourished by PG-SGA while MUST screening found 85 (42.7%) as well-nourished and 114 (57.3%) as malnourished. Malnourished patients were significantly older than well-nourished patients with a mean age of 81.6 (SD 8.5) years and 77.3 (SD 8.4) years respectively and both groups had more females, similar number of co-morbidities, similar CCI and were on polypharmacy but more nourished patients 62 (68.1%) were on Calcium and Vitamin D supplements **(Table 13)**. Residential status of the majority of the patients prior to acute admission was home but more well-nourished patients were independent in mobility. The most common presenting diagnosis was respiratory illness and the next most common presentation was miscellaneous problems like sepsis (n = 29; 31.9%). Anthropometric and laboratory parameters of patients in the two groups are shown in **(Table 14).**

Table 13 Baseline Demographics of patients n=199

		Nourished	Malnourished	P value
PG-SGA Diagnosis, n (%)		92 (46.5%)	106 (53.5%)	
MUST Screening, n (%)		85 (42.7%)	114 (57.3%)	
Significant (>5%) weight loss, n (%)		20 (38.7%)	63 (44.3%)	< 0.001
Age, mean (SD)		77.3 (8.4)	81.6 (8.5)	= 0.004
Sex, n (%)				
	Males	34 (50.0%)	34 (50.0%)	= 0.47
	Females	58 (44.6%)	72 (55.4%)	
Cognition, n (%)				
	Normal	90 (97.8%)	102 (96.2%)	= 0.51
	Impaired	2 (2.2%)	4 (3.8%)	
Residential Status, n (%)				
	Home	83 (90.2%)	92 (86.8%)	= 0.35
	Nursing Home	8 (8.7%)	14 (13.2%)	
	Other	1 (1.1%)	0	
No. of comorbidities, mean (SD)		6.2 (2.9)	6.3 (2.9)	= 0.94
CCI, mean (SD)		2.5 (1.9)	2.3 (1.9)	= 0.43
Mobility, n (%)				
	Independent	59 (64.8%)	41 (40.2%)	= 0.002
	Stick	8 (8.8%)	7 (6.9%)	
	Walking frame	22 (24.2%)	48 (47.1%)	
	Bedbound	2 (2.2%)	6 (5.8%)	
No. of Medications, mean (SD)		9.4 (4.7)	9.6 (4.5)	= 0.77
Vitamin D/Calcium supplements, n (%)		62 (68.1%)	63 (59.4%)	= 0.20
Principal Diagnosis, n (%)				
	Respiratory	34 (37.4%)	36 (33.9%)	= 0.41
	Cardiovascular	9 (9.9%)	16 (15.1%)	
	Falls	11 (12.1%)	12 (11.3%)	
	CNS	8 (8.8%)	4 (3.8%)	
	Miscellaneous	29 (31.9%)	38 (35.8%)	
MUST completion rate at admission, n (%)		32 (35.9%)	64 (61.5%)	= 001

PG-SGA, patient-generated subjective global assessment; MUST, malnutrition universal screening tool; SD, standard deviation; CCI, Charlson comorbidity index; CNS, central nervous system

Table 14 Anthropometric and Laboratory parameters of Nourished and Malnourished patients confirmed by PG-SGA

	Nourished	Malnourished	P value
Weight in Kg, mean (SD)	72.3 (18.5)	56.7 (13.3)	< 0.001
BMI in kg/m^2, mean (SD)	25.3 (6.5)	20.6 (5.10)	< 0.001
Handgrip strength in kg, mean (SD)	19.7 (8.2)	16.3 (7.5)	< 0.001
MAC in cm, mean (SD)	29.7 (5.0)	24.7 (4.2)	< 0.001
TST in mm, mean (SD)	19.1 (9.8)	11.1(5.9)	< 0.001
MAMC in cm, mean (SD)	23.8 (3.9)	21.4 (3.3)	< 0.001
PG-SGA score, mean (SD)	5.5 (2.9)	13.3 (4.8)	< 0.001
Albumin in g/L, mean (SD)	35.2 (8.2)	33.4 (19.3)	= 0.01
Hemoglobin in g/L, mean (SD)	124.04 (18.3)	122.03 (21.0)	= 0.47
CRP in mg/L, mean (SD)	48.9 (68.9)	50.3 (62.0)	= 0.97

SD, standard deviation; BMI; body mass index; MAC, midarm circumference; TST, triceps skinfold thickness; MAMC, midarm muscle circumference; PG-SGA, patient generated subjective global assessment; CRP, c-reactive protein

The median (IQR) LOS was significantly longer in malnourished patients compared to well-nourished patients: 8.2 (4.2 – 14.2) versus 3.4 (2.1 – 16.6) (P < 0.001), (Table 14). Malnourished patients had significantly lower HRQoL as indicated by median (IQR) EQ5D index (0.742 (0.533 – 0.8655) vs. 0.801 (0.651 – 0.892); P = 0.02) but there was no statistically significant difference in the mean (SD) VAS scores (57.9 (19.1) vs. 60.3 (20.8); P = 0.40), in malnourished and well-nourished patients respectively. Malnourished patients had significantly more nosocomial complications and the overall in-hospital mortality was 3.4% (n = 7) and all deaths occurred in the malnourished group. Within a year of discharge, an additional 16 malnourished patients had died, an additional 15.2% of the original cohort, producing a cumulative mortality of 23 (21.7%) at 1 year after discharge **(Table 15)** and **(Figure 4)**. Multivariate Cox proportional hazard model **(Table 16)** suggests that malnourished patients have a significantly worse survival even after adjustment for confounders like age, sex, CCI and total number of medications (HR 5.32; 95% CI 1.703 - 14.863), (P = 0.003). Readmission rate was higher in malnourished patients at day 7, 28 and 180 but this was not statistically significant **(Table 15)**.

Table 15 Clinical Outcome comparison between Nourished and Malnourished patients

	Nourished	Malnourished	P value
LOS, median (IQR	5.0 (2.9 – 7.9)	8.2 (4.2 – 14.5)	< 0.001
EQ5D-5L index, median (IQR)	0.801 (0.651 – 0.892)	0.742 (0.533 – 0.8655)	= 0.002
Nosocomial complications, n (%)	16 (17.4%)	36 (33.9%)	= 0.008
In-hospital mortality, n (%)	0	7 (6.6%)	< 0.001
Mortality at 1-year, n (%)	4 (4.3%)	23 (21.7%)	< 0.001
Readmission at 7 days, (%)	2 (2.2%)	8 (7.5%)	= 0.08
Readmissions at 28 days, (%)	10 (10.9%)	17 (16.0%)	= 0.29
Readmission at 90 days, (%)	23 (25.0%)	35 (33.0%)	= 0.21

LOS, length of hospital stay; IQR, interquartile range; EQ5D-5L, European quality of life questionnaire 5 dimensions 5 level

Table 16 Univariate and multivariate analysis of survival with Cox proportional hazard regression model

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Malnourished (PG-SGA)	5.755 (1.9868 – 16.667)	0.001	5.032 (1.703 – 14.863)	0.003
Age	1.043 (0.997 – 1.091)	0.066	1.028 (0.980 – 1.078)	0.256
Female sex	0.874 (0.412 – 1.851)	0.726	0.842 (0.377 – 1.883)	0.677
CCI	1.042 (0.869 – 1.251)	0.651	1.014 (0.836 – 1.231)	0.882
No. of medications	1.040 (0.962 – 1.125)	0.318	1.038 (0.955 – 1.128)	0.372

HR, hazards ratio; CI, confidence interval; PG-SGA, patient generated subjective global assessment; CCI, Charlson comorbidity index

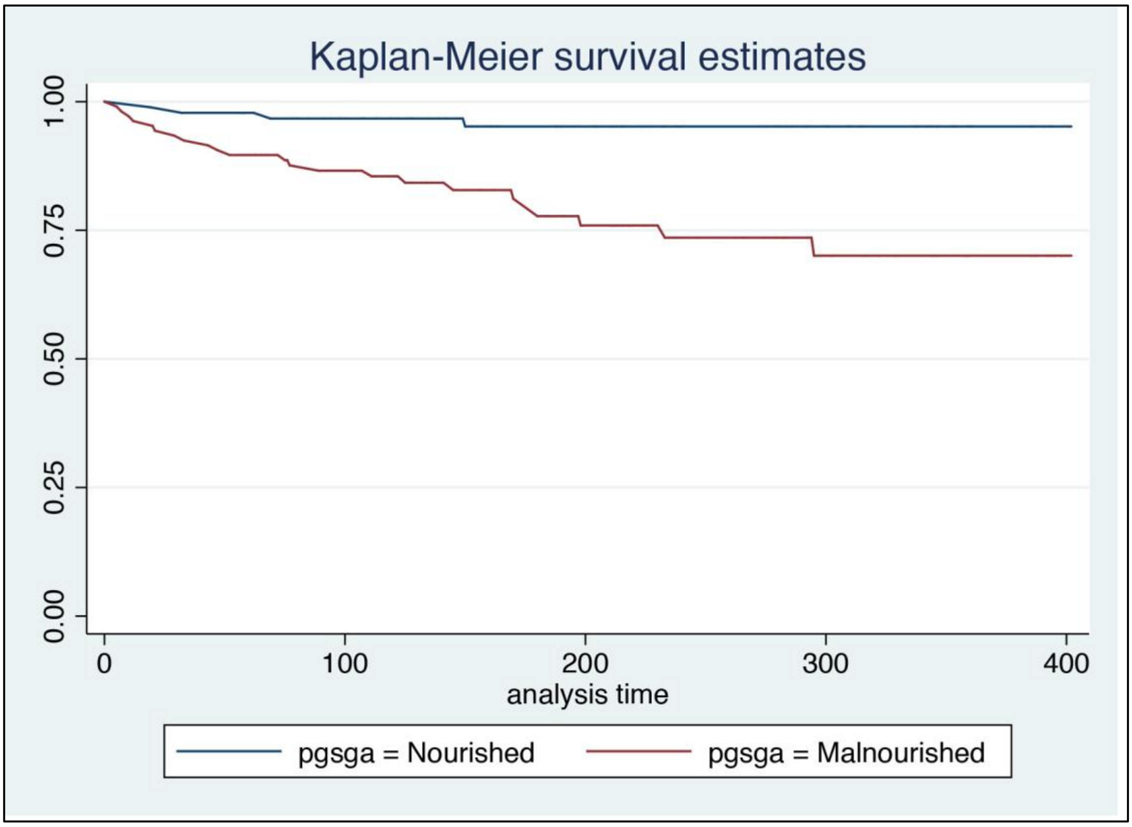

Figure 4 Kaplan-Meier survival curves showing survival difference between nourished and malnourished patients

4.5 Discussion

The present study indicates that nutritional screening is still suboptimal in our hospitals as only 49.7% of patients presenting to general medicine department of our hospital were routinely screened for malnutrition at the time of admission. Porter et al in their study in Australian hospitals also found low nutritional screening rates with the highest rate of screening using the MUST tool of only 61% and they highlighted numerous barriers including workload pressures and lack of awareness among the staff as significant factors and suggested need for a nursing leadership role to establish nutrition screening culture among staff.[276] In the UK, evidence based clinical practice guidelines for nutritional support in adults recommend to screen all patients for malnutrition, as available research indicates that early screening and treatment of malnourished patients can reduce LOS.[277] Studies suggest that hospitalization is associated with a significant decline in nutritional status due to a number of factors including catabolic effects of illness, anorexia due to polypharmacy, dislike for hospital food, nil per oral orders and a missed diagnosis of malnutrition at this crucial phase often results in patients being discharged with a significantly worse nutritional state than they were at the time of hospital admission, which further justifies that we cannot take chances by missing this important but often hidden diagnosis.[66 263]

Our study indicates that malnourished patients' median LOS was about five days longer than of well-nourished patients which significantly increases hospital costs. Kyle et al in their study in hospitalized patients also found a significant association between increased LOS and high risk MUST score.[141] Similarly Correia and Waitzberg in their study in hospitalized patients found significantly longer LOS in malnourished patients (mean 16.7 days vs. 10.1 days) with a significant increase in hospital costs for care of malnourished patients.[40]

Our study shows that there was a significantly higher mortality among malnourished patients at 1-year even after adjusting for confounders like age, sex, CCI and polypharmacy. The Kaplan Meier survival graph **(Figure 4)** suggests that mortality begins to increase within the first few weeks after discharge from hospital and this emphasizes the need for an early nutritional intervention, preferably beginning when the patient is still in the hospital. Our results are similar to Lim et al who found that malnutrition was a significant predictor of mortality at 1-year with an adjusted relative risk of death more than three times that of well-nourished patients.[62]

Our study also confirms that older malnourished patients have relatively poor HRQoL[167] with a median EQ-5D-5L index of 0.742 as compared to nourished patients who had higher median EQ-5D-5L index of 0.801, which was statistically significant. Our results are similar to Rasheed and Woods, who in their study in older hospitalized patients also found in general low HRQoL in hospitalized patients with malnourished patients experiencing a significantly lower HRQoL compared to well-nourished patients in both physical and mental dimensions of EQ-5D.[278] Food and eating are essential for health and inability to eat as a result of loss of appetite, digestive problems or swallowing difficulties affect HRQoL and these problems may be a significant contributor to a low HRQol in unwell hospitalized older patients.[279] The beneficial effects of nutritional intervention gains further significance as there is a correlation between nutrition deficiencies and cognitive decline in the elderly and recent nutritional intervention studies has shown positive preliminary results on cognitive outcomes.[280]

4.6 Limitations

We acknowledge that this is a single centre study and we were not able to recruit a significant number of cognitively impaired patients, mainly due to difficulty in obtaining valid consent. This study is limited to general medical patients with multiple clinical problems and we cannot generalize our results to sub-specialty patients with single organ involvement. A major strength of our study is however that nutritional status was confirmed by a research dietitian, who was blinded to the screening results using a validated and commonly accepted nutrition assessment tool.

4.7 Conclusion

Our study confirms poor health outcomes in acutely unwell older hospitalized general medical malnourished patients and more than half of these patients typically remain undiagnosed and thus miss any opportunity to receive a nutritional intervention. This is an area of concern and indicates lack of adherence to already established nutritional screening protocols and guidelines. We suggest a multidisciplinary approach led by clinicians, nurses and dietitians to address this problem. We suggest educating clinicians and nurses on a regular basis, to reinforce hospital nutritional screening programs and inclusion of MUST in medical and nursing assessment and discharge tools as well as regular audits to check MUST completion rate to address this common but easily treatable condition.

CHAPTER 5: MALNUTRITION AND ITS ASSOCIATION WITH READMISSION AND DEATH IN EARLY AND LATE PERIOD FOLLOWING HOSPITAL DISCHARGE

This chapter is a co-authored publication accepted November 2017. Please refer to appendix 1.3 for the statement of authorship.

Sharma Y, Miller M, Kaambwa B, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition and its association with readmission and death within 7 days and 8-180 days postdischarge in older patients: a prospective observational study. *BMJ Open*. 2017;7(11):e018443. doi: 10.1136/bmjopen-2017-018443.

5.1 Abstract

5.1.1 Objective

The relationship between admission nutritional status and clinical outcomes following hospital discharge is not well established. This study investigated whether older patients' nutritional status at admission predicts unplanned readmission or death in the very early or late periods following hospital discharge.

5.1.2 Design, Setting and Participants

The study prospectively recruited 297 patients ≥60 years old who were presenting to the general medicine department of a tertiary care hospital in Australia. Nutritional status was assessed at admission by using the PG-SGA tool and patients were classified as either nourished (PG-SGA class A) or malnourished (PG-SGA classes B and C). A multivariate logistic regression model was used to adjust for other covariates known to influence clinical outcomes and to determine whether malnutrition is a predictor for early (0-7days) or late (8-180 days) readmission or death following discharge.

5.1.3 Outcome measures

The impact of nutritional status was measured on a combined endpoint of any readmission or death within 0-7 days and between 8-180 days following hospital discharge.

5.1.4 Results

Within seven days following discharge, 29 (10.5%) patients had an unplanned readmission or death whereas an additional 124 (50.0%) patients reached this combined endpoint within 8-180 days post-discharge. Malnutrition was associated with a significantly higher risk of combined endpoint of readmissions or death both within seven days (OR 4.57; 95% CI 1.69 – 12.37, $P < 0.001$) and within 8-180 days (OR 1.98; 95% CI 1.19 – 3.28, $P = 0.007$) following discharge and this risk remained significant even after adjustment for other covariates.

5.1.5 Conclusions

Malnutrition in older patients at the time of hospital admission is a significant predictor of readmission or death both in the very early and in the late periods following hospital discharge. Nutritional state should be included in future risk-prediction models.

5.2 Introduction

Recent decades have witnessed a vast improvement in life expectancy, leading to an increasing number of older patients with multiple chronic problems. While the number of beds for acute patients has declined, unplanned hospital admissions have increased, particularly among the elderly.[281] Older patients with multiple comorbid illnesses experience poor clinical outcomes after hospital discharge, including recurrent unplanned readmissions and mortality.[282] Adverse outcomes following discharge may be indicative of unresolved acute illness, ongoing chronic illness and the development of new medical problems or gaps in outpatient care.[283-285] Although adverse outcomes following discharge are not totally preventable, studies suggest that targeted intervention such as improved discharge planning with a focus on transitional care services may provide beneficial results.[286]

The likelihood of an unplanned admission is highest in the immediate post-discharge period.[287] There may be advantages in predicting readmissions that occur shortly after discharge. However, most studies have only assessed readmission patterns within 30 days of discharge, and few studies have examined readmission patterns up to 180 days post-discharge.[288] Graham et al. have suggested that different risk factors may be responsible for very early and late readmissions and that each type of readmission needs differently targeted interventions that can only be implemented in advance if predictive factors are identified.[289]

Readmission and mortality risk prediction is a complex endeavor and remains poorly understood. A recent meta-analysis of 26 -readmission risk-prediction models for medical patients tested in a variety of populations and settings was used for comparing different hospitals and the appropriate applications of transitional care services; the analysis found these models had a poor predictive ability and suggested a need for high-quality data sources that include clinically relevant variables.[290] None of the studies included in this meta-analysis considered patients' nutritional status during index admission as a determinant of readmissions.

Studies suggest that up to 30% of hospitalized patients may be malnourished at the time of admission and that malnutrition has a negative impact on convalescence and reduces resistance to future infections and diseases causing poor clinical outcomes.[36 291 292] However, few studies have assessed the association between nutritional status at admission and clinical outcomes in the very early and the late periods following hospital discharge. Furthermore, most of these studies are retrospective, and the use of a comprehensive nutritional assessment tool, like the PG-SGA, to diagnose malnutrition is rare. Therefore, this study was designed to determine whether nutritional status at admission, as diagnosed by a qualified dietitian using PG-SGA, influences a combined clinical outcome of readmission or mortality within seven days and between 8-180 days following hospital discharge and whether malnutrition could be used as one of the predictors of early and late readmissions and death.

5.3 Methods

5.3.1 Study design and population

This prospective cohort study, included patients ≥60 years of age admitted to the department of general medicine of a large tertiary care hospital in Australia (FMC, 520 beds), between August 2014 and March 2016. The exclusion criteria were refusal or inability to give informed consent, patients referred to palliative care and non-English-speaking patients, who were excluded due to a lack of funds to hire an interpreter. Ethical approval was obtained from Southern Adelaide Human Research Committee (SA HREC; approval number 273.14-HREC/14/SAC/282) on 21 July 2014. The required sample size for this study, calculated on the basis of a previous study[289] showing early readmission rate of 7.8%, was estimated at five hundred and sixty nine patients but insufficient resources led to the recruitment of only two hundred and ninety seven patients.

5.3.2 Outcomes

The study's primary outcome was a combined endpoint of either the first unplanned readmission to any of the acute-care hospitals in the state of South Australia or death, within 0-7 days and between 8-180 days after hospital discharge. In this study, unplanned readmission was defined as any unscheduled hospitalization to any hospital in the state of South Australia that was not for a planned investigation (e.g., elective endoscopy) or non-emergent treatment (e.g., planned drug infusion). The primary endpoint of readmissions or deaths were recorded from a central computer database, which captures these events for all state hospitals.

5.3.3 Nutritional status assessment

After obtaining written informed consent from patients, it was ensured that nutrition screening with MUST had been performed. It is a standard policy in our hospital to screen all patients with MUST at the time of admission. MUST includes a BMI score, a weight loss score, and an acute disease score and classifies patients as low, moderate or high risk of malnutrition.[143] Following this all participating patients were then referred to a qualified dietitian for confirmation of their nutritional status by PG-SGA. The PG-SGA[157] generates a numerical score while also providing an overall global rating divided into three categories: well-nourished (PG-SGA A), moderately malnourished or suspected of being malnourished (PG-SGA B) or severely malnourished (PG-SGA C). For each PG-SGA component, points (0-4) are awarded depending on the impact on nutritional status. Component scores are combined to obtain total scores that range from 0-35 with scores ≥7 indicating a critical need for nutritional intervention and symptom management.[94] The three different dietitians who were involved in the assessment of nutritional status using the PG-SGA received training prior to the study's commencement. The PG-SGA classes were divided into two categories by combining PG-SGA classes B and C into the malnourished category for easily interpreting patients as nourished (PG-SGA class A) and malnourished (PG-SGA classes B and C). Furthermore, PG-SGA scores were split into a categorical variable with a PG-SGA score of <7, indicative of no critical need for nutrition intervention and ≥7, indicating critical need for intervention.

5.3.4 Covariates

Several known variables that can influence outcomes after hospital discharge were recorded at the baseline. Sociodemographic data, number of hospitalizations during the six months before index admission (current hospital admission) and clinical information were recorded at the baseline. Comorbidity was assessed with the CCI, and the total number of medications were recorded at the time of admission. HRQoL was assessed using the EQ-5D 5L questionnaire, a simple, self-administered instrument which is able to distinguish between 3,125 states of health.[180] A UK-specific algorithm developed using time-trade-off techniques was used to convert the EQ-5D 5L health description into a valuation ranging from -0.281 to 1.[293] A VAS score, which provides an unweighted measure of HRQoL, can also be calculated from the questionnaire. The main diagnosis of index admission was retrieved from medical records and divided into seven categories according to the system affected: respiratory disease, cardiovascular disease, (3) neuropsychiatric disease, gastrointestinal disease, (5) falls, renal disease, and (7) miscellaneous diseases, including infections. The index admission's acuity was gauged from the total number of medical emergency response team (MET) calls and the number of hours spent in the ICU. LOS was determined from the day of admission to the day of discharge. The study recorded any unplanned hospital presentations to any of the hospitals in South Australia within 0-7 days and between 8-180 days after hospital discharge, as well as any recorded deaths at the same time points, using the central hospital computer database.

5.5 Statistics

Demographic variables were assessed for normality using sk test. Data are presented as mean or median (IQR), and student t-test and rank-sum tests were applied as appropriate. Categorical variables are expressed as frequency and percent and compared using Pearson's χ^2 or Fisher's exact test as appropriate.

Univariate logistic regression was used to assess the association between nutritional status and the combined end point of unplanned readmission or death within seven days and between 8-180 days post-discharge. In a multivariate logistic regression analysis, the relationship between readmission/death and nutrition status at admission was adjusted for other variables: age, gender, CCI, principal diagnosis at presentation, number of medications at admission, LOS, number of medical emergency response team calls during index admission and total number of hours spent in the ICU. Variance inflation factor and tolerance values were used to detect collinearity between variables included in the model.[294] A link test was used to confirm that the linear approach to model the outcome was correct. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. A Kaplan Meier survival curve was plotted from time of discharge to the first onset of any of the primary outcomes to detect proportion of patients who did not experience the primary outcome. A Log rank test was used to compare survival proportions in the nourished and malnourished groups. A two-sided $P < 0.05$ was considered to indicate statistical significance. All analysis was performed using STATA version 13.1 (StataCorp, College Station, Texas, USA).

5.6 Results

This study recruited 297 patients, and nutrition status, as determined by PG-SGA, was available for 277 patients. Mean age was 80.3 years (SD 8.7, range 60 – 97) with 178 (64.3%) of the patients being females and the majority of patients came from home. There was no difference in the nutrition status between males and females (mean PG-SGA score 9.7 (SD 5.8) vs. 9.2 (SD 5.3), P = 0.44) in males and females respectively) and the nutrition status of patients who came from a nursing home was similar to those who came from home (mean PG-SGA score 9.0 (SD 4.5) vs. 9.4 (SD 5.6), P = 0.70) in nursing home and patients from home, respectively). Patients had multiple comorbidities (mean number of comorbidities 6.2, SD 2.7, range 0 – 16), and the mean CCI was 2.3 (SD 1.8). The median LOS for the index hospitalization was 7 (IQR 3.4 – 14.6) days. Within seven days after discharge, 29 (10.5%) patients had an unplanned readmission or death (primary endpoint). Among the 29 patients who had the primary endpoint within seven days, 13 (44.8%) had been admitted prior to the index admission. The primary endpoint occurred in 124 (50.0%) patients within 8-180 days post-discharge and 69 (55.7%) of these patients had been admitted in the six months prior to the index admission. Patients who were malnourished at the time of index admission were significantly older (P = 0.001), had lower quality of life (P = 0.03) and stayed longer (P = 0.02) in the hospital as compared to the nourished patients. Respiratory illness, miscellaneous diseases including sepsis and cardiovascular diseases were the three main diagnoses during index hospitalization with 86 (28.9%), 67 (22.6%) and 55 (18.5%) cases, respectively.

5.6.1 Association of malnutrition with very early and late unplanned readmissions and mortality

Table 17 shows the baseline characteristics according to the occurrence of combined endpoint of readmission or death within 0-7 days and 8-180 days of discharge, respectively. Malnutrition risk, as determined by the MUST score, and the classification of patients as being malnourished per PG-SGA class were significantly higher in subjects who developed the combined endpoint both within 0-7 days (83% vs. 51%) and 8-180 (60% vs. 43%) days post-discharge (P < 0.05). Similarly, a significantly higher proportion of patients who were in critical need of nutrition therapy (as indicated by PG-SGA score of ≥ 7) at the time of index admission suffered the combined endpoint both within 0-7 days (P = 0.002) and 8-180 days (P = 0.02) following hospital discharge **(Table 17)**.

Table 17 Baseline characteristics according to primary endpoint (readmission/death) at 0-7 days and 8-180 days post-discharge

	Readmission/death within 0-7 days (n = 29)	**No readmission/death within 0-7 days (n = 248)**	P value	**Readmission/ death within 8-180 days (n = 124)**	**No readmission/death within 8-180 days (n = 124)**	P value
Age, mean (SD)	81.2 (7.6)	80.2 (8.8)	0.74	80.3 (8.6)	80.0 (9.0)	0.77
Female sex, n (%)	13 (44.8)	165 (66.5)	0.02	80 (64.5)	85 (68.5)	0.50
Total comorbidities, mean (SD)	6.8 (3.0)	6.1 (2.7)	0.20	6.6 (2.9)	5.7 (2.5)	0.012
CCI, mean (SD)	2.8 (2.1)	2.2 (1.8)	0.09	2.4 (1.8)	2.1 (1.8)	0.16
Total medications, mean (SD)	9.1 (4.5)	9.6 (4.4)	0.56	10.3 (4.5)	8.9 (4.2)	0.007
Principal diagnosis at index admission, n (%)						
Respiratory						
CVS	13 (44.8)	72 (29.0)	0.34	33 (26.6)	39 (31.5)	0.02

	Readmission/death within 0-7 days (n = 29)	No readmission/death within 0-7 days (n = 248)		Readmission/ death within 8-180 days (n = 124)	No readmission/death within 8-180 days (n = 124)	
Neuropsychiatric	6 (20.7)	44 (17.7)		28 (22.6)	16 (12.9)	
GIT	2 (6.9)	23 (9.3)		11 (8.9)	12 (9.7)	
Falls	2 (6.9)	17 (6.9)		11 (8.9)	6 (4.8)	
Renal	0	21 (8.5)		4 (3.2)	17 (13.7)	
Miscellaneous	0	16 (6.5)		6 (4.8)	10 (8.1)	
	6 (20.7)	55 (22.2)		31 (25.0)	24 (19.4)	
LOS, median (IQR)	13.3 (6.7 - 35.9)	6.8 (3.2 - 13.7)	0.004	7.9 (3.6 - 15.2)	5.7 (3.1 - 11.5)	0.11
MUST score[a], mean (SD)	1.9 (1.4)	1.1 (1.2)	0.001	1.3 (1.3)	0.9 (1.2)	0.03
Nutrition status PG-SGA[b], n (%)						
Nourished	5 (17.2)	121 (48.8)	0.001	50 (40.3)	71(57.3)	0.008
Malnourished	24 (82.8)	127 (51.2)		74 (59.7)	53 (42.7)	
Patients with PG-SGA ≥7, n (%)	25 (86.2)	142 (57.3)	0.002	80 (64.5)	62 (50.0)	0.02
HRQoL, mean (SD)						
EQ-5D index[c], mean (SD)	0.678 (0.226)	0.709 (0.222)	0.49	0.700 (0.229)	0.717 (0.217)	0.31
VAS[d], mean (SD)	55.2 (17.1)	59.5 (20.1)	0.28	55.9 (20.4)	62.8 (18.1)	
Total MET calls, mean (SD)	0.24 (1.0)	0.13 (0.4)	0.38	0.10 (0.32)	0.15 (0.53)	0.95
Total ICU hours, mean (SD)	4.3 (19.3)	1.9 (13.4)	0.53	2.3 (15.5)	1.5 (11.0)	0.62

SD, standard deviation; CCI, Charlson comorbidity index; CVS, cardiovascular; GIT, gastrointestinal; LOS, length of hospital stay; IQR, interquartile range; MUST, malnutrition universal screening tool; PG-SGA, patient generated subjective global assessment; HRQoL, health related quality of life; EQ-5D, European quality of life 5 dimension; VAS, visual analogue scale; MET, medical emergency team; ICU, intensive care unit

[a]Higher MUST score indicates high risk for malnutrition, [b]PG-SGA class dichotomized to PG-SGA A (nourished) and PG-SGA B and C (malnourished), [c]Higher EQ-5D index indicates better HRQoL, [d]Higher VAS indicates better HRQoL

Table 18 Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for early readmission/death (0-7days)

Variable	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)[a]	P value
Malnourished	4.57 (1.69 – 12.37)	0.001	5.01 (1.69 – 14.75)	0.009
Age	1.00 (0.96 – 1.05)	0.73	1.00 (0.94 – 1.05)	0.80
Female sex	0.42 (0.19 – 0.89)	0.03	0.42 (0.17 – 1.04)	0.06
Total comorbidities	1.08 (0.95 – 1.23)	0.25	1.15 (0.96 – 1.38)	0.13
CCI index	1.16 (0.96 – 1.40)	0.12	1.08 (0.84 – 1.39)	0.55
Medications during index admission	0.97 (0.88 – 1.05)	0.47	0.91 (0.81 – 1.02)	0.12
LOS of index admission	1.03 (1.01 – 1.04)	0.001	1.03 (1.00 – 1.05)	0.02
Admission in last 6 months prior to index admission	0.77 (0.53 – 1.12)	0.13	0.66 (0.27 – 1.58)	0.35
Principal diagnosis index admission				
Reference (Resp.	-	-	-	-
illness)	0.63 (0.23 – 1.75)	0.38	0.63 (0.20 – 2.04)	0.44
CVS	0.61 (0.16 – 2.32)	0.48	0.34 (0.06 – 1.93)	0.23
CNS	0.54 (0.13 – 2.59)	0.44	0.42 (0.07 – 2.36)	0.33
GIT	-	-	-	-
Falls	-	-	-	-
Urinary	0.61 (0.23 – 1.61)	0.31	0.35 (0.11 – 1.12)	0.07
Miscellaneous				
ICU hours during index admission	1.03 (0.99 – 1.02)	0.56	1.01 (0.97 – 1.05)	0.63
Total MET calls index admission	1.55 (0.95 – 2.54)	0.08	0.84 (0.31 – 2.22)	0.72

[a]Odds ratio determined using multivariable logistic regression (using early/late readmissions as outcome variable)
CI, confidence interval; CCI, Charlson comorbidity illness; LOS, length of hospital stay; CVS, cardiovascular; CNS, central nervous system; GIT, gastrointestinal; ICU, intensive care unit; MET, medical emergency team

Malnutrition was associated with a higher risk of the combined endpoint of readmissions and death within seven days after discharge (OR 4.57; 95% CI 1.69 – 12.37; P < 0.001) **(Table 18).** After adjusting for covariates, including age, gender, CCI, LOS, number of medications, principal diagnosis at current admission and hours spent in the ICU during index admission, the association was even stronger for the combined end-point (OR 5.01; 95% CI 1.69 – 14.75; P = 0.009) **(Table 18)**.

Similarly, between 8-180 days post-discharge, malnourished patients had higher odds to have a combined end point of readmission and death (OR 1.98; 95% CI 1.19 – 3.28, P = 0.007), and this remained significant even after adjustment for the above covariates (OR 1.97; 95% CI 1.12 – 3.47, P = 0.002) **(Table 19)**. The P-value for the Hosmer-Lemeshow goodness-of-fit was > 0.05 for both the adjusted models, indicating a good fit. The variance inflation factors and tolerance were near 1.00 for all variables, excluding significant collinearity. The link test confirmed that the linear approach to model the outcomes was correct. The Kaplan Meier survival curve **(Figure 5)** shows that the nourished group had significantly fewer readmissions and deaths at 180 days than the malnourished group (log rank $\chi^2 = 11.4$, P < 0.001).

Table 19 Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for late readmission/death (8-180days)

Variable	**Unadjusted OR (95% CI)**	**P value**	**Adjusted OR (95% CI)[a]**	**P value**
Malnourished	1.98 (1.19 – 3.28)	0.007	1.97 (1.12 – 3.47)	0.009
Age	1.00 (0.98 – 1.03)	0.81	1.00 (0.97 – 1.03)	0.94
Female sex	0.86 (0.51 – 1.44)	0.56	0.93(0.52 – 1.66)	0.83
Total comorbidities	1.14 (1.04 – 1.25)	0.006	1.07 (0.95 – 1.22)	0.30
CCI index	1.11 (0.97 – 1.28)	0.13	1.03 (0.86 – 1.23)	0.85
Medications during index	1.08 (1.02 – 1.14)	0.008	1.05 (0.98 – 1.12)	0.17

Variable	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)[a]	P value
admission				
LOS of index admission	1.01 (0.99 – 1.02)	0.45	1.01 (0.99 – 1.02)	0.52
Admission in last 6 months prior to index admission	1.55 (0.96 – 2.53)	0.07	1.38 (0.79 – 2.40)	0.26
Principal diagnosis index admission				
Reference (Resp. illness)	-	-	-	-
CVS	1.58 (0.75 – 3.27)	0.22	2.06 (0.91 – 4.70)	0.08
CNS	1.09 (0.44 – 2.71)	0.85	1.12 (0.41 – 3.04)	0.81
GIT	2.03 (0.71 – 5.73)	0.18	1.91 (0.58 – 6.28)	0.29
Falls	0.26 (0.08 – 0.85)	0.03	0.26 (0.07 – 0.89)	0.03
Urinary	0.83 (0.28 – 2.41)	0.72	0.71 (0.21 – 2.32)	0.57
Miscellaneous	1.40 (0.70 – 2.79)	0.34	1.36 (0.63 – 2.92)	0.44
ICU hours during index admission	0.99 (0.98 – 1.01)	0.53	1.01 (0.98 – 1.03)	0.64
Total MET calls index admission	0.76 (0.41 – 1.39)	0.36	0.66 (0.32 – 1.34)	0.25

[a]Odds ratio determined using multivariable logistic regression (using early/late readmissions as outcome variable)
CI, confidence interval; CCI, Charlson comorbidity illness; LOS, length of hospital stay; CVS, cardiovascular; CNS, central nervous system; GIT, gastrointestinal; ICU, intensive care unit; MET, medical emergency team

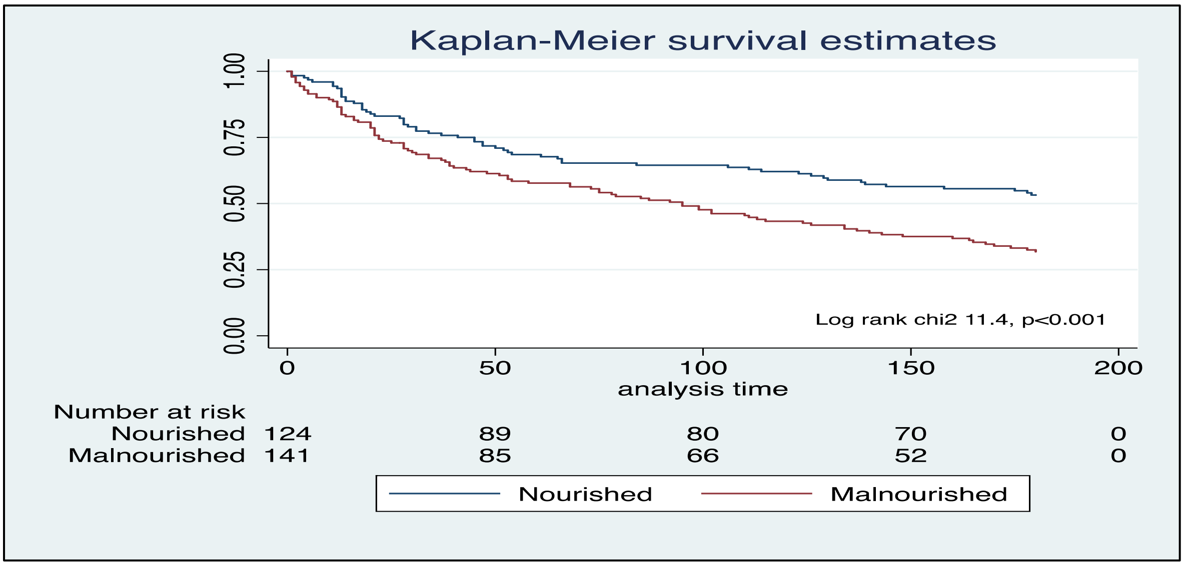

Figure 5 Kaplan-Meier survival curve for combined outcome in nourished and malnourished

5.7 Discussion

The present study's results indicate that malnutrition at admission, as determined by the PG-SGA, was a significant predictor of a combined end-point of readmission or mortality in older general-medical patients, during both the early and late periods after hospital discharge. Malnutrition was associated with an almost four-fold increased risk of readmission or mortality within seven days after discharge, and the risk almost doubled between 8-180 days after discharge. Malnutrition remained a significant predictor even after adjustment for other covariates that could have influenced the clinical outcome.

One appealing explanation for these results is that the acute condition responsible for the index admission weakens the patient's overall health, and malnutrition further compounds this problem with a consequent higher risk of complications or exacerbations of previously stable comorbidities.[295] The post-discharge period is a fragile period, referred to as –'post-hospital syndrome'.[296] This syndrome has been described as a period of vulnerability due to impaired physiological systems, depleted reserves, and lower body resistance against health threats, on top of the recent acute illness responsible for the index admission. The current study's results introduce another dimension to this theory: impaired nutritional status may play a significant role in the post-discharge period beyond seven days. The acute illness and the stress of the index admission may exacerbate malnutrition, possibly inducing a relapse or predisposing the patient to new acute illnesses that increase the risk of readmission or mortality.[297 298]

The present study's results are in line with Mogensen et al., who found that malnourished patients who survived intensive care admission had higher 90-day mortality (OR 3.72; 95% CI 1.2 - 6.3) and that malnutrition was a significant predictor of their 30-day unplanned hospital readmission.[299] Studies in heart-failure patients have suggested that malnutrition may contribute to the progression of the underlying heart disease due to low-grade inflammation leading to poor outcomes and was a significant predictor of readmissions.[103]

Older general-medical patients are known to have substantial long-term morbidity and mortality. Known risk factors for adverse events following discharge include multiple comorbidity, severity of index admission and institutional care rather than domiciliary care.[282 300] Hospital readmissions represent a multifaceted problem that require a better understanding.[295] Presumably there are other unknown factors that influence patient outcomes after discharge. The present study illustrates that early and late post-discharge patient outcomes appear to be associated with the presence of malnutrition during admission. While causation cannot be inferred from an observational study, the malnutrition-post-discharge outcome has biological plausibility.

To date, no study has included nutritional status in the development of a predictive tool for readmissions and this area needs further research. Studies do suggest that nutritional intervention initiated early during hospitalization, by providing high-energy protein supplements with a continuation post-hospital discharge, does have a favorable impact on nutritional parameters and reduces the length of hospital stay; however, its impact on mortality and readmissions is unclear, and such an intervention may be too late for some.[104 301] While the ideal intervention to improve nutritional status in hospitalized patients has yet to be identified, the solution may lie in recognizing and managing malnutrition in the community before any hospital admission.[51]

5.8 Limitations

This study has several limitations. First, it is a single-centre study in a tertiary care hospital. The case mix of patients discharged from this hospital may differ from that of other hospitals; thus, the results may not be generalizable particularly to community hospitals, although it is likely to be similar to other academic hospitals in Australia. The study was unable to adjust its analysis for functional status or other factors, such as appropriateness of drugs, clinical stability at discharge or social factors that might influence readmission. This study involved older general-medical patients who frequently suffer from multiple comorbidities, and our results may not be applicable to relatively younger sub-specialty patients with single organ system involvement.

One of the study's strengths is that it was a prospective study and that the malnutrition diagnosis was confirmed by a dietitian using a comprehensive nutrition assessment tool. The study also assessed all readmissions in all state hospitals, unlike some other studies that were only able to capture readmissions to a single hospital.

5.9 Implications

This study has several implications. Transitions of care should focus not only on the acute condition but also on the patient's nutritional status, because the latter may increase the risk of readmission or death. There is a need for future well-designed studies to examine the beneficial effects of an intervention targeting malnutrition and whether this intervention prevents readmissions and mortality. In the interim, nutritional intervention should be most effective if begun early during admission and it should be continued in the community following discharge by referral to either a community dietitian or follow-up at an outpatient dietetic clinic. Overall, public health policies to optimize nutrition of those over 60 years of age may result in a reduction in health-care utilization.

5.10 Conclusion

Impaired nutritional status at admission predicts poor clinical outcomes in both early and late post-discharge periods as determined by readmissions and mortality in older general-medical patients and a targeted nutritional intervention may prove beneficial in malnourished patients.

CHAPTER 6: VALIDITY OF MUST AGAINST PG-SGA IN GENERAL MEDICAL PATIENTS

This chapter is a co-authored publication accepted in 2017. Please refer to appendix 1.4 for the statement of authorship.

Sharma Y, Thompson C , Kaambwa B, Shahi R, Miller M. Validity of the Malnutrition Universal Screening Tool in Australian hospitalized acutely unwell patients. *Asia Pacific Journal of Clinical Nutrition.* 2017;26:994-1000. doi: 10.6133/apjcn.022017.15.

6.1 Abstract

6.1.1 Background

MUST is a commonly used nutritional screening tool in hospitalized patients. Very few studies have validated MUST against a reference assessment tool in older hospitalized patients.

Aims

In the present study, we aimed to validate the MUST for nutritional screening in acutely hospitalized older general medical patients against a reference assessment tool – PG-SGA.

6.1.2 Methods

One hundred and thirty two patients recruited as part of an ongoing randomized control trial, looking into cost effectiveness analysis of an extended ambulatory nutritional intervention in patients discharged from acute care contributed data for this analysis. In addition to performance of MUST and PG-SGA the following nutritional parameters were measured: weight loss >5% in previous 3-6 months, handgrip strength, TST, MAC and MAMC. HRQoL was determined using the EuroQoL Questionnaire (EQ-5D-5L). Sensitivity, specificity, predictive values and concordance were calculated to validate MUST against PG-SGA.

6.1.3 Results

MUST when compared to PGSGA gave a sensitivity of 69.7%, specificity of 75.8%, positive predictive value of 75.4%, negative predictive value of 70.1% and kappa

statistics showed 72.7% agreement (k = 0.49) for detecting malnutrition. The MUST score had significant inverse correlation with body mass index, TST and MAMC but not with Handgrip strength. Malnourished patients (PG-SGA class B/C) were found to have a significantly worse HRQoL.

6.1.4 Conclusion

This is the first study to demonstrate that MUST can be confidently administered with respect to validity in acutely hospitalized older general medicine patients to detect malnutrition. In this study, significant weight loss in the preceding 3-6 months does seems to have validity, which was almost comparable to MUST, to predict risk of malnutrition and further research is needed to verify this finding.

6.2 Introduction

Malnutrition is common in the older population and its prevalence depends upon the clinical setting, ranging from 10-30% in the community to as high as 70% in the acute care settings.[302] Diagnosis of malnutrition is often missed in hospitalized patients due to a number of factors including lack of awareness of this condition among medical and nursing staff, low priority given other medical conditions, lack of understanding of available screening tools and also time-poor clinicians in busy acute care settings.[274] Further to this, factors such as cognitive impairment, the number of comorbidities and altered taste sensation make older patients an even more vulnerable group.[303 304]

It is well established that malnutrition is associated with adverse clinical outcomes for patients including a longer LOS, higher number of nosocomial complications during hospitalization, increases risk for infections, higher number of falls and leads to a high morbidity and mortality.[77 305-307] Given the high prevalence of malnutrition in hospitalized patients, experts have recommended screening all patients for malnutrition by using a valid nutrition screening tool.[141 245] If the patient is found to be at risk of malnutrition, practitioners must confirm with a more extensive nutritional assessment tool such as the PG-SGA, and then initiate an individualized nutrition care plan.[146] The PG-SGA is a version of SGA designed for the nutritional assessment of oncology patients and is dependent on information received from the patient. Nutrition screening aims to identify patients who are malnourished or at significant risk of malnutrition, and patients identified at risk are further referred for an in-depth nutritional assessment.[308] In the last couple of decades, a number of screening tools have become available and the Malnutrition Universal Screening Tool developed by British Association for Parenteral and Enteral Nutrition (BAPEN) is a rapid screening tool which has been found to have content validity (comprehensiveness of the tool), face validity (issues which are relevant to the purpose of the test) and internal consistency.[131 309] The MUST was primarily developed for use in the community and includes a BMI score, a weight loss score, and an acute disease score.[126] A total MUST score of 0 indicates low risk, 1 indicates medium risk, ≥2 indicates high risk of malnutrition.[137] MUST is designed to identify need for nutritional treatment, as well as establishing nutritional risk on the basis of knowledge about the association between impaired nutritional status and impaired function.[129 138] It has been documented to have a high degree of reliability (low inter-observer variation) with a k = 0.88-1.00.[274] This tool has recently been extended to other health care settings, including hospitals, where again it has been found to have excellent inter-rater reliability with other tools (k ≥ 0.783), and predictive validity (LOS, mortality in elderly wards, and discharge destination in orthopedic patients).[274]

The SGA is a method of nutritional assessment based on a medical history and physical examination, whereby each patient is classified as well-nourished (SGA A) or suspected of being malnourished (SGA B), or severely malnourished (SGA C).[134] It has been validated against objective parameters, measures of morbidity and quality of life and has a high degree of inter-rater reliability.[151 309 310] A further development of SGA is PG-SGA, which incorporates a score in addition to global assessment. Please refer to section PG-SGA for further details.

In the absence of a ‘gold standard’ for diagnosing malnutrition it is difficult to establish the validity of nutrition screening tools.[309] So far only one study[275] has verified MUST against PG-SGA in radiation oncology patients and no published study has confirmed the validity of MUST against PG-SGA in older general medical patients. This study was carried out to verify the validity of the MUST against PG-SGA in detecting malnutrition in acutely hospitalized older general medical patients admitted to a large Australian tertiary care hospital.

6.3 Materials and Methods

A total of 132 hospitalized patients were recruited from November 2014 to August 2015. These patients are participants in an RCT (registration number ACTRN1261400083362) investigating the cost effectiveness of an extended ambulatory nutritional intervention in patients who are discharged from acute care. Patients admitted to general medicine wards of FMC were conveniently sampled and screened for eligibility for study participation, based on certain inclusion and exclusion criteria. Inclusion criteria were age ≥60 years admitted under general medicine ward and exclusion criteria were palliative patients, Indigenous, non-English speaking patients or residing outside metropolitan Adelaide and also patients who were unable to give a valid consent. Ethics approval for the study was obtained from Southern Adelaide Human Research Ethics Committee on 21st July 2014 (No. 273.14-HREC/14/SAC/282).

6.3.1 Procedure

Potential participants who were admitted to the general medicine wards of Flinders Medical Centre were identified and an information package about the study was provided and explained to the participants. Written informed consent was obtained from all participants or legal guardians (if participants had dementia/cognitive impairment).

6.3.2 Data Collection and Measures

Baseline data on demographics, health and medical history was obtained from medical records and case notes. The following demographic characteristics of patients were recorded: age, sex, pre-hospital residential status, and mobility at the time of admission. Clinical characteristics recorded were: principal presenting diagnosis, number of co-morbidities, CCI, number of medications and vitamin and calcium supplementation. The MUST score was obtained from the case notes, where available. In Flinders Medical Centre, it is expected that all patients who are admitted under general medicine have the MUST completed electronically, as a part of initial nursing assessment, and a hard copy is inserted in the case notes. Where MUST was not found in the case notes, a member of the research team either asked the assessment nurse to perform MUST or completed the MUST themselves. All consenting patients were then referred to a research dietitian who was blinded to the MUST nutritional risk score and performed PG-SGA, as well as anthropometric measurements, including hand grip strength with a hand held dynamometer in patients' dominant hand, MUAC measured at midpoint between acromion process and olecranon using a steel measuring tape, TSF using calibrated Harpenden skinfold caliper on the right side and MAMC was determined using formula MAMC = MUAC - (0.3142 × TSF (mm) = in cm. The PG-SGA was scored consistent with the literature.[311] The EuroQoL EQ-5D-5L questionnaire was also completed by all participants, to assess the impact of nutritional status on HRQoL. Please refer to section EQ-5D-5L for further details.

6.4 Data Analysis

Data analysis was performed using STATA (version 13.1). Descriptive analysis was conducted for all the demographic variables. Sensitivity, specificity and positive and negative predictive values were calculated to determine whether the MUST is a valid nutritional screening tool among hospitalized older general medical patients. Sensitivity is defined as the percentage of malnourished patients correctly identified by the MUST and specificity is the percentage of well-nourished patients correctly identified by MUST. Predictive values are the likelihood that the MUST correctly predicts the presence or absence of malnutrition, compared to PG-SGA. A receiver operating characteristic curve (ROC)[312] interpreted relative areas under the curves, and kappa statistics were used to determine the proportion of agreement between the MUST and PG-SGA. The value of kappa varies from 0 to 1, with a value of <0.20 = poor, 0.20 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.60 to 0.80 = substantial, and >0.81 = perfect agreement.[313] Statistical significance was reported at the P value < 0.05 (two tailed). For comparison, all patients with a MUST score of 0 were classified as nourished and those with a score of ≥1 were classified as malnourished. Similarly patients who were PG-SGA class A were classified as well-nourished and PG-SGA class B and C as malnourished.

6.5 Results

The mean age of participants was 79.5 years (range 60 – 97, SD 9) with the majority being female (n = 83; 62.9%) and living at home (n = 118; 90.1%) **(Table 20)**. The mean number of co-morbidities was 6.2 (range 0 – 15; SD 2.94) and mean CCI was 2.3 (range 0 – 9; SD 1.9). More than half of the participants (n = 64; 50.8%) needed some sort of support (stick or walking frame) for mobilization and 2 (1.6%) were bed bound while 60 (47.6%) participants were independent in mobility **(Table 20)**. The mean number of medications was 8.7 (range 0 – 23; SD 4.4) and 51 (38.6%) of participants were on Vitamin D and calcium supplementation. The majority of participants presented with a principal diagnosis of respiratory illness (n = 47; 35.6%) with 19 (14.3%) presenting with falls and another 46 (34.8%) had miscellaneous diagnoses including sepsis **(Table 20)**. Sixty-seven (51.2%) patients were found to have had an initial MUST screening performed at the time of admission. **Table 21** describes that according to PG-SGA, 66 patients (51.6%) were malnourished and 62 (48.4%) were well-nourished, while MUST found 65 (49.2%) patients as malnourished and 67 (50.8%) well-nourished **(Table 21)**. The median LOS of participants was 5.5 days, and malnourished patients stayed 4.5 days longer than nourished patients with $P<0.001$ **(Table 21)**. EQ-5D-5L utility scores were significantly lower in malnourished patients compared with well-nourished patients, with median EQ-5D-5L index of 0.697 (IQR 0.501 – 0.838) in malnourished and 0.804 (IQR 0.656 – 0.899) in well-nourished patients with $p = 0.004$ **(Table 21)**.

Table 20 Participant demographic, health and physical characteristics (n = 132)

Characteristics	Mean (range) (SD)
Demographic characteristics	
Age in years, mean (SD)	79.5 (60 – 97) (SD 8.6)
Sex (women), n (%)	83 (62.9%)
Residential status, n (%)	
Home	118 (90.1)
Nursing Home	12 (9.2)
Others	1 (0.8)
Mobility, n (%)	
Independent	60 (47.6%)
Stick	11 (8.7%)
Walking frame	53 (42.1%)
Bed bound	2 (1.6%)
Health characteristics	
Admission diagnosis, n (%)	
Respiratory disease	47 (35.6%)
Cardiac problem	11 (8.3%)
Falls	19 (14.4%)
CNS disease	9 (6.8%)
Other	46 (34.9%)
No of co-morbidities, mean (SD)	6.2 (0 – 15) (2.9)
CCI index, mean (SD)	2.4 (0 – 9) (1.9)
Patients on vitamin D/calcium, n (%)	51 (38.6)
MUST tool completion at admission, n (%)	67 (51.2%)
Physical assessments according to gender	
Weight in kg, mean (SD)	
Men	73.3 (42.1 – 130) (19.4)
Women	60.6 (35 – 117.5) (15.9)
BMI in kg/m^2[a], mean (SD)	
Men	24.2 (14.6 – 42.3) (6.1)
Women	23.9 (14.3 – 44.5) (5.7)
Handgrip strength, kg[a], mean (SD)	
Men	25.3 (11.5 – 44.5) (8.1)
Women	14.6 (2 – 27.5) (5.4)

Characteristics	Mean (range) (SD)
TST in mm[a], mean (SD)	
Men	12.4 (3.7 – 33.2) (6.6)
Women	17.9 (3.4 – 46.7) (10.2)
MUAC in cm, mean (SD)	
Men	28.1 (20.4 – 40.4) (5.5)
Women	26.4 (17.9 – 37.8) (4.6)
MAMC in cm, mean (SD)	
Men	24.2 (18.1 – 35.6)
Women	21.0 (14.9 – 28.7) (3.0)
EQ-5D-5L index[a], median (IQR)	
Men	0.704 (0.185 – 1) (0.211)
Women	0.700 (0.030 – 1) (0.200)

SD, standard deviation; CCI, Charlson comorbidity index; CNS, central nervous system; MUST, malnutrition universal screening tool; BMI, body mass index; TST, triceps skinfold thickness, MUAC, midupper arm circumference, MAMC, midarm muscle circumference, EQ-5D-5L, European quality of life 5 dimensions 5 level

Table 21 Characteristics of nourished and malnourished patients

	Nourished	Malnourished	P value
PG-SGA n (%)	62 (48.4%)	66 (51.6%)	
MUST n (%)	65 (49.2%)	67 (50.8%)	
LOS (days) median (IQR)	3.5 (2.5 - 11)	8 (4 - 14)	< 0.001
EQ-5D-5L index (median) (IQR)	0.697 (0.501 - 0.838)	0.804 (0.656 - 0.899	= 0.004

PG-SGA, patient generated subjective global assessment; MUST, malnutrition; LOS, length of hospital stay universal screening tool; IQR, inter quartile range; EQ-5D-5L, European quality of life questionnaire 5 dimensions 5 level

Table 22 describes that MUST results, when compared with PG-SGA, showed that 46 patients (69.6%) were correctly classified as malnourished (true positive) and 47 patients (70.1%) were correctly classified as well-nourished (true negative). In contrast, 15 (22.3%) were wrongly classified as malnourished (false positive) and 20 patients (33.3%) were wrongly classified as well-nourished despite being identified as malnourished by PG-SGA. When compared with PG-SGA, MUST had a sensitivity of 69.7% and specificity of 75.8% with a positive predictive value of 75.4% and a negative predictive value of 70.1% and an area under the ROC curve of 0.73, indicating good agreement **(Figure 6)**. Kappa statistics showed 72.7% agreement with k = 0.45, P<0.001 indicating good agreement between the MUST and PG-SGA. Eighty-one patients (62.3%) lost less than 5% weight in the preceding three to six months and 49 (37.7%) had more than 5% weight loss. More patients 38 (58.5%) patients, who were classified as malnourished by PG-SGA, lost more than 5% weight as compared with 27 (41.5%), who lost less than 5% weight (P < 0.001). Kappa statistics showed 70.8% agreement (k = 0.42; P<0.001) and the area under the ROC curve was 0.71**(Figure 6)**, indicating a good agreement between percent weight loss and nutritional status as measured by the PG-SGA.

Table 22 Nutrition risk compared with Nutrition status (PG-SGA)

PG-SGA	**MUST**		
	Positive (at risk)	Negative (not at risk)	Total
Malnourished	46 (true positive)	20 (false negative)	66
Well-nourished	15 (false positive)	47 (true negative)	62
Total	61	67	128

PG-SGA, patient generated subjective global assessment; MUST, malnutrition universal screening tool

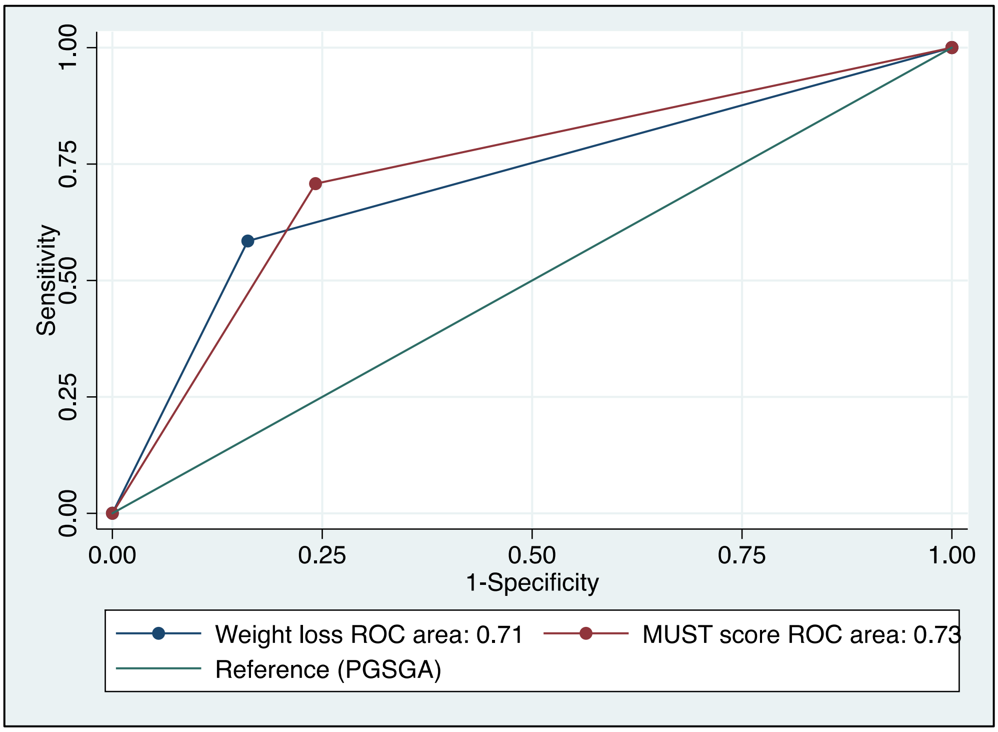

Figure 6 Receiver operating characteristic (ROC) curve agreement between MUST and PG-SGA and between weight loss and PG-SGA

6.6 Discussion

The current study demonstrated the validity of MUST compared with a reference nutrition assessment using PG-SGA in older acutely unwell patients in general medical units of a large tertiary hospital. The MUST tool was shown to be reasonably effective in identifying patients at risk of malnutrition, when compared with PG-SGA with a sensitivity of 69.7%, a specificity 75.8%, a positive predictive value 75.4% and a negative predictive value of 70.1%. Additionally, kappa statistics demonstrated good agreement: kappa = 0.45, P < 0.001.

There are few studies comparing MUST with PG-SGA in acutely hospitalized patients with multiple co-morbid illnesses. Boleo-Tome et al,[275] in their study on cancer patients undergoing radiotherapy, compared MUST with PG-SGA and found significant agreement with a k = 0.86 and higher sensitivity (80%) and specificity (89%), indicating high performance and strong capacity to effectively detect patients at nutrition risk, however, they included only cancer patients with a wide age range, 18-95 years. Stratton et al in their study in hospitalized general medical patients found excellent agreement (k = 0.783) between the MUST and SGA (two category) in newly admitted patients, although the investigator did not categorize any patients into the malnourished group when using SGA,[309] however we cannot apply these validity results to PG-SGA as this study used SGA for comparison.

Undernutrition is often overlooked in hospitalized patients, despite adoption of strict guidelines to screen all patients for malnutrition. In our study, MUST was expected to be completed on all patients but actual completion rate was only 51.2%, highlighting that malnutrition screening is still suboptimal. Missed diagnosis of malnutrition is not only detrimental for patient care but is also costly for hospitals as malnutrition is considered as a comorbidity or complication under the AR-DRG classification system for case mix-based funding.[222] Gout et al in their study in Australian hospitalized patients, found poor recognition and documentation of malnutrition with only 15% of malnourished patients correctly diagnosed with consequent substantial shortfall of AU$1,850,540 in reimbursements in one financial year.[255]

Our study confirms that malnourished patients have significantly increased LOS and MUST screening may be useful to predict hospital LOS, as malnourished patients stayed 4.5 days longer than well-nourished patients. Kyle et al, in their study in hospitalized patients, also found significant association between increased LOS and high risk MUST score.[141] Similarly, Correia and Waitzberg, in their study in hospitalized patients found significantly longer LOS in malnourished patients (mean 16.7 days vs 10.1 days) with significant increase in hospital costs for care of malnourished patients.[40]

The MUST does not need time-consuming calculations, incorporates objective and subjective clinical parameters reflecting changes in nutritional status and unlike PG-SGA, can be used by any trained professional without nutritional expertise.[131 309] Our study found statistically significant inverse correlations between the MUST score and anthropometric measures like BMI, TST and MAMC, indicating that MUST score predicts fat and lean body mass. Both lean body mass and fat mass are measures of nutritional status, with lean body mass a reliable indicator of muscle mass, whereas fat mass reflects energy storage.[314] Noori et al, in their study on maintenance hemodialysis patients, found that higher fat mass in both males and females and higher lean body mass in females were associated with greater survival.[314] Anthropometric measurement may offer an alternative method of assessing nutritional status in those patients, where height and weight are difficult to assess and have been shown to be significant predictors of mortality in older people.[315 316]

We also found that a history of significant weight loss (≥5% weight loss) in the preceding three to six months had a good correlation with the nutritional status, with a ROC area 0.71 against PG-SGA, which almost matches the MUST tool. Boleo-tome et al, in their study on cancer patients also found that percent weight loss is a valid and reliable nutrition parameter when compared to the PG-SGA, with a high sensitivity, specificity, positive and negative predictive values to detect undernourished patients.[275] The use of weight loss has, however, been questioned in the past given the influence of many non-nutritional factors and because many patients may not remember their weight in the recent past.[317] Further research is needed to confirm this finding, as a history of significant weight loss may be a useful marker of malnutrition and may solely be used to classify patients as malnourished, especially in busy acute care settings, where there is reluctance to perform screening tool tests.

Our study found overall low HRQoL in hospitalized elderly patients with a mean EQ-5D-5L score of 0.70, compared to 0.80 (mean EQ-5D-3L) in the general population.[318] Furthermore, malnourished patients had statistically significantly worse HRQoL compared to well-nourished patients (median EQ-5D-5L scores: 0.697 versus 0.804). Our results are similar to Rasheed and Woods, who in their study on older hospitalized patients also found in general low HRQoL in hospitalized patients, with malnourished patients experiencing a significantly lower HRQoL compared to well-nourished patients in both physical and mental dimensions of EQ-5D-3L.[278] Food and eating are essential for health and inability to eat as a result of loss of appetite, digestive problems or swallowing difficulties affect HRQoL and these problems may be a significant contributor to a low HRQol in unwell hospitalized elderly patients.[279]

A major strength of our study was that the research dietitian who conducted PG-SGA was blinded to the nutritional status of the participants based on MUST score and this may have removed bias to score patients based on a subjective component of PG-SGA. In addition, our study was one of the first comparing MUST and PG-SGA among older hospitalized general medical patients with multiple co-morbid illnesses, as there have not been many studies among this nutritionally vulnerable group. A major limitation of our study is that we were not able to recruit a significant number of patients who were cognitively impaired or had dementia, mainly due to difficulty in obtaining consent and also as our study included elderly general medical patients with multiple clinical problems, our findings cannot be generalized to younger patients or those admitted to sub-specialties with single organ involvement. Further studies are needed to verify our findings in this group of patients. We also acknowledge that this is a single centre study limited to acutely unwell older patients, and are results are not applicable to relatively stable medical or surgical patients.

6.7 Conclusion

Our study indicates that MUST is a reasonably good screening tool as compared with PG-SGA among older acutely unwell general medical patients, and malnutrition screening is still suboptimal in hospitalized patients, leading to a significant number patients being discharged with a missed diagnosis of malnutrition. Our research suggests that despite establishment of hospital policies, MUST screening is still sub-optimal and this deficiency needs to be addressed as this could pay dividends in terms of improved quality of care. We suggest further studies to confirm our findings and further efforts should be made to screen all patients for malnutrition.

CHAPTER 7: INVESTIGATIONS OF THE BENEFITS OF EARLY MALNUTRITION SCREENING WITH TELEHEALTH FOLLOW UP IN ELDERLY ACUTE MEDICAL ADMISSIONS

This chapter is a co-authored publication accepted in 2017. Please refer to appendix 1.5 for statement of authorship.

Sharma Y, Thompson C, Kaambwa B, Shahi R, Hakendorf P, Miller M. Investigation of the benefits of early nutrition screening with telehealth follow up in elderly acute medical admissions. *Quarterly Journal of Medicine*. 2017;110(10):639-647. doi: 10.1093/qjmed/hcx095.

7.1 Abstract

7.1.1 Background

The benefit of providing early nutrition intervention and its continuation post-discharge in older hospitalized patients is unclear. This study examined efficacy of such an intervention in older patients discharged from acute care.

7.1.2 Methods

In this RCT, 148 malnourished patients were randomized to receive either a nutrition intervention for three months or usual care. Intervention included an individualized nutrition care plan plus monthly post-discharge telehealth follow-up whereas control patients received intervention only upon referral by their treating clinicians. Nutrition status was determined by the PG-SGA tool. Clinical outcomes included changes in LOS, complications during hospitalization, HRQoL, mortality and re-admission rate.

7.1.3 Results

Fifty-four males and 94 females (mean age, 81.8 years) were included. Both groups significantly improved PG-SGA scores from baseline (a reduction in PG-SGA score indicates improvement in nutritional status). There was no between- group differences in the change in PG-SGA scores and final PG-SGA scores were similar at three months 6.9 (95% CI 5.6 – 8.3) vs. 5.8 (95% CI 4.8 – 6.9), (P=0.09), in control and intervention groups respectively. Median total LOS was 6 days shorter in the intervention group (11.4 (IQR 16.6) vs. 5.4 (IQR 8.1); P = 0.01). There was no significant difference in complication rate during hospitalization, HRQoL and

mortality at 3-months or readmission rate at 1, 3 or 6 months following hospital discharge.

7.1.4 Conclusion

In older malnourished inpatients, an early and extended nutrition intervention showed a trend towards improved nutrition status and significantly reduced LOS.

7.2 Introduction

Malnutrition is widely prevalent in older hospitalized patients with reported prevalence rates of 62.9% in Spain[319] and 32% according to a nutritional status survey across 56 hospitals, in acute care settings in Australia and New Zealand.[320] Older patients are more prone to malnutrition due to in general a higher number of co-morbidities[321] and changes unique to ageing, such as decrease in senses of taste and smell[322] which decreases the flavor of food and loss of dentition which limits food intake.[323] Nutrition status deteriorates during hospital admission and a recent study suggests that 20% patients who stayed in hospital for more than a week had further nutritional decline.[324] The deterioration of nutritional status during hospital admission is due to a number of factors including higher protein catabolism[325], anorexia associated with inflammation[326], polypharmacy, nil per oral orders pending investigations and dislike for hospital food.[57 327 328] This often leads to patients being discharged in rather a worse nutritional and functional state than at the time of hospital admission. Malnutrition is undeniably associated with adverse clinical outcomes both for the patients in terms of higher morbidity and mortality[78] and for the health care delivery in terms of higher costs of managing these patients mainly due to increased LOS and increased risk of residential care placement.[329] Data regarding nutritional supplementation in malnourished patients with chronic diseases are inconclusive due to methodological differences in the studies, and hence the benefit of nutritional supplementation is still an area of controversy.[243 263] A meta-analysis[51] of protein energy supplementation in older people, involving 62 trials and 10,187 patients, found beneficial effects in terms of weight gain and reduction in mortality in malnourished patients but found insufficient evidence in reducing complications, improving function or HRQoL. The authors found most studies in their review had a short intervention time and suggested a need for future studies of sufficient duration to detect any meaningful differences in morbidity. The benefits of nutritional intervention initiated during hospital admission may be lost if continuity of care is not adequately addressed at the time of discharge but there is little research supporting the role of dietetic counseling and nutrition care plans across the continuum of care.[330]

This study was therefore designed to compare usual care in older malnourished patients with an individualized nutrition screening and intervention, which included dietary modification and ONS, initiated early during hospitalization and extending for a period of three months post-discharge with monthly telehealth follow up. The primary outcome of interest was any improvement in nutritional status as determined by PG-SGA score at the end of 3 months of intervention. In addition, we wanted to determine whether this extended nutritional intervention leads to any beneficial effects on clinical outcomes like LOS, complication rate, mortality, HRQoL and re-admission rates.

7.3 Methods

7.3.1 Design

This study was designed as a RCT comparing extended nutrition intervention with usual care, in older patients admitted to an acute medical ward, with follow-up at 3 months post-discharge. Ethical approval was obtained from Southern Adelaide

Human Research Committee (SAC HREC) approval number (273.14-HREC/14/SAC/282) on 21st July 2014.

7.3.2 Randomization

An independent biostatistician prepared the randomization schedule and random blocks of 8 were used and treatment allocations were randomly permuted and balanced within blocks. The randomization sequence was concealed in consecutively numbered, sealed opaque envelopes by an independent research colleague and stored in a centrally accessible and locked office. After obtaining written informed consent, the researcher contacted central office to open these sealed envelopes to allocate patients to either control or intervention groups. From this point the participants and the ward dietitian, who provided nutrition intervention were not blinded to group allocation but the research dietitian who conducted the final outcome assessment was blinded to patients' group allocation. In addition the research person overseeing data entry and the biostatistician were blinded.

7.3.3 Patient recruitment

All eligible patients ≥60 years presenting to general medicine department of FMC between November 2014-June 2016, were considered for participation in this study. The exclusion criteria were patients receiving palliative care, patients residing in rural areas, Indigenous Australians and non-English speaking patients and patients unable to give informed consent. Rural patients were excluded due to inadequate funds to travel to rural areas to follow up these participants and Indigenous Australians and non-English speaking subjects were excluded due to lack of funds to seek services of an Aborigine's Liaison Officer/interpreter.

After obtaining written informed consent, baseline assessments were conducted by a member of the research team, including completion of the MUST and HRQoL determined using the EQ-5D-5L. All participating patients were then referred to a research dietitian, who confirmed their nutritional status by using PG-SGA and also performed anthropometric assessments including BMI, TST, MUAC and handgrip strength. Only patients who were confirmed as malnourished by PG-SGA (PG-SGA class B and C) were included in the study and were randomized to either the intervention or the control group and patients in the intervention group were immediately referred to the ward dietitian to initiate the nutrition intervention, whereas patients in the control group were allowed to follow the usual protocol currently operative in FMC, which is that they will see a dietitian only upon referral by their treating clinicians.

7.3.4 Intervention

Nutrition intervention was initiated by the ward dietitian within 24 hours upon receiving referral from the research dietitian as studies indicate that early nutrition intervention has beneficial effects in preventing catabolic effects associated with acute illness.[331] There were three research dietitians and different ward dietitians involved in the care of the patients. The research dietitians performed nutritional assessments at the beginning and end of the study and received training in performing PG-SGA while ward dietitians delivered the nutritional intervention.

The nutrition intervention was aimed to meet 100 percent of patients' energy and protein requirements for ideal body weight, calculated using commonly adopted predictive equations[76] along with an adequate intake of essential vitamins and minerals. Intervention patients received an individualized nutrition intervention by the dietitian, depending upon their underlying medical conditions, protein, energy, vitamin and mineral requirements and food preferences. Nutritional strategies employed by the dietitian included provision of ONS (1-2.2 kcal/ml and 0.05-0.12 gm of protein/ml), mid-meal snacks and food fortification with consideration given to individual patients' food preferences and taste. The ONS utilized were Resource (Nestle Heath Science) (475 kcal, 19.7 g protein) and Sustagen (Nestle Heath Science) (248 kcal, 12.5g protein), which in addition to protein provided a range of nutrients. Multivitamins were not separately prescribed but were left to the discretion of the treating clinicians. In addition, the patients and their care-providers received dietetic counseling, to augment their energy intake by using a range of strategies including recommendation of energy and nutrient dense food items, increasing the number of meals they ate, and consumption of energy, protein and nutrient-rich snacks. Patients who needed assistance with meals were flagged, so that a ward based staff member provided help during meals. The frequency of contact between patient and dietitian during the hospital stay varied depending upon individual patients' needs and the LOS. If the dietitian thought that the patient was unable to achieve their daily energy and nutrient requirements then they received almost daily input. Where patients were discharged to a nursing home then the dietitian contacted the nursing home manager and forwarded the recommended nutritional care plan to be followed. The hospital covered the cost of commercial ONS at the time of discharge for patients where ≥50% of the patient's daily energy requirements were determined to be required from supplements.

All intervention patients were contacted by a monthly telephone call by the research dietitian for 2 months. During this interview, a structured format was used by the dietitian to collect information about patients' recent weight, compliance with the dietetic plan and any side effects with supplementation. In addition, patients received dietetic counseling with a focus to reinforce compliance with the intervention. Compliance with the dietetic plan was assessed by using a 24-hour self-reported dietary recall. In this trial, the dietitian assessed the patients as compliant to the nutritional care plan if they were able to meet at least 75% of their energy and protein requirements.

7.3.5 Control group

Patients randomized to the control group followed usual care currently operative in FMC. Currently all patients undergo nutrition screening by the use of MUST and patients identified as high risk for malnutrition are referred to the dietitian. However, dietetic input occurs only if clinicians refer the patients and even if a dietitian sees them during hospital admission, they may not be followed after discharge. In this study, the control patients were flagged as malnourished and this was documented in the case notes for clinicians to make decisions regarding nutritional care. If control patients got referred for a dietetic advice, then they were offered the same nutritional care plan as the intervention group only for the period of their hospitalization but received no post discharge follow up care.

7.3.6 PG-SGA

Research dietitians experienced in using the scored PG-SGA tool confirmed the nutritional status of the participants at the beginning and end of the study. Please refer to section PG-SGA for description of PG-SGA.

7.3.7 EQ-5D 5L

The EuroQoL (EQ-5D 5L) was used to assess HRQoL in this study. EQ-5D 5L was developed jointly by a group of European-based researchers with the intent of constructing a simple, self-administered instrument that provided a composite index score representing the preference for a given health state and VAS measured from 0-100, which represents overall HRQoL.(Kind, 1996 #119)

7.3.8 Anthropometric measures

Weight was measured in light clothes without shoes with a high specification portable electronic scale (Wellsweigh digital chair scale, Australia) to the nearest 0.1kg and height was measured with a portable stadiometer to the nearest 0.1 cm. Height was calculated from ulna length in patients who were unable to stand and BMI was calculated as weight (kg)/height (m^2).

TST was measured by Harpenden skin fold caliper (Baty international, West Sussex, United Kingdom) to the nearest 0.2mm. Measurements were taken on the right arm at the mid-acromiale-radiale, with the patient seated, arm relaxed by the side and palm facing upward.

MUAC was measured to the nearest 0.1cm by using a flexible steel measuring tape (KDS, Tokyo, Japan) around the upper arm at the point of mid-acromiale-radiale and MAMC was calculated using a formula: MAMC in cm = 0.342 × TST
Handgrip strength was measured using a hand-held dynamometer (TTM, Tokyo, Japan). Participants were instructed to stand with legs straight and feet approximately 15cm apart, and hold the dynamometer in their dominant hand and perform maximum isometric contraction for 3 seconds. The test was repeated within 15 seconds and the highest of the three consecutive measurements was used for data analysis.

7.3.9 Outcome

Final assessment was done at the end of 3 months in a dietary clinic at FMC and home visits were carried out for patients who were unable to attend this appointment. It was ensured that final assessment was performed by a different dietitian not involved in assessment or care of the patient at the time of admission and was blind to patients' group allocation. The primary outcome was the change in nutrition status as determined by PG-SGA score and other outcomes of interest were clinical measures including LOS, complications during hospital admission, mortality (both in hospital and overall mortality) and readmissions within 1, 3 and 6 months of discharge. The hospital computer database was used to determine LOS, incidence of nosocomial complications during admission-both infective and non-infective, mortality, incidence of hospital readmissions, including emergency department presentations and whether patients received DRG coding for malnutrition at discharge.

7.4 Statistical Methods

This study was powered to detect between group differences in nutrition score as measured by scored PG-SGA and previous studies[156] have suggested that a mean (SD) shift of 3 in PG-SGA score is clinically meaningful. *G* Power3* software was used to calculate sample size- assuming an effect size of 0.35, alpha = 0.05 and power of 80% the estimated required sample size was 86 (43 in each group) was calculated to be sufficient.

Variables were tested for normality using sk test. Basic descriptive statistics were used and continuous variables were expressed as mean values or median interquartile (IQR) ranges and were compared using an appropriate parametric (Student t) test or nonparametric (Mann-Whitney U) test. Categorical variables were expressed as numbers and percentages and were compared using and χ^2 statistics or Fishers exact test as appropriate. PG-SGA score was defined as mean (SD) and paired student t test was used to measure change in scores from the baseline and unpaired student t test was applied to test differences in the scores between control and intervention groups at the end of intervention. Logistic regression was used to determine the odds ratio by creating a new outcome variable (PG-SGA score at the end of intervention ≤ 7 as nourished and ≥ 8 as malnourished) in the two groups. Both anthropometric and HRQoL variables were defined as mean (SD) and paired student t tests were used to measure change in scores from the baseline and unpaired student t tests were applied to test between group differences at the end of intervention. Regression analysis was applied to determine any differences in HRQoL in two groups with compliance with the intervention used as confounding variable. LOS was adjusted for in hospital mortality and inter-hospital transfers and hospital at home LOS was included to determine total LOS. Rank sum test was used to compare the differences in LOS of two groups, as this variable was not normally distributed. Logistic regression was used to determine odds of patients staying in hospital for more than one week by creating a new outcome variable for LOS (LOS $\leq$ 7 days or LOS > 7 days). A Kaplan Meier survival curve was plotted and Log rank test statistic was used to evaluate the equality of survival distribution between control and intervention group. All tests were 2-sided and a P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using STATA software (version 13.1).

7.5 Results

We assessed 1520 patients **(Figure 7)** for participation in this study of which 776 did not meet inclusion criteria and 744 patients refused to participate citing various reasons –belief they were not malnourished (305), too busy with other medical appointments (101), too unwell to participate (69), not interested (67) and refusal to modify diet or use supplements (202). A total of 148 patients were screened and randomized to control (n = 70) and intervention groups (n = 78) during the study period and out of them complete data was available for analysis for 46 patients in control and 57 patients in the intervention group. The main reasons for patients being lost to follow-up were loss of contact, consent withdrawal and death.

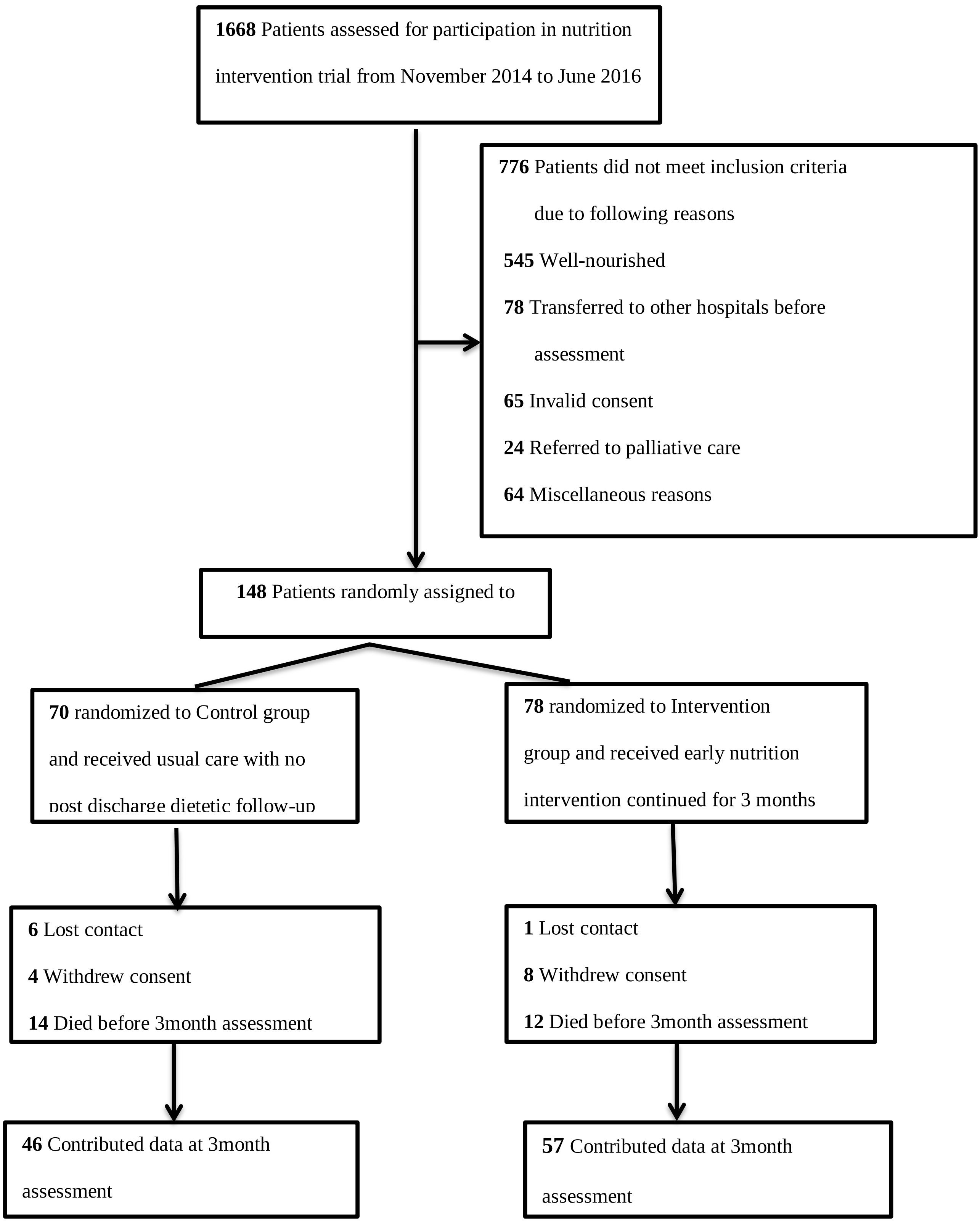

Figure 7 Study flow diagram

The mean age of the participants was 81.8 (8.7) with a range of 60 to 97 years indicative of the older population in the general medical units. Both groups had a higher number of females with the majority of patients residing at home pre-admission and had a similar number of comorbidities and the CCI and other baseline characteristics were similar between the two groups **(Table 23)**. There was no difference in the severity of malnutrition at baseline, as reflected by PG-SGA class B (moderate malnutrition) and C (severe malnutrition) and mean PG-SGA scores were also similar 13.3, (95% CI 12.2 – 14.5) vs. 12.1, (95% CI 11.0 – 13.2) in control and intervention groups, respectively **(Table 23)**. The baseline HRQoL indices as reflected by EQ-5D-5L index and VAS were also similar in both groups **(Table 23)**. **Table 24** indicates that the nutritional intervention provided an additional mean 2739, (95% CI 2457.3 – 3230.3) kilojoules of energy and 36.5, (95% CI 31.5 – 41.5) grams of protein to the intervention patients (energy and protein requirements were only determined in intervention patients) and the majority of these patients received additional snacks, fortified foods and drinks. At 1 and 2 months post-discharge telephone follow up, the participants reported good compliance with the prescribed intervention at 73% and 77.2%, respectively. Forty-three (61.4%) control patients received dietitian input during hospital admission with no post-discharge outpatient dietetic follow-up.

Table 23 Baseline characteristics of participants

Characteristics		Control (n=70)	Intervention (n=78)	P value
Age, mean (95% CI), y		81.6 (79.5 – 83.6)	82.0 (80.0 – 83.9)	0.76
Gender, n (%)	Male	23 (32.9)	31 (39.7)	
	Female	47 (67.1)	47 (60.3)	0.38
Residence before admission, n (%)	Home	66 (94.3)	68 (87.2)	0.11
	Nursing Home	4 (5.7)	10 12.8)	
Cognition, n (%)	Normal	67 (95.7)	74 (94.9)	0.56
	Impaired	3 (4.3)	4 (5.1)	
No of co-morbidities, mean (95% CI)		6.3 (5.6 – 6.9)	6.1 (5.5 – 6.6)	0.64
CCI, mean (95% CI)		2.3 (1.9 – 2.8)	2.2 (1.8 – 2.7)	0.82
Medications at admission, mean (95% CI)		10.1 (9.0 – 11.2)	8.8 (7.8 – 9.7)	0.07
Patients on Vitamin D/Calcium at admission, n (%)		24 (34.3)	34 (43.6)	0.24
Mobility at admission, n (%)	Independent	32 (45.7)	30 (39.5)	0.78
	Stick	8 (11.4)	9 (11.8)	
	Walking frame	26 (37.1)	34 (44.7)	
	Bed bound	4 (5.7)	3 (4.0)	
Principal diagnosis at admission, n (%)	Respiratory	29 (41.4)	20 (25.6)	0.30
	Cardiovascular	8 (11.4)	14 (18.0)	
	Falls	10 (14.3)	13 (16.7)	
	CNS	3 (4.3)	6 (7.7)	
	Miscellaneous	20 (28.6)	25 (32.1)	
Hemoglobin, mean (95% CI), g/dL		12.0 (11.5 – 12.4.)	12.2 (11.7 – 12.7)	0.48
C-RP, mean (95% CI), mg/L		59.8 (42.2 – 77.6))	51.7 (34.5 – 68.9)	0.51
Albumin, mean (95% CI), g/dL		3.1 (3.0 – 3.3)	3.3 (3.1 – 3.4)	0.14
Weight, mean (95% CI), Kg		57.6 (54.3 – 60.9)	55.7 (52.9 – 58.6)	0.40

Characteristics		Control (n=70)	Intervention (n=78)	P value
Characteristics		**Control (n=70)**	**Intervention (n=78)**	**P value**
BMI, mean (95% CI), kg/m2		21.8 (20.7 – 22.8)	20.6 (19.7 – 21.5)	0.09
Handgrip strength mean (95% CI), kg		16.0 (14.0 – 17.9)	16.8 (14.9 – 18.7)	0.52
MUAC, mean (95% CI), cm		24.7 (23.6 – 25.8)	24.7 (23.7 – 25.6)	0.95
TST, mean (95% CI), mm		11.2 (9.6 – 12.8)	10.1 (8.8 – 11.3))	0.26
MAMC, mean (95% CI), cm		21.3 (20.5 – 22.1)	21.5 (20.7 – 22.3)	0.70
MUST score, mean (95% CI)		1.5 (1.1 – 1.8)	1.8 (1.5 – 2.1)	0.12
PG-SGA class, n (%)	PG-SGA B	60 (87.0)	67 (90.5)	0.50
	PG-SGA C	9 (13.0)	7 (9.5)	
PG-SGA score, mean (95% CI)		13.3 (12.2 – 14.5)	12.1 (11.0 – 13.2)	0.11
EQ-5D-5L index, mean (95% CI)		0.674 (0.617 – 0.730)	0.693 (0.639 – 0.747)	0.63
VAS, mean (95% CI)		58.0 (53.7 – 62.4)	56.4 (51.8 – 60.9)	0.60

SI conversion factors: To convert Hemoglobin to g/L multiply by 10; CRP to nmol/L multiply by 9.5; Albumin to g/L multiply by 10
Abbreviations: CI, confidence interval; CCI, Charlson comorbidity index; CNS, Central nervous system; C-RP, C-reactive protein; BMI, body mass index; MUAC, mid upper arm circumference; TST, triceps skinfold thickness; MAMC, mid arm muscle circumference; MUST, Malnutrition universal screening Tool; PG-SGA, Patient generated subjective global assessment; EQ5D, European quality of life questionnaire; VAS, visual analogue scale
[a]Higher PG-SGA score indicates worse nutrition status; [b]Higher EQ5D index indicates better quality of life

Table 24 Nutrition intervention provided in the study

Calories supplemented in kilojoules/day, mean (95% CI)	2739.0 (2457.3 – 3230.3)
Protein supplemented gm/day, mean (95% CI)	36.5 (31.5 – 41.5)
Vitamins supplemented n (%)	3 (5.3)
ONS supplemented n (%)	24 (42.1)
Mid meal snacks provided n (%)	44 (81.5)
Fortified meals/drinks provided n (%)	30 (55.6)
Compliance at 1 month follow-up phone call	73%
Compliance at 2 month follow-up phone call	77.2%

CI, confidence interval; ONS, oral nutrition supplements

Table 25 shows changes in anthropometric measures over 3 months with a mean reduction in BMI -0.36, (95% CI -0.92 – -0.19) from baseline, in the control group as compared to an increase of 0.41, (95% CI 0.09 – 0.90) from baseline, in the intervention group, and the between-group difference in BMI was statistically significant (P = 0.04). Intervention patients also showed a trend towards greater improvement in handgrip strength and mid-upper arm circumference from baseline as compared to the control group but between-group differences in these parameters were not statistically significant. Both groups showed similar improvements in PG-SGA scores from baseline -6.2, (95% CI -8.1 – -4.2) vs -5.9, (95% -7.3 – -4.4) (a reduction in score is indicative of improvement in nutritional status), in control and intervention patients respectively **(Table 25)**. Logistic regression, with PG-SGA score categorized as outcome variable, suggested that intervention patients were less likely to remain malnourished at the end of 3 months, although this was not statistically significant (OR 0.46; 95% CI 0.20 – 1.08, P = 0.07). Although no significant between-group differences in PG-SGA scores were noted at the end of 3 months **(Table 26)**, a trend favoring further improvement in nutritional status was noted in intervention patients who were compliant with the intervention (intervention compliant 5.4 (SD 3.4), intervention non-compliant 8.1 (SD 5.2), control 6.9 (SD 4.3), P = 0.08). Similarly HRQoL improved in both groups but intervention patients displayed overall better HRQoL, as reflected by VAS, at the end of 3 months and this was statistically significant (P = 0.03) **(Table 26)**.

Table 25 Changes in nutritional parameters during the study period

	Control n = 46			Intervention n =57			Control	Intervention	
	Baseline	3 months	P value	Baseline	3 months	P value	Differences		P value
Nutrition parameters mean (95% CI)									
Weight, kg	59.02 (54.59 – 63.46)	59.15 (54.69 – 63.60)	0.85	56.07 (52.67 – 59.46)	56.77 (53.25 – 60.29)	0.26	0.13 (-1.17 – 1.42)	0.70 (-0.53 – 1.93)	0.52
BMI, kg/m^2	22.18 (20.76 – 23.61)	21.82 (20.59 – 23.06)	0.20	20. 85(19.75 – 21.95)	21.26 (20.16 – 22.35)	0.11	-0.36 (-0.92 – 0.19)	0.41 (-0.09 – 0.90)	0.04
HGS, kg	16.67 (13.89 – 19.45)	18.23 (15.51 – 20.96)	0.03	16.82 (14.62 – 19.02)	18.65 (16.44 – 20.85)	0.001	1.56 (0.15 – 2.98)	1.82 (0.74 – 2.91)	0.77
MUAC, cm	25.16 (23.83 – 26.49)	25.79 (24.57 – 27.02)	0.05	24.83 (23.69 – 25.96)	25.60 (24.52 – 26.67)	0.005	0.64 (0 – 1.3)	0.77 (0.24 – 1.30)	0.75

	Control n = 46			Intervention n =57			Control	Intervention	
	Baseline	3 months	P value	Baseline	3 months	P value	Differences		P value
TST, mm	11.21 (9.19 – 13.22)	10.28 (8.57 – 11.99)	0.32	10.44 (9.02 – 11.87)	10.40 (9.06 – 11.74)	0.92	-0.93 (-2.8 – 0.94)	-0.04 (-0.99 – 0.90)	0.36
MAMC, cm	21.70 (20.65 – 22.75)	22.63 (21.39 – 23.87)	0.03	21.54 (20.61 – 22.47)	22.33 (21.44 – 23.21)	0.008	0.93 (0.08 – 1.77)	0.79 (0.21 – 1.37)	0.77
PG-SGA score[a]	13.2 (11.6 – 14.8)	6.9 (5.6 – 8.2)	<0.001	11.7 (10.4 – 12.9)	5.8 (4.8 – 6.9)	<0.001	-6.2 (-8.1 – -4.2)	-5.9 (-7.3 – -4.4)	0.79
Hemoglobin, g/dL	11.9 (11.3. – 12.5)	11.9 (11.4 – 12.4)	0.99	12.3 (11.7 – 12.8.)	12.2 (11.8 – 12.7)	0.99	0.05 (-5.4 – 5.4)	-0.02 (-5.1 – 5.0)	0.98
CRP, mg/L	64.4 (39.1 – 89.7)	17.7 (9.2 – 26.1)	0.0003	38.8 (23.3 – 54.2)	10.1 (5.6 – 14.6)	0.0007	-46.7 (-70.6 – -22.9)	-28.7 (-44.5 – -12.8)	0.19
Albumin, g/dL	3.2 (3.0 – 3.4)	3.2 (3.0 – 3.5)	0.65	3.3 (3.2 – 3.5)	3.5 (3.3 – 3.6)	0.04	0.53 (-1.8 – 2.9)	1.3 (0.04 – 2.6)	0.54

	Control n = 46			Intervention n =57			Control	Intervention	
	Baseline	3 months	P value	Baseline	3 months	P value	Differences		P value
EQ-5D 5L index	0.655 (0.582 – 0.728)	0.740 (0.675 – 0.805)	0.03	0.725 (0.665 – 0.784)	0.770 (0.720 – 0.818)	0.10	0.085 (0.008 – 0.162)	0.045 (-0.009 – 0.099)	0.38
VAS	57.1 (51.5 – 62.6)	52.4 (45.2 – 59.7)	0.21	56.6 (51.1 – 62.2)	61.2 (56.8 – 65.6)	0.16	-4.7 (-11.9 – 2.6)	4.6 (-1.8 – 10.9)	0.06

SI conversion factors: To convert Hemoglobin to g/L multiply by 10; CRP to nmol/L multiply by 9.5; Albumin to g/L multiply by 10

BMI, body mass index; HGS, handgrip strength; MUAC, mid upper arm circumference; TST, triceps skinfold thickness; MAMC; mid arm muscle circumference; PG-SGA, patient generated subjective global assessment; C-RP, c-reactive protein; EQ5D 5L, European quality of life questionnaire 5 dimension 5 level; VAS, visual analogue scale

[a] Reduction in PG-SGA score indicates improvement in nutritional status

Table 26 Nutritional parameters and quality of life indices at the end of 3 months

Parameter		Control (n=46)	Intervention (n=57)	P value
Weight, kg [a]		59.1 (54.7 – 63.6)	56.7 (53.3 – 60.3)	0.39
BMI, kg/m^2		21.8 (20.6 – 23.1)	21.3 (20.2 – 22.4)	0.49
HGS, kg		17.8 (15.2 – 20.4)	18.6 (16.4 – 20.8)	0.62
MUAC, in cm		26.0 (24.7 – 27.3)	25.3 (24.3 – 26.4)	0.40
TST, in mm		10.5 (8.7 – 12.3)	10.3 (9.0 – 11.5)	0.83
MAMC, in cm		22.6 (21.4 – 23.9)	22.1 (21.2 – 23.0)	0.47
PG-SGA class [b],	PG-SGA A	28 (60.9)	41 (72.0)	0.50
n (%)	PG-SGA B	17 (37.0)	15 (26.3)	
	PG-SGA C	1 (2.1)	1 (1.7)	
PG-SGA score		6.9 (5.6 – 8.3)	5.8 (4.8 – 6.9)	0.15
Hemoglobin, g/dL		11.9 (11.4 – 12.4)	12.2 (11.8 – 12.7)	0.30
CRP, mg/L		17.7 (9.2 – 26.1)	9.7 (5.5 – 13.9)	0.05
Albumin, g/dL		3.2 (3.0 – 3.5)	3.5 (3.3 – 3.6)	0.06
EQ-5D 5L index		0.740 (0.674 – 0.805)	0.770 (0.721 – 0.818)	0.45
VAS		52.4 (45.2 – 59.7)	61.2 (56.8 – 65.6)	0.03

[a] Data are reported as mean (95% CI) unless otherwise stated
[b] PG-SGA class A (well-nourished), B (moderately malnourished or at risk of malnutrition), C (severely malnourished)
Abbreviations: BMI, body mass index; HGS, handgrip strength; MUAC, mid upper arm circumference; TST, triceps skinfold thickness; MAMC; mid arm muscle circumference; PG-SGA, patient generated subjective global assessment; C-RP, c-reactive protein; EQ-5D 5L, European quality of life questionnaire 5 dimensions 5 Level; VAS, visual analogue scale

The median acute LOS was 3.8 days shorter in the intervention group (8.8 (IQR 4.1 – 13.9) vs. 5.0 (IQR 3.0 – 8.4), P = 0.007 in control and intervention groups respectively) and total LOS (inclusive of hospital at home treatment), was 6 days shorter in the intervention group (P = 0.01). Intervention patients had 72% higher probability of being discharged from hospital within 7 days of admission as compared to the controls (OR 0.28; 95% CI 0.13 – 0.60, P = 0.001) and the proportion of patients with acute and total LOS less than 7 days was significantly higher in the intervention group **(Table 27)**. During hospital admission 1 patient died in control group and 7 died in the intervention group and an additional 21 patients died in control group and 16 in the intervention group up to a period of 2 years. The Kaplan Meier survival curve **(Figure 8)** shows no difference in mortality between the two groups with Log rank, $\chi^2 = 0.09$ and P = 0.76. There was no significant difference in the total number of complications (both infective and non-infective) or the proportion of patients who developed complications during their hospital stay between the two groups and a similar number of patients were discharged to residential care facility. More patients in the intervention group received a malnutrition coding at discharge but this difference was not significant. There was no difference in the total number of medications at the end of 3 months between control and intervention patients. Similarly, readmissions within 1, 3 and 6 months post-discharge were similar between the two the groups **(Table 27)**.

Table 27 Clinical outcomes in control and intervention patients

Parameter	Control	Intervention	P value
Acute LOS[a] in days, median (IQR)	8.8 (4.1 – 13.9)	5.0 (3.0 – 8.4)	0.007
Total LOS (inclusive of hospital at home time in days), median (IQR)	11.4 (5 – 21.6)	5.4 (3.1 – 11.2)	0.01
Proportion of patients with acute LOS ≤7 days, n (%)	22 (37.9)	36 (62.1)	0.002
Proportion of patients with total LOS ≤7 days, n (%)	25 (39.1)	39 (60.9)	0.001
In hospital mortality, n (%)	1 (1.4)	7 (9.0)	0.09
Total mortality, n (%)	22 (31.0)	23 (29.5)	0.84
Total complications, mean (95%	0.73 (0.41 – 1.05)	0.65 (0.33 – 0.98)	0.73

Parameter	Control	Intervention	P value
CI)			
Proportion of patients with complications, n (%)	23 (32.4)	21 (26.9)	0.47
Infective complications, n (%)	7 (9.9)	9 (11.5)	0.74
Non-infective complications, n (%)	21 (29.6)	19 (24.4)	0.48
Proportion of patients discharged to residential facility, n (%)	6 (8.5)	6 (7.7)	0.09
Total readmissions, n (%)	46 (64.8)	46 (59.0)	0.47
Readmissions at 1 month, n (%)	17 (23.9)	14 (18.0)	0.37
Readmissions at 3 month, n (%)	29 (40.9)	26 (33.3)	0.34
Readmissions at 6 months, n (%)	35 (49.3)	37 (47.4)	0.82
Number of medications at end of study, mean (95% CI)	8.5 (7.2 – 9.7)	7.9 (6.9 – 8.8)	0.44
Malnutrition coding, n (%)	25 (35.2)	36 (46.1)	0.18

LOS, length of hospital stay; IQR, interquartile range; CI, confidence interval

[a] LOS adjusted for mortality and transfer to other hospitals

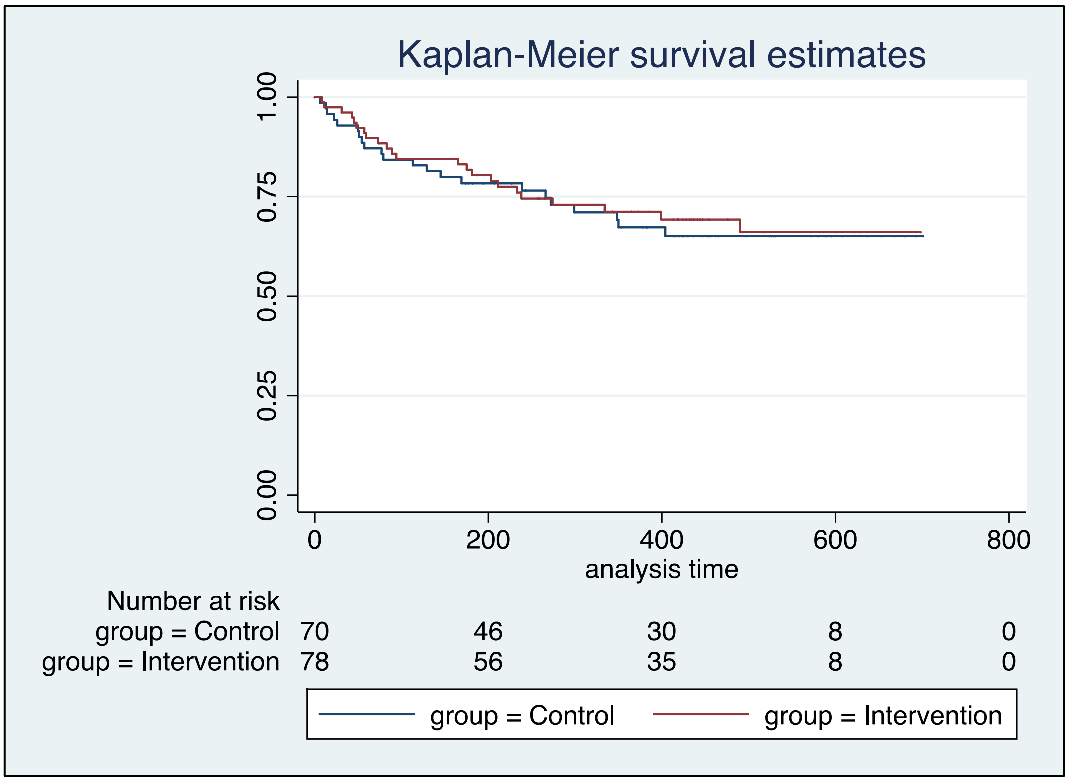

Figure 8 Kaplan Meier survival estimates in Control and Intervention patients recruited up to a period of two years shows on difference in survival, Log rank $\chi 2$ 0.09, P = 0.76

7.6 Discussion

The results of present study shows a trend towards an improved nutrition status, as determined by PG-SGA score, with an early and extended nutrition intervention in older patients discharged from acute care. Nutrition status showed improvement in both groups from baseline and, although no statistically significant difference was noted between the groups at the end of 3-months intervention, some clinically significant differences such as reduced LOS was noted in the intervention patients. Other anthropometric indicators of nutritional status presented a mixed picture of the effects of intervention, which is reflective of the difficulty in measuring nutritional status in older patients (no gold standard and each outcome measure has strengths and limitations). Gariballa and colleagues[332] in their study in acutely unwell hospitalized older patients also found no significant difference in the anthropometric measures in the supplemented group and postulated that the time frame of their intervention (6 weeks) may be too short to produce a significant change. An interesting finding of the present study is the significant improvement in nutritional status of control patients from the baseline. This finding is contradictory to a recent observational study by Marshall et al[37] who followed older rehabilitation patients in the community and found that patients remained malnourished at the end of 12 weeks follow-up. A possible explanation for this discrepancy is that a significant proportion of control patients in our study also received in-hospital dietetic input and it is possible that they continued intervention post-discharge with resultant dilution of the study results. The other reason could be a heightened awareness among control patients about being diagnosed as malnourished and being enrolled in a clinical trial - the ‘Hawthorne effect’- which could have been a motivating factor for the patients or care providers to change their dietary practices, with resultant improvement in their nutritional status.

This study found significant reductions in both acute and total LOS in patients who received the nutritional intervention and we posit that this could be due to a greater improvement in their muscle function and hence mobility, as indicated by an increase in handgrip strength, which could have facilitated early discharge from hospital. It is also possible that early nutrition intervention made a positive impact on recovery from acute illness and could have led to a faster resolution of delirium, as studies have suggested that improved nutritional status enhances immune function with resultant greater ability to fight infections.[333 334] Our results are similar to a study conducted in geriatric units by Holiday et al[44] who also found that early nutrition intervention could help reduce LOS. Hospitalized patients frequently get deconditioned early during admission and a combined modality of early nutrition intervention and physical therapy can reap rich monetary benefits for hospitals in these current resource-crunched times. The stress of acute illness increases muscle catabolism and, in the absence of sufficient energy replacement, amino acids are mobilized for gluconeogenesis, with consequent worsening of muscle function and this increases the risk of falls and respiratory muscle dysfunction predisposing patients to nosocomial pneumonia.[335] Although our study found a trend towards a greater improvement in the nutritional status of the intervention group, this did not translate into a reduction in the number of complications during hospitalization. Our results are in agreement with a recent meta-analysis[104] which found no beneficial effects of nutrition support on hospital acquired infections in medical inpatients. Extended nutritional intervention also produced no significant improvement in mortality in recruited patients over a period of up to 2 years. It is quite possible that older patients in our study with multiple comorbidities had either cachexia, which is known to be less responsive to nutrition intervention,[336] or were in an advanced stage of disease related malnutrition and the nutrition intervention was too late to produce a significant beneficial response. Studies have indicated that treating patients at an early stage of malnutrition is probably more effective than correcting advanced malnutrition.[337] Our findings are in agreement with a meta-analysis conducted by Cawood et al[338] in 2012, who reported mortality data of fifteen RCTs and found no improvement in mortality in the supplemented group. Similarly a recent meta-analysis[339] of nutritional interventions in older patients with hip fracture found no improvement in mortality for up to one year following discharge from hospital.

We found no convincing evidence of an improved HRQoL, as determined by EQ-5D-5L index with this nutrition intervention. HRQoL improved in both groups from baseline and overall QoL as reflected by a VAS, was better in the intervention group at the end of 3 months. The improved HRQoL after discharge probably reflects the effects of recovery from an acute illness rather than effect of this nutritional intervention. Moreover, studies have suggested that older patients with multiple clinical problems have in general low HRQoL.[340] Another reason could be that the study duration of 3 months is too short for a nutrition intervention to produce any significant change in HRQoL. We also found that this nutritional intervention was not associated with a reduction in readmissions within one, three or six months after hospital discharge. Our study findings suggest that a nutrition intervention does not have any positive effect in reducing the recurrence of illnesses in medical patients after hospital discharge.

One of the strengths of this study is the use of PG-SGA for nutrition assessment. PG-SGA which is regarded as a comprehensive assessment tool and gives a better indication of change in nutrition status than parameters like weight, which can be influenced by non-nutritional factors such as hydration status or the use of diuretics. Also this was an RCT with appropriate blinding of the outcome assessor. A number of patients refused to participate in this study due to various reasons highlighting difficulties in engaging older people in clinical trials.[341] We acknowledge that we were unable to recruit non-English speaking and Indigenous Australians, so our study results cannot be generalized to these patients. We did not measure the acuity of admission diagnosis which could have played a significant impact on clinical outcomes like LOS. We recognize that awareness of this trial and enhanced nutritional practices for the intervention patients had the potential to influence the referral practices by the ward staff for the control group. However, an alternative study design to reduce this contamination was not possible as patients identified as malnourished cannot ethically be denied nutritional support, highlighting one of the difficulties in conducting nutritional intervention studies in the elderly.[342]

This study highlights need for rigorous implementation of existing nutrition screening protocols and calls for enhanced dietetic support and hospital reimbursements for provision of nutritional services across the continuum of care.

7.7 Conclusion

Among older hospitalized patients, early and extended nutritional intervention showed a trend towards an improved nutritional status as determined by PG-SGA score and was associated with a much shorter LOS. We suggest early initiation of measures to target hospital malnutrition, however further studies are needed to confirm the impact of extending nutrition intervention into the community.

CHAPTER 8: ECONOMIC EVALUATION OF AN EXTENDED NUTRITIONAL INTERVENTION IN OLDER AUSTRALIAN HOSPITALIZED PATIENTS: A RANDOMIZED CONTROLLED TRIAL

This chapter is a co-authored publication accepted in 2018. Please refer to appendix 1.6 for statement of authorship.

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8.1 Abstract

8.1.1 Background

Prevalence of malnutrition in older hospitalized patients is 30%. Malnutrition is associated with poor clinical outcomes in terms of high morbidity and mortality and is costly for hospitals. Extended nutrition interventions improve clinical outcomes but limited studies have investigated whether these interventions are cost-effective.

8.1.2 Methods

This health economic evaluation was conducted alongside an RCT investigating the benefits of a nutrition intervention in older patients. In the original study, 148 malnourished general medical patients ≥60 years were recruited and randomized to receive either an extended nutritional intervention or usual care. Nutrition intervention was individualized and started with 24 hours of admission and was continued for 3 months post-discharge with a monthly telephone call whereas control patients received usual care. Nutrition status was confirmed by PG-SGA and HRQoL was measured using EQ-5D-5L questionnaire at admission and at 3-months follow-up. A cost-effectiveness analysis [343] was conducted for the primary outcome (incremental costs per unit improvement in PG-SGA) while a cost-utility analysis (CUA) was undertaken for the secondary outcome (incremental costs per QALY gained).

8.1.3 Results

Nutrition status and HRQoL improved in intervention patients. Mean per included patient Australian Medicare costs were lower in intervention group compared to control arm (by AU$907) but these differences were not statistically significant (95%

CI -$2,956 – $4,854). The main drivers of higher costs in the control group were higher inpatient ($13,882 vs. $13,134) and drug ($838 vs. $601) costs. After adjusting outcomes for baseline differences and repeated measures, the intervention was more effective than the control with patients in this arm reporting QALYs gained that were higher by 0.0050 QALYs gained per patient (95% CI: -0.0079 – 0.0199). The probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA was >98% while it was 78% at a willingness to pay $50,000 per QALY gained.

8.1.4 Conclusion

This health economic analysis suggests that the use of extended nutritional intervention in older general medical patients is likely to be cost-effective in the Australian health care setting in terms of both primary and secondary outcomes.

8.2 Introduction

Malnutrition is common in older hospitalized patients with prevalence rates as high as 30% in acute care settings in Australia.[36] Malnutrition is associated with adverse clinical outcomes for patients in terms of higher morbidity and mortality[292] and is costly for the hospitals.[61] The adverse effects associated with malnutrition on patient outcome and recovery results in increased health care use and costs.[237] Health-care costs are increased because malnourished patients stay longer in hospitals, suffer more infectious and non-infectious nosocomial complications, experience frequent hospital re-admissions and have higher utilization of health-care resources in the community[119 221 252 344]. Three recent meta-analyses[115 226 227] have indicated that nutrition intervention has economic benefits but have also suggested that there is a need for further high quality studies to confirm these findings in different age groups and in different health care settings. This is especially so as majority of these studies have been conducted in Europe and very few studies are available in the Australian health care settings.

A recent randomized controlled trial[301] (this study is reported in chapter 7) conducted in a large tertiary hospital in Australia from 2014-2016, assessed efficacy of an early and extended nutrition intervention in older hospitalized patients. In this trial, an individualized nutrition intervention was started within 24 hours of hospital admission and patients ≥60 years age received monthly telehealth follow up for two months following discharge and this intervention was compared to usual care. The main objectives in this trial was to examine whether such an intervention could improve nutritional status and quality of care by reducing adverse clinical outcomes and optimizing use of existing resources.

This trial found a trend towards an improvement in nutritional status and quality of life and a significant reduction in LOS but there was no reduction in mortality or readmissions at three months follow up. Although the resources needed for the intervention were modest and the anticipated improvement in the nutrition status was small[301], no economic evaluation was conducted to examine whether the intervention was worth pursuing from an economic perspective. The objective of the present analysis was to conduct an economic evaluation that assessed whether the individualized nutrition intervention was value for money when considered from a healthcare sector (Australian Medicare) perspective. The results of the evaluation will help determine whether allocation of resources for improvement of nutritional status of older hospitalized patients is justifiable. Consequently, the primary outcome of this evaluation was expressed in terms of incremental costs per unit improvement in the PG-SGA (CEA) and the secondary outcome reported in terms of incremental costs per QALY gained (CUA).

8.3 Methods

8.3.1 Study design

The data for this health economic analysis were obtained from a recently conducted nutrition intervention study[301], which was designed as a RCT (please refer to section 7.3 for details on methodology used in the clinical trial).

8.3.2 Target population

The participants for this study included hospitalized patients aged ≥60 years, who were confirmed as malnourished by a qualified dietitian using PG-SGA tool[345].

8.3.3 Sample size

The sample size was calculated based upon the change in the PG-SGA score from the baseline in the clinical trial[301] which provided data for this economic evaluation. The sample size in the clinical trial was based on the findings of a previous study[156], which has suggested that a shift of 3 (SD 4.1) in PG-SGA is clinically meaningful, assuming an affect size of 0.35, alpha = 0.05 and power of 80% the estimated sample size was 86 (43 in each group) was calculated to be sufficient.

8.3.4 Setting and location

This study included patients presenting to the department of general medicine, FMC, Adelaide, South Australia. FMC is a tertiary level, teaching hospital with 520 beds capacity and the department of general medicine admits approximately 4500 patients per year. Health services at FMC are predominantly funded through the Australian

Medicare Scheme (the primary funder of universal healthcare insurance in Australia). Patients were excluded if they were receiving palliative care, residing in rural areas, or were of indigenous origin or were non-English speaking. Rural, indigenous and non-English speaking subjects were excluded due to lack of funds to travel to rural areas for assessments and seek services of an Indigenous liaison officer/interpreter.

8.3.5 Study perspective

The direct costs of implementing nutritional intervention were determined from the Australian (Medicare) health care perspective. These included costs of hospitalizations, dietitian costs for post-discharge telephone calls, costs of providing nutrition supplements, post-discharge general practitioner and specialist physician visits. Other costs were for any outpatient investigations and procedures, allied health care utilization and medicinal products over the period of 3-months of intervention. Indirect costs, such as those incurred by the patients due to loss of productivity were not included in this analysis.

8.3.6 Comparators

The economic evaluation determined the relative cost-effectiveness/cost-utility of the intervention when compared to the control.

8.3.6.1 Intervention

Please refer to section 7.3.4 (Intervention) in chapter 7 for the details of intervention provided.

8.3.6.2 Control group

Please refer to section 7.3.5 (Control group) in chapter 7.

8.3.7 Time horizon

The costs between the two groups were compared over a period of three months from the time of randomization during hospital admission until the last follow-up.

8.3.8 Discount rates

Discounting (i.e. determining the present value of the future costs and health outcomes) costs and effectiveness measures was not performed, because the time horizon of this study did not exceed 1 year.[346 347]

8.3.9 Choice of nutritional/health outcomes

The primary nutritional outcome in this study, as was the case in the clinical study[301] and for the sake of maintaining consistency, was the unit improvement in the PG-SGA over the 3-month study period. The secondary outcome was QALYs gained over the same period and based on the responses to the EQ-5D-5L questionnaire.[187]

8.3.9.1 PG-SGA

The nutrition status of the participants was confirmed with PG-SGA by an experienced dietitian. Please refer to section PG-SGA for details regarding this tool.

8.3.9.2 HRQoL and QALYs

QALYs gained were chosen as an outcome as they facilitate comparisons between interventions for disparate services and are recommended for use by decision makers including the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.[348]

QALY estimates, calculated using the area-under-the-curve method,[346] were based on responses to the EQ-5D-5L which were scored using UK value sets.[187]

The EQ5D 5L is a self-reported questionnaire and measures a patient's health across five different domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression[186]. Using these responses, the EQ-5D-5L is able to distinguish between 3,125 states of health. A UK-specific algorithm developed using time-trade-off techniques was used to convert the EQ-5D 5L health description into a valuation ranging from -0.281 to 1.[187] Scores less than 0 represent health states that are worse than death.[182] The EQ-5D-5L has been validated in different clinical populations including patients with multiple chronic illnesses, rehabilitation and orthopedic patients awaiting joint replacement surgery and has been found to have a stronger convergent validity coefficient (Spearman's coefficient 0.51-0.75) and a higher absolute informativity (Shannon's index) as compared to the EuroQol 5 Dimensions 3 Levels (EQ-5D-3L).[188 349 350]

8.3.10 Measurement of effectiveness

No effectiveness data were obtained from secondary sources as our analysis relied upon data from our original trial.[301]

8.3.11 Estimating resources and cost

Data on the volume and total costs of healthcare utilization, measured from the health care perspective, were readily provided by Medicare Australia. Cost data were provided in the form of Medical Benefits Schedule (MBS) data (number and costs of GP visits, specialist attendances, non-specialist attendance, diagnostic procedures and other medical services such as pathology and telehealth services); Pharmaceutical Benefits Schedule (PBS) data (quantity and costs of pharmaceuticals) and; centralised costing (AR-DRG) data[351] (number and costs of public hospital inpatient episodes). Patient consent was sought before obtaining MBS, PBS and AR-DRG data. Costs associated with the intervention itself (primarily dietitian staff costs for making follow-up telephone calls (30 minutes per month for two months i.e. two phone calls per patient for all patients) and costs of supplements for the entire study period for nearly half (36) of the patients) were estimated by combining staff time spent/number of supplements provided and published information on wage rates obtained from published resources ($37.16 per hour for an accredited dietitian) and unit costs for supplements sourced from hospital accounts records ($6 per package per day). All costs are reported in Australian dollars at 2016/17 unit prices.[346]

8.4 Analytical methods

8.4.1 Descriptive statistics

Continuous variables were expressed as mean (SD) values or median (IQR) ranges and were compared using an appropriate parametric (Student t) test or nonparametric (Mann-Whitney U) test. Categorical variables were expressed as frequencies and percentages and were compared using χ^2 statistics or Fishers exact test as appropriate. LOS was adjusted for in-hospital mortality.

8.4.2 Economic Evaluation

Two types of economic evaluation (CEA and CUA) were used in this study. Their choice was informed by the types of outcomes measured in the main trial.[301] CEA is a type of economic evaluation whose outcomes are expressed in terms of natural units such as life expectancy or change in PG-SGA scores, while outcomes in CUA are reported in terms of QALYs.[352] Consequently, the primary outcome of this evaluation was expressed in terms of incremental costs per unit improvement in PG-SGA (CEA) and the secondary outcome reported in terms of incremental costs per QALYs gained (CUA). An incremental approach was used in order to determine, where appropriate, the incremental cost effectiveness ratios (ICERs) expressed as the incremental cost per unit improvement in the PG-SGA (primary outcome) and incremental costs per quality adjusted life year QALY gained (secondary outcome). The ICERs were calculated as incremental costs divided by incremental changes in outcomes. The economic evaluation was conducted using an intention-to-treat approach.

Within-trial economic evaluation with respect to the primary and secondary outcomes was undertaken allowing for bivariate uncertainty with bootstrapping of participant costs and outcomes to maintain the covariance structure. To account for uncertainty due to sampling variation in cost-effectiveness/cost-utility, non-parametric bootstrapping[353] were applied on participant level data to derive 5,000 paired estimates of mean differences in costs and outcomes. These bootstrapped pairs were summarized within cost effectiveness planes (CEPs).[354] The probability of the intervention being more cost effective, compared to the usual care arm at different willingness-to-pay thresholds, was depicted using Cost effectiveness acceptability curves (CEACs).

Due to the presence of missing data on costs and outcomes **(Tables 28, 29 and 30)**, multiple imputation was used to account for missing values prior to conducting the base-case economic evaluation.[355] Imputed values were generated by use of an iterative Markov chain Monte Carlo method premised on multivariate normal regression.[356] To appropriately characterize the uncertainty about the right value to impute, each missing value in the dataset was replaced with a set of 50 plausible values. Standard complete-case procedures were then applied to each of the 50 resultant multiply imputed datasets before combining the results using Rubin's rules.[357] The following variables were used to predict missing values in the imputation procedure: study arm, age, gender, cognitive status, length of stay, total number of comorbidities and malnutrition diagnosis. In both the base-case and sensitivity analyses, only adjusted outcomes (adjusted for baseline differences and correlation between repeated measurements) were used.

Sensitivity analyses were carried out to test the robustness of the base case results and they focused on evaluating the effect of missing cost and outcome data values on the economic evaluation results (i.e. comparing results based on complete cases and those estimated using multiple imputed values). All analyses were conducted in Microsoft Excel (2010) and Stata version 14.1.

8.5 Results

8.5.1 Descriptive statistics

A total of 1668 patients **(Figure 7)** admitted to the Department of General Medicine were assessed for participation in this study, whereof 892 met the inclusion criteria. Of the 892, 744 patients refused to participate due to various reasons **(Figure 7)**. One hundred and forty eight patients were therefore recruited and randomized to the control (n = 70) and intervention (n = 78) groups. The baseline clinical characteristics **(Table 28)** were similar between the two groups with regard to age, gender distribution, CCI, number of medications and principal clinical diagnosis. There was no difference in severity of malnutrition at baseline as determined by PG-SGA score and HRQoL as determined by EQ-5D-5L was similar between the two groups **(Table 28)**. Nutritional intervention provided an additional mean 655 (95% CI 587.3 – 772.1) kcal of energy and 36.5 (95% CI 31.5 – 41.5) grams of protein and 73% and 77.2%

patients were compliant with the intervention at 1 month and 2 months post-discharge, respectively. LOS was significantly shorter in the intervention patients (9.9 (SD 7.2)) vs. 6.9 (SD 5.3), P < 0.005) days, in control and intervention groups, respectively **(Table 30)**.

Table 28 Baseline characteristics of participants

Characteristics		Control (n=70)	Intervention (n=78)	P value
Age, mean (95% CI), y		81.6 (79.5 – 83.6)	82.0 (80.0 – 83.9)	0.76
Gender, n (%)	Male	23 (32.9)	31 (39.7)	
	Female	47 (67.1)	47 (60.3)	0.38
Residence before admission, n (%)	Home	66 (94.3)	68 (87.2)	0.11
	Nursing Home	4 (5.7)	10 12.8)	
Cognition, n (%)	Normal	67 (95.7)	74 (94.9)	0.56
	Impaired	3 (4.3)	4 (5.1)	
No of co-morbidities, mean (95% CI)		6.3 (5.6 – 6.9)	6.1 (5.5 – 6.6)	0.64
CCI, mean (95% CI)		2.3 (1.9 – 2.8)	2.2 (1.8 – 2.7)	0.82
Medications at admission, mean (95% CI)		10.1 (9.0 – 11.2)	8.8 (7.8 – 9.7)	0.07
Principal diagnosis at admission, n (%)	Respiratory	29 (41.4)	20 (25.6)	0.30
	Cardiovascular	8 (11.4)	14 (18.0)	
	Falls	10 (14.3)	13 (16.7)	
	CNS	3 (4.3)	6 (7.7)	
	Miscellaneous	20 (28.6)	25 (32.1)	
BMI, mean (95% CI), kg/m2		21.8 (20.7 – 22.8)	20.6 (19.7 – 21.5)	0.09
PG-SGA score, mean (95% CI)		13.3 (12.2 – 14.5)	12.1 (11.0 – 13.2)	0.11
EQ-5D-5L index		0.6746 (0.617 – 0.729)	0.6934 (0.638 – 0.746)	0.62

CI, confidence interval; CCI, Charlson comorbidity index; CNS, central nervous system; BMI, body mass index; PG-SGA; patient generated subjective global assessment; EQ-5D-5L, European quality of life questionnaire 5 dimensions 5 levels

Table 29 Mean costs per patient (AUD)

Costs[a]	**Control**		**Intervention**		**Difference (Bootstrapped 95% CI)**
Base Case Analysis (imputed cases)[b]	n	Mean	n	Mean	
3 month MBS costs					
GP Costs	70	347 (38)	78	311 (32)	-37 (-134 – 59)
Specialist Attendance Costs	70	20 (5)	78	12	-7 (-19 – 4)
Non-Specialist Attendance Costs	70	251 (43)	78	243 (36)	-8 (-122 – 100)
Diagnostic Procedures costs	70	200 (40)	78	197 (31)	-4 (-111 – 94)
Other Medical Service costs[c]	70	396	78	253 (34)	-143 (-291 – 2)
Total MBS costs	**70**	**1,216 (128)**	**78**	**1,008 (97)**	**-208 (-529 – 149)**
3 month PBS costs					
Total drug costs	**70**	**838 (186)**	**78**	**601 (57)**	**-237 (-703 – 47)**
3 month Inpatient (DRG) costs					
Total DRG costs	**70**	**13,882 (1,390)**	**78**	**13,134 (1,439)**	**-748 (-4,584 – 3,310)**
Intervention costs					
Total intervention costs	**70**	**0**	**78**	**286 (30)**	**286 (225 – 352)**
Total Costs	**70**	**15,936 (1,397)**	**78**	**15,029 (1,430)**	**-907 (-4,854 – 2,956)**
Sensitivity analysis (complete cases)[d]					
3 month MBS costs					
GP Costs	62	348 (43)	65	307 (39)	-41 (-151 – 92)
Specialist Attendance Costs	62	21	65	13	-9 (-20 – 8)
Non-Specialist Attendance Costs	62	247 (48)	65	251 (48)	4 (-108 – 142)
Diagnostic Procedures costs	62	200 (42)	65	211 (39)	10 (-108 – 121)

Costs[a]	Control		Intervention		Difference (Bootstrapped 95% CI)
Other Medical Service costs[c]	62	389 (73)	65	248 (47)	-141 (-334 – 5)
Total MBS costs	**62**	**1,205 (143)**	**65**	**1,029 (132)**	**-176 (-495 – 226)**
3 month PBS costs					
Total drug costs	**59**	**855 (217)**	**65**	**610 (65)**	**-245 (-832 – 99)**
3 month Inpatient (DRG) costs					
Total DRG costs	70	13,882 (1,390)	78	13,134 (1,439)	-748 (-3,310 - 4,584)
Intervention costs					
Total intervention costs	**70**	**0**	**78**	**286 (30)**	**286 (225 – 352)**
Total Costs	**59**	**17,024 (1,595)**	**60**	**12,078 (917)**	**-4,947 (-9,030 – -1,451)**

[a] MBS Medical Benefits Schedule, PBS Pharmaceutical Benefits Schedule, DRG Australian Refined Diagnosis Related Groups (AR-DRGs) cost weights used to cost hospital admissions, GP General Practioner, Total costs = MBS costs + PBS costs + DRG costs + Intervention costs

[b] Multiply imputed values. Multiple imputations carried out to account for up to 29 or 19% missing data on cost estimates

[c] Examples of other medical costs include pathology and telehealth services as well as allied-health care attendances

[d] Analysis restricted to non-missing total cost estimates (119 or 81%).

Table 30 Outcomes of study

Outcomes[a]		Control		Intervention	Difference (Bootstrapped 95% CI)
	n	Mean	n	Mean	
Base Case Analysis (imputed cases)[b]					
EQ-5D-5L and QALY gains					
EQ-5D-5L at baseline	70	0.6746 (0.0284)	78	0.6934 (0.0276)	0.1088 (-0.0489 – 0.0916)
EQ-5D-5L at 3 months	70	0.5787 (0.0407)	78	0.6358 (0.0349)	0.0571 (-0.0556 – 0.1560)
Unadjusted QALYs	70	0.1578 (0.0064)	78	0.1659 (0.0067)	0.0081 (-0.0090 – 0.0265)
Adjusted[c] QALYs					0.005 (-0.0079 – 0.0199)
PG-SGA Scores					
PG-SGA Scores at baseline	70	13.3286 (0.5817)	78	12.1123 (0.4951)	-1.2163 (-2.6163 – 0.1793)
PG-SGA Scores at 3 months	70	7.3770 (0.4098)	78	5.9136 (0.4054)	-1.4634 (-2.4801 – -0.1896)
Unadjusted improvement in PG-SGA Scores[d]	70	5.9516 (0.6594)	78	6.1987 (0.5547)	0.2471 (-1.4931 – 1.8661)
Adjusted[c] improvement in PG-SGA Scores[d]					1.3238 (0.0240 – 2.3858)
Inpatient stay					
LOS in days	69	9.9 (7.2)	71	6.9 (5.3)	3.0 (0.9 – 5.1)
Sensitivity analysis (complete cases)[e]					
EQ-5D-5L and QALY gains					
EQ-5D-5L at baseline	69	0.6736 (0.0290)	77	0.6926 (0.0272)	0.0189 (-0.0537 – 0.1003)
EQ-5D-5L at 3 months	60	0.5672 (0.0487)	69	0.6360 (0.0407)	0.0688 (-0.0553 – 0.2043)
Unadjusted QALYs	59	(0.1553 (0.0076)	69	0.1658 (0.0075)	0.0105 (-0.0096 – 0.0291)

Outcomes[a]		Control		Intervention	Difference (Bootstrapped 95% CI)
	n	Mean	n	Mean	
Adjusted[c] QALYs					0.0060 (-0.0086 – 0.0216)
PG-SGA Scores					
PG-SGA Scores at baseline	69	13.3478 (0.5848)	74	12.0946 (0.5240)	-1.2532 (-2.9491 – 0.2727)
PG-SGA Scores at 3 months	46	6.9783 (0.6167)	57	5.8070 (0.5185)	-1.712 (-2.7446 – 0.3698)
Unadjusted improvement in PG-SGA Scores[d]	46	6.1739 (0.8876)	57	5.8596 (0.7081)	-0.3143 (-2.4223 – 1.8485)
Adjusted[c] improvement in PG-SGA Scores[d]					0.9849 (-0.5601 – 2.5912)

[a] EQ-5D-5L, European quality of life 5 dimensions 5 levels; QALY, quality adjusted life years; PG-SGA, patient adjusted subjective global assessment; LOS, length of hospital stay
[b] Multiply imputed values. Multiple imputations carried out to account for up to 12% of the EQ-5D-5L utility scores (2 or 1% of baseline and 19 or 1% of 3-month EQ-5D-5L scores)
[c] These scores have been adjusted for baseline differences
[d] These PG-SGA scores were reverse scored so that a positive score reflects an improvement in nutrition status
[e] Trial participants with complete information on baseline and 3-month outcomes

8.5.2 Incremental costs and outcomes

8.5.2.1 Base case analysis results

Table 29 presents a breakdown of mean healthcare costs per participant over a 3 months follow-up period. In the base case, mean per participant total Australian Medicare costs were lower in the intervention group compared to the control arm (by $907 per patient) but these differences were not statistically significant (95% CI: -

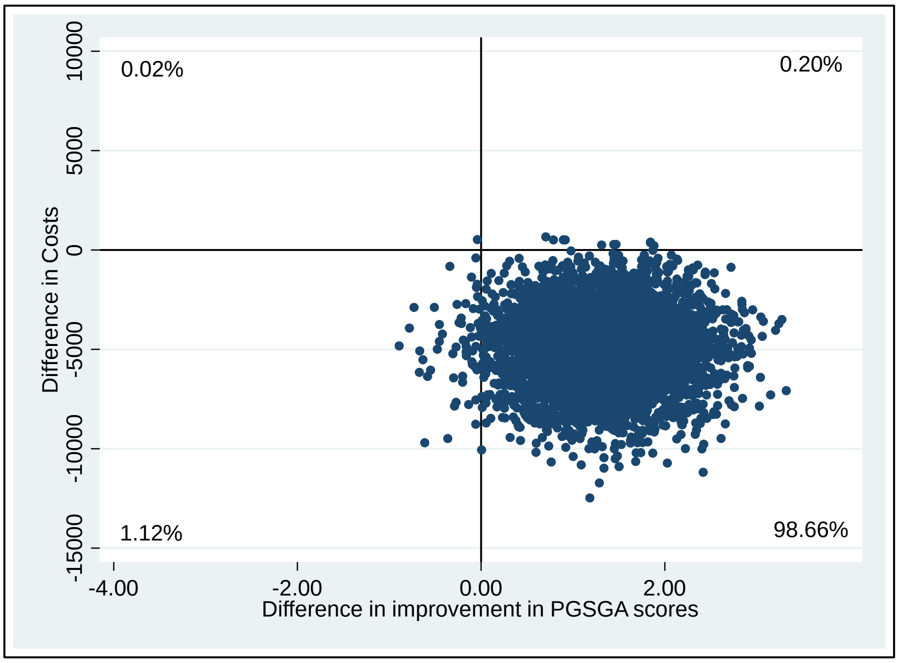
$2,956 – $4,854). The main drivers of the higher costs in the control group were higher inpatient ($13,882 vs. $13,134) and drug ($838 vs. $601) costs. When the adjusted outcomes in the base case were considered **(Table 29)**, the intervention was more effective than the control with participants in this arm reporting unit improvements in the PG-SGA that were higher by 1.3238 units (95% CI 0.0240 – 2.3858) and QALYs that were higher by 0.0050 QALYs gained per patient (95% CI -0.0079 – 0.0199). In line with best practice guidelines,[347 358] ICERs relating to both the primary and secondary outcomes are not presented, as the intervention was both cheaper and more effective regardless of outcome considered.

The CEPs in the base case analysis **(Figure 9)** shows some uncertainly in the cost-effectiveness results but most of the bootstrapped paired estimates of mean differences in costs and outcomes appear in south-east and south-west quadrants. The CEACs **(Figure 10)** show that the probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA scores was above 98% while it was 78% at a willingness to pay of $50,000 per QALY gained, the implicit cost-effectiveness threshold used in Australia.[359]

8.5.2.2 Sensitivity analysis results

In the base case analysis, multiple imputation was used to deal with the missing data on costs (29 observations or 20%), PG-SGA scores (45 observations or 30%) and EQ-5D-5L responses (19 observations or 13%). In the sensitivity analysis, ignoring the missing data and using complete case analysis **(Tables 29 and 30)** did not have an effect on the incremental effectiveness. This is because the intervention was still more effective by 0.9849 units of improvement in the PG-SGA score (95% CI -0.5601 – 2.5912) and by 0.0060 QALYs gained per patient (95% CI -0.0086 – 0.0216), but was even more cheaper per patient (by $4,947; 95% CI $1,451 – $9,030). These figures did not change the final interpretation because the intervention still outperformed the control.

a) Improvement in Patient-Generated Subjective Global Assessment (PG-SGA) scores over 3 months



b) Quality Adjusted Life Years (based on EuroQoL 5 dimensions 5 levels (EQ-5D-5L) responses) gained score over 3 months

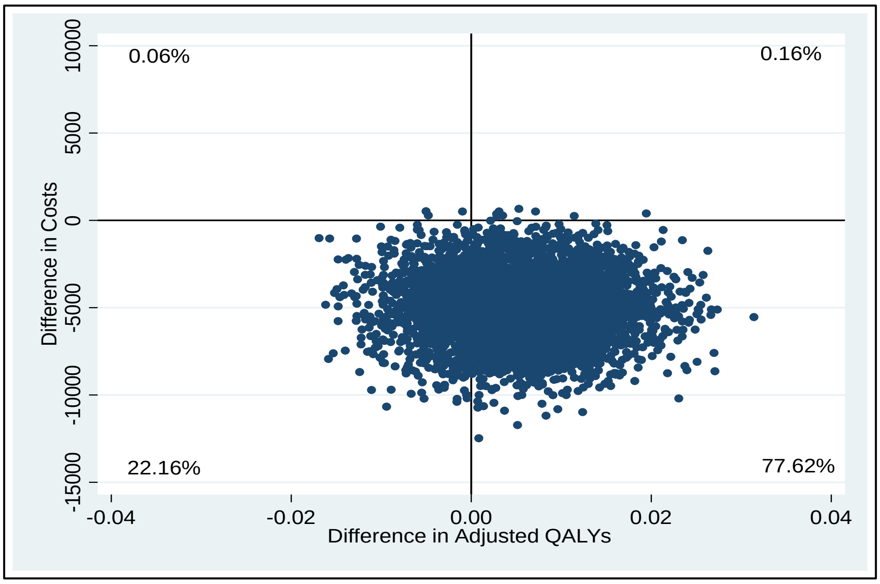
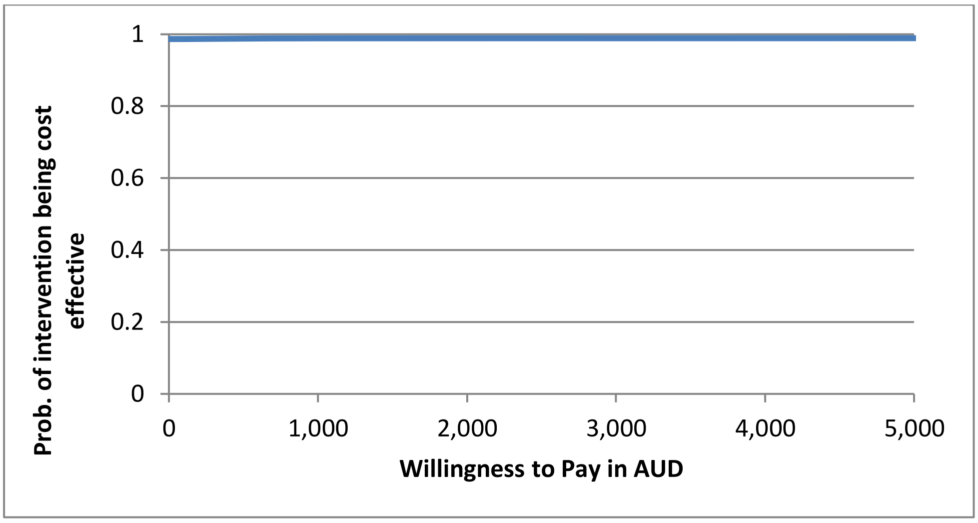


Figure 9 Cost-effectiveness planes

a) Improvement in Patient Generated Global Assessment (PG-SGA) scores over 3 months



b) Quality Adjusted Life Years (based on EuroQol 5 dimensions 5 levels (EQ-5D-5L) responses) gained score over 3 months

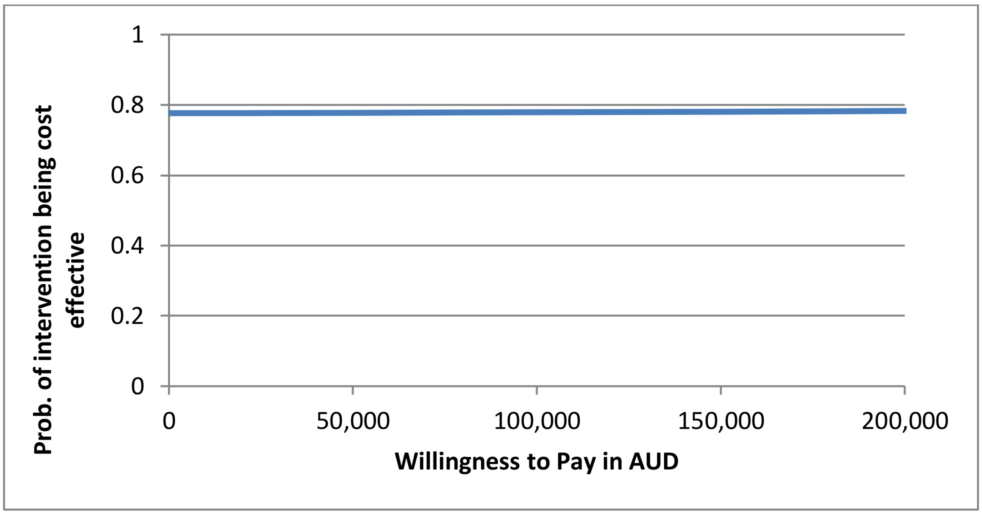


Figure 10 Cost effectiveness acceptability curves

8.6 Discussion

The findings of this study indicate that, in older general medical malnourished patients, the health care costs were lower while nutrition status and HRQoL was better among those in the individualized nutrition intervention arm compared to those in the group that received usual care with no post discharge dietetic follow-up. The differences in costs and HRQoL outcomes were however not statistically significant. In line with best practice guidelines,[360 361] therefore, our analysis focused on determining the likelihood of the intervention being cost-effective as opposed to hypothesis testing relating to whether the cost and QALY differences were statistically significant. Our results show that probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA was >98% while it was 78% at a willingness to pay $50,000 per QALY gained. One of the strengths of this study is the use of PG-SGA for nutritional assessment, which has been demonstrated to have high sensitivity and specificity for the diagnosis of malnutrition and has been recommended as a predictive tool for clinical outcomes.[156] Yet, very few costing studies have utilized this stool for nutritional assessment.

At least two reasons may explain the statistically insignificant cost and HRQoL differences between the two trial arms. The first may be because the original trial[301] from which the data for this study were obtained was not powered to detect differences in costs and HRQoL, a result seen elsewhere[360 361]. Another reason specific to HRQoL could be a short duration of nutrition intervention in our study. The impact of nutrition intervention on utilities is complex and may not be evident after a short period of intervention. After initiating nutrition intervention the temporal pattern that usually follows is – first improvement in nutrition parameters like weight then functional outcomes and lastly improvement in HRQoL.[233] Future nutrition intervention trials of sufficiently long duration may help verify this hypothesis.

The intervention was shown to have had lower mean Medicare costs than the control. The cost drivers for the higher mean costs per patient in the control group were higher inpatient and drug costs. This could be related to the overall significantly longer LOS for the control patients with resultant higher utilization of health care resources. Studies have suggested that malnutrition contributes to the development of new complications such as delirium,[298] predisposes to pressure ulcers[362] and increases risk of falls,[363] all of which may contribute to the prolongation of the duration of hospitalization. Early nutrition intervention on the other hand may quickly improve the protein status and hence muscle function[364] as reflected by an increase in handgrip strength[365] and may lessen the risk of hospital acquired infections and may contribute to faster resolution of delirium.[238] It is possible that extension of this intervention following hospital discharge was associated with a sustained improvement in the nutrition status of intervention patients with a consequent reduction in the 'post-hospital syndrome'.[296] This may have led to a reduction in the utilization of primary health care resources (e.g. reduced GP visits) with consequent reduction in overall costs.

Our results are in line with a meta-analysis by Russell et al[61] who found that use of ONS in surgical and older medical patients both in hospital and community settings can reduce LOS and complications with resultant net cost savings per patient. Our study is different from the studies used in the above meta-analysis in that we used a nutritional intervention tailored to individual patients needs rather than ONS alone, as studies have suggested poor compliance with ONS,[366] especially in the older population. Similarly Gianotti et al[367] found reduced treatment costs in patients who received enteral nutrition among patients undergoing major abdominal or cancer surgery and hypothesized that nutrition therapy helps improve splanchnic microperfusion with resultant lesser number of post-operative complications but in contrast to our study, this study included only surgical patients and limited nutrition intervention to the perioperative period. Norman et al[368] in their study in malnourished patients aged 50.6 ±16.1 years, with benign gastrointestinal disease found that 3-month nutritional supplementation with ONS increased HRQoL and was cost-effective from a German statutory health insurance perspective. Unlike our study, which included older patients with multiple comorbidities, however, this study was restricted to a relatively younger population of patients with benign gastrointestinal disease and nutrition intervention commenced only at the time of discharge. Our study results are also in line with the findings of three recent meta-analyses conducted in different patient groups,[115 226 227] which suggest that the use of enteral medical nutrition in the management of DRM can be an efficient intervention from a health economic perspective and may lead to cost-savings.

Although malnutrition is common in older hospitalized patients, it is often poorly recognized by the clinicians with resultant fewer malnourished patients receiving treatment.[67] Economic evaluation offers a framework within which complex changes can be synthesized to aid in policy making. Our finding suggests that if similar intervention were to be delivered to all malnourished patients ≥60 years of age in general medical service of our hospital in 2015-16, a per-patient cost saving of AU$907 will translate to a total savings of AU$1.86 million and if applied to the State of South Australia total cost savings of AU$9.05 million can be achieved. This study suggests that there is an opportunity to improve the health of malnourished older patients at a low marginal cost. Very few interventions have achieved health gains in this population at a lower cost.[369] In the current climate of economic constraints in healthcare, this study provides convincing evidence of the economic benefits of nutrition intervention.

8.7 Limitations of study

Although the use of a randomized controlled study provides robust evidence for assessing the utility of nutrition intervention, this study had limitations when assessing economic value. Our analysis did not consider several factors, which could bias the results by either underestimating or overestimating the cost-effectiveness of nutritional supplementation. While we included the direct medical costs, we did not consider broader or indirect costs such as those borne by patients and their families privately or by nursing homes and costs associated with loss of work due to periods of absence for patients or their carers. Additionally, our study duration is limited to 3 months and long-term impact of such a nutrition intervention is unknown. Our study did have missing data on some costs and outcomes, however principled and robust methods were used to deal with these missing data. Finally, the difference in QALY gains in this study can be considered to be small and therefore our result on the effectiveness should be interpreted with caution. The overall economic evaluation results nevertheless considered these QALY gains jointly with cost differences as is appropriate.

Due to differences in design and organization of health-care systems, our study results cannot be generalized to other settings and countries and further studies are needed to contribute to the evidence of cost utility of nutritional therapy.

8.8 Implications

Our study adds clinical and economic evidence of the benefits of initiating an early nutrition intervention with continuation in the community to improve health outcomes in older hospitalized malnourished population and justifies allocation of resources to improve the nutrition status of an elderly population.

8.9 Conclusion

For both primary (change in PG-SGA scores) and secondary outcomes (QALY gains), the results of our health economic analysis suggest that the use of early and extended nutritional intervention in older general medical patients is likely to be cost-effective in the Australian health care setting as the intervention was both cheaper and more effective than the comparator. This conclusion was supported further by results of the CEACs that showed that the intervention had a high likelihood of being the cost-effective option over a range of willingness to pay values.

CHAPTER 9: GENERAL DISCUSSION AND FINAL CONCLUSIONS

This thesis has identified factors responsible for a missed opportunity to screen for malnutrition in older hospitalized patients, which was found to be widely prevalent and was missed in over half of the general medical inpatients. This research confirms adverse consequences of malnutrition measured in terms of a longer LOS, a higher risk of nosocomial complications and a poorer HRQoL. Malnutrition at hospital admission also emerged as a significant predictor of a combined clinical outcome of readmission or death in both early and late periods following hospital discharge. MUST was found to be a valid malnutrition screening tool when compared against the PG-SGA and a history of recent significant weight loss emerged as a reasonably good indicator of malnutrition risk in hospitalized older patients. Finally, early and extended nutrition intervention was found to beneficial in improving the nutritional status and LOS in older general medical patients and was found to be a cost-effective strategy.

9.1 Synthesis of Findings

As reported by others,[20 113 118 119 370], this study found that over 50% of older general medical patients missed nutrition screening during their hospital stay. This study compared characteristics of patients who missed nutritional screening with MUST with those who underwent nutritional screening. Three factors were found to be associated with a reduced rate of nutritional screening in older general medical hospitalized patients. These factors included: a higher BMI at the time of hospital admission, patients' location away from the home wards and overnight admissions.

This study found that patients with a higher BMI were less likely to undergo nutritional screening by MUST. Other studies[127 261] also suggest that patients' overall physical appearance influence nutritional screening and patients who appear well-nourished are less likely to be screened. It is possible that in a busy clinical situation some guess work is used by the health care professionals to decide whom to screen. Patients who visually look "healthy" or "fit" may miss nutritional screening with a false perception that they are unlikely to be malnourished. The results of this study are in line with Raja et al,[127] who also found that patients with a higher BMI often miss nutrition screening. However, Venzin et al[371] in their study involving 430 patients with a mean age of 63±19 years found that the prevalence of malnutrition was underestimated only in less than 5% patients by the physicians' clinical judgement. However, in this study the physicians were instructed to define patients' nutrition status based on history, physical examination and laboratory investigations at the time of hospital admission. The authors acknowledged that although the physicians received no training to detect malnutrition they could still have been sensitized for malnutrition which could have led to good results. Overall, the findings of our research indicate that there is a need to educate staff that patient's appearance is not an accurate method for determining their nutrition status and patients who look 'fit' can still be malnourished and clinical judgment should not supersede nutritional screening.

Patients' logistics after admission were identified as another factor which might influence nutritional screening. This study found that patients who were placed in the home ward after admission from the emergency department (ED) were more likely to undergo nutrition screening than those located in the outlier wards. This could be due to the fact that staff work more efficiently in a familiar area and have more time to screen patients than those taking care of the outliers. Studies suggest that the care provided in the outlier wards may not be most appropriate and more timely as it could be, as staff taking care of the outlier patients may not have specific expertise for the patients' condition.[266 372 373] Some empirical evidence[265] on outlier patients also suggest that the patients who are chosen for medical outliers are more medically "fit". Implicitly, patients who are classified as "fit" may be perceived by the staff to be of low priority and this may in turn lead them to skip the routine screening procedures.[265] An Australian study[374] also found that medical outliers have a higher frequency of medical emergency response team (MET) calls leading to higher workload on staff who do not know the patients as well. This may result in suboptimal patient care with resultant poor clinical outcomes. Other reason for suboptimal nutrition screening in the outlier patients could be related to the unavailability of proper equipment (e.g. absence of calibrated weighing scales) in the outlier wards which could either hamper or delay routine assessments on these patients.[146] This finding demands that patients should be preferably located in the home ward and if possible outliers should be discouraged. In light of the findings of this study, the hospitals may need to revisit their policies regarding outlying patients as there is an evidence suggesting worse quality of care and this may lead to poor clinical outcomes.[265]

Finally this study found that patients who had overnight admissions were less likely to undergo nutritional screening than those who were admitted during morning shifts. It is possible that this could be related to fewer staff availability afterhours than during day shifts. However, this hypothesis needs confirmation as our study did not investigate the staff availability at different time shifts. Studies suggest that although nurses acknowledged the importance of nutrition screening but they experienced difficulty in raising nutrition care above other nursing responsibilities due to time constraints and the need for multitasking.[375] Thus in a busy health care setting to priortize care, some screening or assessments are either omitted or may be left for completion by other staff[127] and this may lead to missed opportunity to screen patients for malnutrition.

Two studies (chapters 4 and 5) included in this thesis confirmed adverse clinical consequences of malnutrition in medical inpatients. Malnutrition was found to be associated with a longer LOS, poor HRQoL, higher in-hospital mortality and increased risk of either death or readmission in both early and late periods following hospital discharge in older general medical patients.

This research confirms findings of other similar studies[42 58 62 67] that malnutrition lengthens hospital stay in older hospitalized patients. This study found that malnourished patients suffered a higher number of nosocomial complications than well-nourished patients and this could have contributed towards a longer LOS. Previous studies[376-378] also suggest that malnourished patients are at an increased risk of hospital-acquired pneumonia (HAP) because of respiratory muscle dysfunction and immunosuppression. Studies suggest that malnourished patients are slow to recover from infections because of a poor response to antibiotics and they often need treatment for an extended duration.[87] Older malnourished patients frequently have gastroparesis which leads to poor absorption of orally administered medications.[379] Gastroparesis also causes nausea and vomiting[380], and this may delay discharge from hospital. Other reasons for a longer LOS in malnourished patients could be related to poor mobility and a greater risk of deconditioning and accidental falls because of the negative effects of malnutrition on skeletal muscle function.[93 381]

Similar to other studies,[97 278 382] this study confirmed a poor HRQoL in older malnourished general medical patients. However, the relationship between nutrition status and HRQoL appears to be complex, and may be influenced by other factors such as mood, difficulties in eating and anorexia.[279 383] The nature of these associations demands further clarification; for instance whether there is a causal relationship between eating difficulties, depression, anorexia and poor HRQoL. As the present study was an observational study, so no causal relation can be drawn between malnutrition and poor HRQoL.

Malnourished general medical patients were at a high risk of either readmission or death post-hospital discharge. This evidence is in line with some other studies[62 299 384] and suggests that malnutrition predisposes to either new illnesses or leads to flare-up of existing co-morbidities, with resultant poor outcomes for these patients. The ‘post-hospital syndrome’[296] is a well-known phenomenon where after a recent acute hospitalization, patients are vulnerable due to limited physiological reserves.[385] The risk factors for this syndrome include: deconditioning, polypharmacy, sleep deprivation, poorly controlled pain and malnutrition.[296 386] All these factors usually exist at the time of index admission and if not properly managed during hospital admission, will work in various combinations post discharge and will lead to either an unplanned readmission or in extreme cases even death. Malnutrition has been identified as one of the risk factors for this syndrome because nutrition status frequently declines during hospital stay and it also contributes to deconditioning.[387]

The strong association of malnutrition with adverse clinical outcomes can also be explained by the complicated synergistic effects of malnutrition, inflammation and atherosclerosis (MIA syndrome).[388 389] MIA syndrome is a well known phenomenon in patients with end-stage renal disease who are on renal replacement therapy.[390] Chronic inflammation and atherosclerosis are common in older people[391] due to ageing itself and due to associated co-morbidities (e.g. chronic kidney disease, diabetes, congestive heart failure) and malnutrition may act synergistically to increase inflammation with resultant poor clinical outcomes. Chronic inflammation leads to endothelial dysfunction which may be associated with hypertension and unstable coronary artery disease - common complications in hospitalized patients with resultant poor clinical outcomes.[392 393]

This study tested the validity of MUST against PG-SGA in older hospitalized general medical patients. This study found that MUST had a lower sensitivity (69.7%), specificity (75.8%), positive predictive value (75.4%) and negative predictive value (70.1%) as compared to the PG-SGA (used as reference standard). The level of agreement between two tools was 72.7% (k = 0.49) and MUST score was found to have a significant inverse correlation with all anthropometric measures except handgrip strength. These results indicate that MUST is a reasonable good screening tool in detecting malnutrition among older general medical patients. A specific finding of this study was that significant weight loss (≥5%) in the previous 3-6 months correlated well with nutrition status as determined by PG-SGA (area under ROC curve 0.71) which was almost comparable to the MUST (area under ROC curve 0.73).

Limited studies have validated the MUST against PG-SGA in hospitalized patients. A study[275] in radiation oncology patients compared MUST against PG-SGA and found a relatively higher sensitivity (80%) and specificity (89%) in detecting malnutrition as compared to our study. However, this study included only cancer patients with a wide age range (18–95 years) as compared to our study which included older (≥60 years) general medical patients with multiple co-morbidities. A Korean study found that MUST was a valid tool to screen malnutrition in older hospitalized patients (sensitivity 80% and specificity 98%) when compared against a combined index for malnutrition, which was calculated using four different tools and used as a reference.[46] Other studies have compared MUST against SGA in a mixed population of medical and surgical patients and found its validity to be fair (sensitivity and specificity 70-80%)[394] and comparison against NRS 2002[142] and MNA[395] also revealed fair to good validity (sensitivity and specificity >80%).

The purpose of using a screening tool is to identify patients at risk of malnutrition and then to select those individuals for further evaluation and potential intervention.[396] MUST is an easy-to-use tool with straight forward, objective questions.[126] A recent study suggests that MUST correlates better with ESPEN criteria for the new definition of malnutrition and can efficiently screen malnourished patients.[396]

However, our study found that, in general medical patients, the negative predictive value of MUST was around 70% which indicates that MUST has a 30% probability of missing patients who are ‘at risk’ of malnutrition. This highlights deficiencies of the existing nutrition screening tools including MUST and there is no ‘gold standard’ tool available at this stage to detect malnutrition.

Another significant finding of this study is that a history of significant (≥5%) weight loss in past 3-6 months can also be a good predictor of a patient’s nutrition status. The ROC area for significant recent weight loss as compared to the PG-SGA was 0.71 which was similar to the MUST. Boloe-Tome et al[275] also found that a history of recent significant weight loss is a reliable predictor of nutrition status in cancer patients with sensitivity, specificity, positive and negative predictive values that were comparable to that of the MUST (with PG-SGA used as the reference standard). Others have questioned the validity of weight loss as a screening tool because a number of non-nutritional factors, e.g. hydration status may influence weight changes.[317] Moreover, many patients may not remember their weight in the recent past and may use guesswork about their recent weight change.

The study presented in chapter seven of this thesis found benefits of starting an early and extended nutrition intervention in older hospitalized malnourished patients. The findings of this study suggests that there was a trend towards an improved nutrition status in the intervention group at the end of 3 months of the study period and in terms of clinical outcomes there was as a significant shortening of LOS in the intervention group but other clinical outcomes were similar between the two groups.

A significant finding of this study was an improvement in the nutrition status of both control and intervention patients from their baseline. These findings are contrary to an observational study conducted by Marshall et al[397], who found that, in geriatric rehabilitation patients, nutrition status declined in patients who receive usual care over a period of 12 weeks of observation. In our study, however, some control patients also were referred for dietetic intervention during their hospital stay. There was a heightened staff awareness of an ongoing nutrition intervention trial in the department of medicine and this could have been one of the reasons for an increased referral of the control patients to a dietitian. It is quite possible that some of the control patients continued intervention and/or sought additional dietetic support following hospital discharge. The so called 'Hawthorne effect'[398 399] is a well known phenomenon, where after being made aware of the diagnosis of 'malnutrition', control patients could have modified their behavior and changed their dietary practices. This could have been the reason for an improved nutrition status observed in these patients over the duration of study and could have diluted the beneficial results of the intervention. We think that this could be the reason why a significant difference in the nutrition scores, as determined by the PG-SGA, was not observed between the two groups at the end of the intervention.

With regards to the clinical outcomes, this study found a significant shortening of LOS (5.0 days; 95% CI 3.0 – 8.4 vs. 8.8 days; 95% CI 4.1 – 13.9), P = 0.007) in the intervention group. Holyday et al[44] in their study in geriatric patients found that early nutrition intervention can significantly improve LOS (19.5 ± 3 days versus 10.6 ± 1.6 days, P = 0.013). Similarly, Somanchi et al[210] in their study involving older hospitalized patients also found that early nutrition screening and intervention led to a significant reduction in LOS (6.1 ± 5.3 versus 8.7 ± 11.7 days, $P < 0.05$). It is possible that early nutrition intervention negated the catabolic effects of acute illness with a consequent reduction in muscle dysfunction and thus less deconditioning occurred in the intervention patients. This could have led to an early mobilization in intervention patients during their hospital admission, which, in turn, could have facilitated their early discharge from hospital. It is also possible that intervention patients, because of their improved nutrition status, showed a quicker response to treatment (e.g. to antibiotics) than the control patients. Evidence[400 401] shows that an improvement in the nutrition status of hospitalized patients increases their ability to fight infections because of enhanced immunity and improves their respiratory muscle function lowering their risk of acquiring HAP. A meta-analysis[401] in critically ill patients also confirmed that nutrition intervention reduces the risk of nosocomial pneumonia (OR 0.54; 95% CI 0.35 – 0.84, P = 0.007) and decreases the duration of mechanical ventilation (mean 2.25 days; 95% CI 0.5 – 3.9, P = 0.002), with a resultant shortening of ICU and total hospital LOS.

This study found that nutrition intervention led to a modest improvement in HRQoL, which was reflected only in the VAS component of the EuroQol questionnaire (61.2; 95% CI 56.8 – 65.6) versus 52.4; 95% CI 45.2 – 59.7, P = 0.03). Neelmaat et al[233] in their study involving older hospitalized patients also found no significant improvement in HRQoL, determined by the EuroQoL questionnaire, in intervention patients who received protein and energy supplementation for a period of 3 months following discharge. Similarly, Johansen et al[402] in their study involving hospitalized patients (mean age of 62 ± 1.6 years) who received individualized nutrition intervention, found no significant improvement in HRQoL, determined using the SF-

QoL questionnaire, and measured at 28 days of starting nutrition intervention. Evidence suggests that the improvement in HRQoL after acute hospitalization probably reflects the effects of recovery from an acute illness rather than improvement due to the nutrition intervention itself.[196] Moreover, older general medical patients often have an overall poor HRQoL because of multiple comorbidities.[340] It is also possible that the duration of intervention in our and others' studies was too short to produce any discernible differences in HRQoL. Evidence[403] suggests that after starting an intervention the temporal pattern that follows is: first improvement in nutritional parameters (e.g. weight), then muscle function and finally HRQoL.

This study found no difference in the number of complications during hospital admission or mortality (both in-hospital and long-term) in the two groups of patients. Our study findings are in line with a recent systematic review[104] which included 22 RCTs and 3736 acutely hospitalized patients and found that nutrition intervention did not produce any significant reduction in hospital acquired infections (overall 6% vs. 7.6%; OR 0.75, 95% CI 0.50 – 1.11) in intervention and control groups, respectively. Similar to the findings of this meta-analysis,[104] our study also found that nutrition intervention was not associated with any significant improvement in mortality. This could be related to the advanced age of our study participants, who in addition had an element of cachexia due to the presence of multiple comorbidities. Cachexia is known to be less responsive to nutrition intervention.[336] It is also possible that some of the study patients were already in an advanced stage of DRM and nutrition intervention was probably too late in these patients to produce any significant impact. Studies have indicated that treating patients at an early stage of malnutrition is probably more effective than correcting advanced malnutrition.[337]

An economic evaluation was carried out alongside the original clinical trial and included a CEA and a CUA. CEA is a type of economic evaluation whose outcomes are expressed in terms of natural units such as life expectancy or change in nutrition scores, while outcomes in CUA are expressed in terms of costs per quality adjusted life years (QALY).[352] The objective of this evaluation was to determine whether the individualized nutrition intervention was value for money when considered from a healthcare sector (Australian Medicare) perspective. The primary outcome of this evaluation was expressed in terms of incremental costs per unit improvement in the PG-SGA (CEA) and the secondary outcome was reported in terms of incremental costs per QALY gained (CUA). This economic analysis found that the mean per included patient Australian Medicare costs were lower (- AU$907; 95% CI - 4854 – 2956) in the intervention group as compared to the control group. The main drivers of higher costs in the control patients were higher inpatient ($13,882 vs. $13,134) and pharmaceutical costs ($838 vs. $601) as compared to the intervention patients. When adjusted outcomes in the base case were considered, the intervention was found to be more effective with unit improvement in PG-SGA higher by 1.3238 units (95% CI 0.0240 – 2.3858)) and QALYs gained higher by 0.0050 QALY per patient (95% CI - 0.0079 – 0.0199) as compared to control group. The cost effectiveness planes (CEPs) in the base case analysis showed that most of the bootstrapped paired estimates of mean differences in costs and outcomes were in the south-east and south-west quadrants, indicating that the intervention was not only effective but also less costly. The cost effectiveness acceptability curves (CEACs) showed that the probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA scores was above 98% while it was 78% at a willingness to pay $50,000 per QALY gained, which was within the implicit cost-effectiveness thresholds used in Australia.

This study found lower mean Australian Medicare costs in the intervention group when compared to the control group. The cost drivers for the higher mean costs in the control patients were due to higher inpatient and drug costs. The reason for the higher costs in the control patients could have been due to the significantly longer LOS. This could have resulted in higher utilization of heath care resources by the control patients. Studies suggest that malnutrition contributes to the development of new complications (e.g. delirium)[298], predisposes patients to pressure ulcers[362] and increases risk of falls[363], these factors could have been responsible for a longer LOS in control patients. On the other hand, early provision of nutrition intervention may lead to an improved muscle function[364], lesser deconditioning[404], fewer nosocomial infections[401] and may result in faster resolution of delirium[238]. These factors could have facilitated a quicker discharge from hospital in the intervention patients. It is also possible that the extension of the intervention following hospital discharge was associated with a sustained improvement in the nutrition status of the intervention patients with a consequent reduction in the 'post-hospital syndrome'.[296] This may have led to a reduction in the utilization of primary health care resources (e.g. reduced GP visits) with a consequent reduction in overall health-care costs.

The findings of this health economic evaluation are in line with a systematic review[227], which included nine studies and included both medical and surgical inpatients and compared ONS use versus routine care during hospitalization. This systematic review found that the use of ONS during hospitalization was cost-effective (net cost savings per patient £924; 95% CI £63.2 – £1911.9) in patients of different age groups, nutrition status and underlying medical conditions. This review found that the cost savings were associated with an improvement in a range of other clinical outcomes, such as reduced LOS, complications and mortality. Neelemaat et al[233] in their study involving 210 older hospitalized patients, provided a multicomponent nutritional intervention and compared ONS versus usual care for 3 months. This study found that the intervention resulted in no significant extra costs (mean difference €445 (95% CI -2779 – 3939) and was associated with a significant improvement in functional limitations, measured using the Longitudinal Ageing Study Amsterdam (LASA) functional limitations questionnaire (mean difference -0.72; 95% CI -1.15 – -0.28). In this study, the ICER of €618/point improvement in functional limitations showed that the intervention was cost-effective with a probability of 40%.

Our study results are also in line with the study by Zhong et al[369] who in their health economic analysis involving 622 older malnourished patients hospitalized with CHF, AMI, pneumonia and COPD (conducted alongside a multicentre RCT) and used nutrient-dense ONS containing a high concentration of protein and beta-hydroxy-beta-methylbutyrate versus placebo. The intervention resulted in 0.011 QALY gains (using SF-36 questionnaire) over a 90-day follow-up period and was found to be cost-effective at US$34,000 per QALY gained, a value below the benchmark of US$50,000 to US$100,000 per QALY.

The economic benefits of ONS in hospitalized patients has also been shown by a large US study[405] containing information on 44 million adult inpatient episodes over a period of 11 years. This study found ONS supplementation was associated with a shorter LOS (-2.3 days (95% CI -2.42 to -2.16) and episode cost decreased by $4734 (95% CI -$4754 to -$4714).

9.2 Limitations

There are several limitations in the studies included in this thesis. We did not compare clinical outcomes between patients who missed nutrition screening and those who underwent nutrition screening. It is quite possible that patients who missed nutrition screening were already under the care of a dietitian and thus were not screened. We did not measure referrals to the dietitian between the two groups and it is possible that some of the malnourished still got dietetics referral. In clinical practice dietetic referrals do occur by word of mouth at clinical huddles. Finally it is possible that nutrition screening did happen but staff failed to enter this information either into the case-notes or the electronic database. We suggest that future studies should also include the health-staff perspective on nutrition screening, as this may help discover new factors which are still unidentified.

We did not measure the effect of new medications which were started during hospital admission on clinical outcomes. It is possible that polypharmacy could have partly contributed to the adverse clinical outcomes in malnourished patients. Another limitation is that very few cognitively impaired patients were enrolled in these studies due to lack of a valid consent. Studies have identified that patients with dementia are a vulnerable group prone to malnutrition and cognitive impairment is regarded as a strong risk factor for the development of malnutrition.[406 407] This concept gains further significance in light of findings of a recent study which suggest that, among older patients, with mild to moderate Alzheimer's disease, malnutrition is a significant predictor of a rapid cognitive decline (OR 1.61; 95% CI 1.06 – 2.63, P = 0.028).[408] Studies also suggest that malnutrition is associated with sleep disturbances, psychological problems, and immobility and malnutrition increases falls risk in patients with dementia.[409 410]

We did not determine the impact of malnutrition on functional status, an aspect which is of relevance to patients. Functional dependency has been reported to predict nutrition status particularly in older patients.[411] This is important, in that early nutrition intervention may offset impairments in functioning for these patients.[412 413]

This study did not take into account the effect of psychiatric illness with malnutrition, as depression is one of the leading causes of weight loss in older patients.[414] A recent Chinese study suggests that 10% of older patients with depression are malnourished.[415] It is difficult to establish a causal relation between malnutrition and depression. Numerous studies[416-418] have found a correlation between micronutrient deficiency (e.g. vitamin D deficiency) and depression with suggestions that these deficiencies are associated with low levels of neurotransmitters like serotonin[419] which may contribute to depressive symptoms. Thus early correction of micronutrient deficiencies gains significance in older patients who manifest depressive symptoms.

In regards to the validation of MUST against PG-SGA, the results of this study should be taken with caution as there is a potential for selection bias because not many cognitively impaired patients participated in this study. Furthermore, this study validated MUST in a specific population of older patients, and the extrapolation of these results to other populations (e.g. patients admitted under sub-specialty teams, younger patients etc.) should be done cautiously. This study did not compare the predictive validity (e.g. LOS, mortality etc.) of MUST against PG-SGA. It is possible that a number of patients who had subclinical malnutrition escaped diagnosis because micronutrient deficiencies are not into taken into account by the currently available nutrition screening tools including MUST.[420]

Moreover, nutrition screening tools like MUST have been designed primarily to detect undernutrition. Since one component of the MUST is BMI, so patients with a low BMI will get a high nutrition risk score. The accuracy and reliability of MUST when applied to obese patients is likely to be low and application of this tool in obese patients will most likely miss undernutrition.[421] Therefore, in obese patients, a history of recent significant weight loss may be a more accurate measure of nutrition decline. However, further research is needed to verify this hypothesis.

The results of the nutrition intervention study should be taken with caution due to the following limitations. This study did not take into account the acuity of admission diagnosis on the clinical outcomes. It is possible that the severity of admission diagnosis could have affected clinical outcomes like LOS and mortality and hence the impact of nutrition intervention on LOS should be interpreted with caution. This study did not determine the impact of nutrition intervention on functional parameters (e.g.

activities of daily living, gait speed, balance etc.) which are of relevance to patients and determine their independent functioning. Although this study provided an individualized nutrition intervention, it did not take into account the effect of polypharmacy and pharmaceutical reconciliation was not done. Studies[422 423] suggest that polypharmacy reduces nutrient absorption and this could have reduced the beneficial effects of nutrition intervention. As this study included only older general medical patients and not many cognitively impaired patients were involved, so the results are not generalizable to the sub-specialty patients or cognitively impaired patients. Another limitation was failure to recruit non-English speaking and Indigenous Australian patients due to lack of funding for availing ourselves of the services of an interpreter/Indigenous liaison officer. Finally this study did not measure the effects of micronutrient (e.g. vitamin D) supplementation on clinical outcomes as only a few intervention patients received a multi-vitamin supplement.

Although the use of a randomized controlled study design provides a robust evidence for assessing the utility of nutrition intervention, this study had limitations when assessing economic outcomes. This study did not consider several factors, which could bias the results by either underestimating or overestimating the cost-effectiveness of nutritional supplementation. While this study included direct medical costs, broader or indirect costs such as those borne by the patients and their families privately and costs associated with loss of work due to periods of absence for patients or their carers were not considered. The follow-up period of this study was three months only. It can be questioned whether a follow-up period of three months is long enough to find any significant effects on HRQoL and the long term impact of nutrition intervention on costs is unknown. This study did have some missing data in terms of some costs and outcomes, however principled and robust methods were employed to deal with the missing data. The difference in QALY gains in this study can be considered to be small and therefore our results on effectiveness should be interpreted with caution. This study was powered to detect differences in nutrition score as determined by PG-SGA but underpowered to detect cost differences. This is reflected by the wide confidence intervals around the cost differences. This is a common problem in economic evaluations conducted alongside clinical trials. Because of the heavily skewed distribution data, a very large sample size is needed to detect cost differences.[424] Finally, due to differences in design and organization of health-care systems, the results of this study cannot be generalized to other health-care settings and countries.

9.3 Future implications and suggestions for improvement

The results from the present study have identified some barriers which could prevent nutrition screening of hospitalized patients. Some of the factors responsible for missed nutrition screening can be improved by employing a range of strategies which can lead to a culture shift and hence may improve compliance with evidence-based practice. This may include interactive educational sessions highlighting importance of nutritional screening, multi-faceted interventions or decision support models.[425] This will not be possible without organizational support, including a policy directive from the clinical management hierarchy. Nursing managers and clinicians can act as leaders in implementing nutrition screening strategies and an enthusiastic staff member can act as a ‘champion’ who might build enthusiasm of other staff.[426]

Future studies looking into the clinical consequences of malnutrition should take into account the effect on patients' nutrition outcomes of polypharmacy, the functional aspect (e.g. use of the Barthel index) and measures of psychological health (e.g. the Geriatric depression scale), as these three factors are commonly associated with malnutrition. In addition, micronutrient deficiencies (e.g. vitamin D levels) can be measured, because, subclinical micronutrient deficiencies are not taken into account by the currently available nutrition screening tools.[427]

Further studies are needed to confirm the validity of MUST in older medical patients. Future studies should compare not only the face and construct validity but also the predict validity of MUST against the reference standard tools, to determine whether MUST accurately predicts clinical outcomes in general medical patients. There is a need to test MUST in a broad range of general medical patients including cognitively impaired and younger patients.

Future studies can also verify whether using the single parameter of recent significant weight loss accurately predicts risk of malnutrition. If confirmed, then further research can determine whether this parameter alone can be used for nutrition screening because this may obviate the need for anthropometric measures. This may help improve nutrition screening rates in hospitalized patients because evidence suggests that a lack of proper equipment for measuring height and weight is a major obstacle in the performance of nutrition screening.[32]

MUST seems to be a useful screening tool in older hospitalized general medical patients. However, users should always be aware of the limitations of MUST and hence clinical judgment should always play a major role in deciding which patients needs further assessment by a dietitian.

Older patients with multiple comorbidities may have a component of cachexia which may not be responsive to standard nutritional intervention.[336] Recent research[428] in cancer patients suggests that use of increased amounts of high-quality proteins and/ or nutrients aimed at modulating the inflammatory response (e.g. n-3 long-chain polyunsaturated fatty acids (n-3 PUFA)) may be useful in cachexia. Future studies can use high-energy ONS containing high protein levels and n-3 PUFA, to see if this intervention is also beneficial in older patients. Use of these agents in cancer patients on chemotherapy has led to a greater improvement in body weight and muscle mass compared to a standard ONS/diet[428 429] but whether they can be beneficial in older patients needs verification.

The duration of nutrition intervention required to produce a beneficial effect on HRQoL is not clear at this stage and future studies can be extended further (e.g. six months) to see the effects of nutrition intervention on HRQoL. The effect of nutrition intervention on the psychological health of older hospitalized patients is unclear[430] and future studies can employ tools like the GDS to verify the effects of nutrition intervention. Finally very few studies have determined whether exercise provides additional improvements to muscle strength alongside nutritional support in nutritionally vulnerable older adults. Future research involving a multimodal strategy of exercise and nutritional supplementation in older, frail malnourished patients can answer this question.

Future nutrition intervention studies should extend for a longer duration (e.g. six months) to see whether economic benefits are sustained. There is a need for future studies to test the cost-effectiveness of nutrition intervention in a broad range of general medical patients (e.g. younger patients and patients with cognitive impairment). Use of protein and energy supplementation in older patients with or at risk of malnutrition presents an opportunity for health care services to reduce hospitalization costs for a relatively small additional investment. However, there is a paucity of health economic evaluations in the Australian health care settings.[115] Further high quality comprehensive economic evaluations along side clinical effectiveness trials are needed to demonstrate the cost-effectiveness of nutrition interventions for the treatment of malnutrition. Demonstration of the clinical and economic benefits of treating hospital malnutrition may convince the clinicians and hence improve the uptake of evidence-based guidelines into clinical practice. These studies will also be of help to the policy makers to decide the allocation of resources in current times of economic constraints.

9.4 Conclusion

There is no denying the fact that malnutrition is widely prevalent in hospitalized patients leading to adverse outcomes for the patients and proves costly for the hospitals. This thesis has confirmed a high prevalence rate of malnutrition in older general medical patients and found that a significant proportion of these patients missed nutrition screening during their hospital stay. Factors which influenced nutrition screening were identified and this research verified that malnourished general medical patients have poor clinical outcomes. Malnutrition was also identified as a significant predictor of unplanned readmissions and mortality in the post-discharge period. Furthermore, this study found that an individualized nutrition intervention, when initiated early during hospital admission and extending into the community following discharge, was beneficial for these patients. An economic evaluation proved that the nutrition intervention was a cost-effective strategy in these patients.

There is a need for a consistent effort on the part of health care professionals to target hospital malnutrition. Further studies involving patients of different age groups and from different sub-specialities are needed to confirm the beneficial effects of nutrition intervention. These studies may convince policy makers to allocate resources to improve the nutrition status of hospitalized patients and quality of care.

APPENDICES

APPENDIX 1.1: AUTHOR CONTRIBUTIONS

This chapter is a co-authored publication.

Sharma Y, Miller M, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition screening in acutely unwell elderly patients. *British Journal of Nursing*.2016;25(18):1006-1014.

YS contributed to the design of the study and was involved in collection, analysis, interpretation of data in addition to preparing and editing the manuscript to its final form. MM and CT helped in design of study, interpretation of data and review of literature. RS was involved in data collection. PH and CH extracted data and provided statistical input.

Malnutrition screening in acutely unwell elderly inpatients

Yogesh Sharma, Michelle Miller, Rashmi Shahi, Paul Hakendorf, Chris Horwood and Campbell Thompson

ABSTRACT

Background: The rate of malnutrition among hospitalised elderly patients in Australia is 42.3%. Malnutrition is known to lead to significant adverse outcomes for the patients and increase hospital costs through increased use of resources. Aim: This study assessed nutrition screening adequacy and investigated factors associated with missed opportunity to diagnose malnutrition. Methods: A prospective cross-sectional study involving 205 general medical patients aged ≥60 years admitted acutely in a tertiary hospital over a period of 1 year. Patients who were not given initial nutritional screening were noted and all patients underwent nutritional assessment. The researchers assessed demographic data and performed univariate analysis of factors responsible for missed nutritional screening. Results: Only 99 patients (49.5%) were screened for malnutrition and 100 (50.3%) missed initial nutritional screening (data incomplete for 6 patients). Of those screened, more were malnourished (n=64; 61.5%) than those not screened (n=40; 38.5%), $p<0.001$. There was no significant difference in screening rates over the weekends and public holidays compared with weekdays ($p=0.14$). Time of day ($p=0.03$) and ward location ($p=0.001$) were significant factors, which determined nutrition screening. Conclusion: This study indicates common associations that might explain low inpatient screening rates for malnutrition; these include apparently adequate nutritional status, lower staff to patient ratios and outlier ward locations. Ensuring consistent nutrition screening with appropriate therapeutic interventions for patients and educational interventions for staff could pay dividends not only in terms of improved patient health but also in terms of hospital reimbursement.

Key words: Malnutrition ■ Nutrition screening ■ Elderly patients

Yogesh Sharma, Consultant Physician, Department of General Medicine, Flinders Medical Centre, South Australia and Senior Lecturer, School of Medicine, Flinders University, South Australia

Michelle Miller, Professor, Nutrition & Dietetics Department, Flinders University, South Australia

Rashmi Shahi, Lecturer, Faculty of Medicine, Nursing & Health Sciences, Monash University, Melbourne, Australia

Paul Hakendorf, Clinical Epidemiologist, Department of Clinical Epidemiology, Flinders Medical Centre, South Australia

Chris Horwood, Clinical Epidemiologist, Department of Clinical Epidemiology, Flinders Medical Centre, South Australia

Campbell Thompson, Professor of Medicine, Discipline of Medicine, University of Adelaide, South Australia

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Malnutrition is defined as a state of nutrient insufficiency, as a result of inadequate nutrient intake or inability to absorb or use ingested nutrients (Hoffer, 2001). Malnutrition is widely prevalent in hospitalised patients with reported worldwide prevalence rates of 13-78% (Kubrak and Jensen, 2007) depending on the setting and whether medical or surgical inpatients—one study in Australia found that overall 42.3% of all inpatients were malnourished (Lazarus and Hamlyn, 2005), while 28% of adults were found to be malnourished at admission in the UK (Russell and Elia, 2010). Prevalence of malnutrition is even higher in the elderly population as many changes associated with ageing, for example, decrease in taste acuity and smell, deteriorating dental health and decline in physical activity, may affect nutrient intake and make this group more prone to malnutrition (Landi et al, 1999; Corish and Kennedy, 2000). Malnutrition increases the risk of infections owing to impaired immune response, predisposes patients to pressure ulcers, impairs wound healing, increases risks of falls and is associated with high mortality (Baldwin and Parsons, 2004; Reid, 2004; Rosenthal, 2004). Complications associated with malnutrition lead to an increased length of hospital stay with consequent increased use of healthcare resources and also lead to frequent readmissions and increased risk of residential care placement; all with significant increases in healthcare costs (Raja et al, 2004; Mudge et al, 2011).

In 1974, Butterworth described malnutrition as a 'skeleton in the hospital closet' as it often goes undiagnosed and untreated (Butterworth, 1974). The diagnosis of malnutrition is often missed in hospitals owing to a number of factors including a lack of knowledge of malnutrition among health professionals and busy clinical settings with increasing emphasis on discharging patients home early (Adams et al, 2008). Eide et al (2015) found that there is a lack of clarity whether nutritional screening is the responsibility of the treating clinician or nurses, and a lack of understanding among health professionals of the various screening tools available further compounds the problem (Gout et al, 2009). Given the high prevalence of malnutrition in hospitalised patients and a possibility that even patients with a normal body mass index (BMI) can still be malnourished (Kyle et al, 2003) the American Society for Parenteral and Enteral Nutrition (Mueller et al, 2011) has recommended screening all patients presenting to the hospital for malnutrition by using a valid screening tool such as the Malnutrition Universal Screening Tool (MUST) (British Association for Parenteral and

APPENDIX 1.2: AUTHOR CONTRIBUTIONS

This chapter is a co-authored publication.

Sharma Y, Thompson C, Shahi R, Hakendorf P, Miller M. Malnutrition in acutely unwell hospitalized patients – 'The skeletons are still rattling in the hospital closet". *The Journal of Nutrition Health and Ageing*. 2017;21(10):1210-1215. doi: 10.1007/s12603-017-09

YS contributed to the study design, data collection, statistical analysis, data interpretation and wrote the manuscript. RS was involved in data collection and interpretation. PH provided statistical input. CT and MM were involved in study design, data interpretation and critically reviewed the manuscript.

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MALNUTRITION IN ACUTELY UNWELL HOSPITALIZED ELDERLY - "THE SKELETONS ARE STILL RATTLING IN THE HOSPITAL CLOSET"

Y. SHARMA[1,2], C. THOMPSON[3], R. SHAHI[4], P. HAKENDORF[5], M. MILLER[6]

1. Department of General Medicine, Flinders Medical Centre, Adelaide, South Australia; 2. School of Medicine, Flinders University, Adelaide, South Australia; 3. Discipline of Medicine, University of Adelaide, South Australia; 4. Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia; 5. Department of Clinical Epidemiology, Flinders Medical Centre, Adelaide, South Australia; 6. Department of Nutrition and Dietetics, Flinders University, Adelaide, South Australia. Corresponding author: Michelle Miller, Flinders University, Australia, michelle.miller@flinders.edu.au

Abstract: *Introduction:* Malnutrition is common in hospitalized patients with prevalence rates of up to 30% in Australian hospitals with adverse consequences for both the patients and health care services. Despite formulation of nutritional screening protocols, not all hospitalized patients get nutritional screening. Real life screening rates of hospitalized elderly patients are unknown. *Aim*: The present study explored nutrition screening rate in acutely unwell elderly patients admitted in a large tertiary hospital and how these patients fared depending upon their nutrition status. *Methods*: A prospective cross-sectional study involving 205 general medical patients ≥60years recruited between November 2014 and November 2015. The number of patients who missed nutrition screening were noted and all patients underwent nutritional assessment by a qualified dietitian using PG-SGA and quality of life was measured using EQ-5D 5L. A survival curve was plotted and multivariate cox proportional hazard model was used to adjust for confounders. *Results*: Only 99 (49.7%) patients underwent nutritional screening. One hundred and six (53.5%) patients were confirmed as malnourished by PG-SGA. Malnourished patients had significantly longer length of hospital stay and had worse quality of life. Mortality was significantly higher in malnourished patients at one year (23 (21.7%) vs 4 (4.3%); $p<0.001$) and cox proportional hazard model suggests that malnutrition significantly affects survival even after adjustment for confounders like age, sex, Charlson index and polypharmacy. *Conclusion:* This study confirms that nutrition screening is still suboptimal in elderly hospitalized patients with adverse consequences and suggests need for review of policies to improve screening practices.

Key words: Malnutrition, hospitalized elderly, nutrition screening.

Introduction

Malnutrition is defined as a state of nutrient insufficiency, as a result of inadequate nutrient intake or inability to absorb or use ingested nutrients (1, 2). Malnutrition is widely prevalent in hospitalized patients with reported worldwide prevalence rates of 13-78% depending upon the type of setting (3). In Australia, a retrospective analysis from two hospitals in New South Wales, found that 30% of patients were malnourished and 53% of patients were at risk of malnutrition (4). Malnutrition is associated with adverse clinical outcomes, as it increases risk of infections due to impaired immune response, predisposes patients to pressure ulcers, impairs wound healing, increases risks of falls and is associated with high mortality (5-8). Malnutrition is also detrimental to health care services as it is associated with increased length of hospital stay, increased utilization of health care resources, frequent readmissions and increased risk of placement with consequent increase in costs (9-12).

Malnutrition is often described as a skeleton in the hospital closet as it often goes under diagnosed and under treated (13). Diagnosis of malnutrition is often missed in hospitals due to a number of factors including low awareness of malnutrition, busy clinical settings with increasing emphasis on discharging patients home early, lack of clarity as to whether nutritional screening is a responsibility of the treating clinician or nurses and lack of understanding of the various available screening tools (14). Historically, diagnosis of malnutrition is made by the examining clinician based on the history of weight loss and clinical examination but given the high prevalence of malnutrition in hospitalized patients and a possibility that even patients with a normal or high BMI (15) can still be malnourished or at high risk of malnutrition, experts have now recommended screening all patients presenting to the hospital, for malnutrition by using a valid screening tool like the Malnutrition Universal Screening tool (MUST) and then if the screening is positive to confirm by a reference assessment tool like the Patient generated subjective global assessment tool (PG-SGA).

MUST has been validated in a number of clinical settings and is commonly used in hospitals to screen patients for risk of malnutrition. The MUST includes a Body Mass Index (BMI) score, a weight loss score, and an acute disease score. The MUST is designed to identify need for nutritional treatment as well as establishing nutritional risk on the basis of knowledge about the association between impaired nutritional status and impaired function (16-18). It has been documented to have a high degree of reliability (low inter-observer variation) with a k=0.88-1.00 (19). Subjective Global assessment (SGA) is a method of nutritional assessment based on a medical history and physical examination, whereby each patient is classified as well nourished (SGA A) or suspected of being malnourished

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APPENDIX 1.3: AUTHOR CONTRIBUTIONS

This chapter is a co-authored publication.

Sharma Y, Miller M, Kaambwa B, Shahi R, Hakendorf P, Horwood C, Thompson C. Malnutrition and its association with readmission and death within 7 days and 8-180 days postdischarge in older patients: a prospective observational study. *BMJ Open*. 2017;7(11):e018443. doi: 10.1136/bmjopen-2017-018443.

YS was involved in study design, recruitment, statistical analysis, data interpretation and wrote the manuscript. MM, BK, RS and CT were involved in study design and analysis. PH and CH provided statistical input. YS, MM, BK and CT critically reviewed final manuscript before submission

Open Access Research

BMJ Open

Malnutrition and its association with readmission and death within 7 days and 8–180 days postdischarge in older patients: a prospective observational study

Yogesh Sharma,[1,2] Michelle Miller,[3] Billingsley Kaambwa,[4] Rashmi Shahi,[5] Paul Hakendorf,[6] Chris Horwood,[6] Campbell Thompson[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Yogesh Sharma;
Yogesh.Sharma@sa.gov.au

ABSTRACT

Objective The relationship between admission nutritional status and clinical outcomes following hospital discharge is not well established. This study investigated whether older patients' nutritional status at admission predicts unplanned readmission or death in the very early or late periods following hospital discharge.

Design, setting and participants The study prospectively recruited 297 patients ≥60 years old who were presenting to the General Medicine Department of a tertiary care hospital in Australia. Nutritional status was assessed at admission by using the Patient-Generated Subjective Global Assessment (PG-SGA) tool, and patients were classified as either nourished (PG-SGA class A) or malnourished (PG-SGA classes B and C). A multivariate logistic regression model was used to adjust for other covariates known to influence clinical outcomes and to determine whether malnutrition is a predictor for early (0–7 days) or late (8–180 days) readmission or death following discharge.

Outcome measures The impact of nutritional status was measured on a combined endpoint of any readmission or death within 0–7 days and between 8 and 180 days following hospital discharge.

Results Within 7 days following discharge, 29 (10.5%) patients had an unplanned readmission or death whereas an additional 124 (50.0%) patients reached this combined endpoint within 8–180 days postdischarge. Malnutrition was associated with a significantly higher risk of combined endpoint of readmissions or death both within 7 days (OR 4.57, 95% CI 1.69 to 12.37, P<0.001) and within 8–180 days (OR 1.98, 95% CI 1.19 to 3.28, P=0.007) following discharge and this risk remained significant even after adjustment for other covariates.

Conclusions Malnutrition in older patients at the time of hospital admission is a significant predictor of readmission or death both in the very early and in the late periods following hospital discharge. Nutritional state should be included in future risk prediction models.

Trial registration number ACTRN No. 12614000833662; Post-results.

Strengths and limitations of this study

- The research was a large prospective observational study evaluating the association between nutritional status and readmission or death in medical inpatients ≥60 years old.
- A dietitian used a comprehensive and valid nutritional assessment tool to confirm the malnutrition diagnosis.
- Readmissions presenting to all other hospitals were captured.
- The single-centre study included only older medical patients.

INTRODUCTION

Recent decades have witnessed a vast improvement in life expectancy, leading to an increasing number of older patients with multiple chronic problems. While the number of beds for acute patients has declined, unplanned hospital admissions have increased, particularly among the elderly.[1] Older patients with multiple comorbid illnesses experience poor clinical outcomes after hospital discharge, including recurrent unplanned readmissions and mortality.[2] Adverse outcomes following discharge may be indicative of unresolved acute illness, ongoing chronic illness and the development of new medical problems or gaps in outpatient care.[3–5] Although adverse outcomes following discharge are not totally preventable, studies suggest that targeted intervention such as improved discharge planning with a focus on transitional care services may provide beneficial results.[6]

The likelihood of an unplanned admission is highest in the immediate postdischarge period.[7] There may be advantages in predicting readmissions that occur shortly after discharge. However, most studies have only assessed readmission patterns within 30 days of discharge, and few studies have

APPENDIX 1.4: AUTHOR CONTRIBUTIONS

This chapter is a co-authored publication.

Sharma Y, Thompson C , Kaambwa B, Shahi R, Miller M. Validity of the Malnutrition Universal Screening Tool in Australian hospitalized acutely unwell patients. *Asia Pacific Journal of Clinical Nutrition.* 2017;26:994-1000. doi: 10.6133/apjcn.022017.15.

YS was involved in study design, recruitment, statistical analysis, data interpretation and wrote the manuscript. MM, BK, RS and CT were involved in study design and analysis. YS, MM, BK and CT critically reviewed final manuscript before submission

Original Article

Validity of the Malnutrition Universal Screening Tool (MUST) in Australian hospitalized acutely unwell elderly patients

Yogesh Sharma FRACP[1,2], Campbell Thompson FRACP[3], Billingsley Kaambwa PhD[4], Rashmi Shahi PhD[5], Michelle Miller PhD[6]

[1]*Department of General Medicine, Flinders Medical Centre, Flinders Drive, Bedford Park, SA, Australia*
[2]*School of Medicine, Flinders University, Adelaide, SA, Australia*
[3]*School of Medicine, The University of Adelaide, SA, Australia*
[4]*Health Economics Unit, Repatriation General Hospital, Daw Park, SA, Australia*
[5]*Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia*
[6]*Nutrition and Dietetics Department, Flinders University, Adelaide, SA, Australia*

Background and Objectives: This study validated the Malnutrition Universal Screening Tool (MUST) for nutritional screening in acutely unwell elderly patients against a reference assessment tool – Patient-Generated Subjective Global Assessment (PG-SGA). **Methods and Study Design:** One hundred and thirty two acutely admitted general medical patients contributed data for this study. In addition to performance of MUST and PG-SGA the following nutritional parameters were measured: weight loss >5% in previous 3-6 months, handgrip strength, triceps skinfold thickness, Mid-arm circumference, Mid-arm muscle circumference (MAMC). Quality of life (QoL) was determined using the EuroQoL Questionnaire (EQ-5D 5 level). Sensitivity, specificity, predictive values and concordance were calculated to validate MUST against PG-SGA. **Results:** MUST when compared to PG-SGA gave a sensitivity of 69.7%, specificity of 75.8%, positive predictive value of 75.4%, negative predictive value of 70.1% and kappa statistics showed 72.7% agreement (k=0.49) for detecting malnutrition. The MUST score had significant inverse correlation with body mass index, Triceps skinfold thickness and Mid-arm muscle circumference but not with Handgrip strength. Malnourished patients (PG-SGA class B/C) were found to have a significantly worse QoL. **Conclusions:** This study demonstrates that MUST can be confidently administered with respect to validity in acutely unwell general medical elderly patients to detect malnutrition. In this study, significant recent weight loss also seems to have validity, almost comparable to MUST, for predicting the risk of malnutrition. Further research is needed to verify this finding, as a single item may be more feasible to complete than an instrument consisting of two or more items.

Key Words: PG-SGA, EQ-5D, hospital length of stay, weight loss, anthropometric measures

INTRODUCTION

Malnutrition is common in the elderly population and its prevalence depends upon the setting, ranging from 10-30% in the community, to as high as 70% in the acute care setting.[1] Diagnosis of malnutrition is often missed in hospitalized patients due to a number of factors, including lack of awareness among medical and nursing staff, low priority given other medical conditions, a lack of understanding of available screening tools and also time-poor clinicians in busy acute care settings.[2] Further to this, factors such as cognitive impairment, the number of comorbidities and altered taste sensation make elderly patients an even more vulnerable group.[3,4]

It is well established that malnutrition is associated with adverse clinical outcomes, including increased length of hospital stay, increased complications during hospitalization, increased risk of infections, accidental falls and high morbidity and mortality.[5-8] Given the high prevalence of malnutrition in hospitalized patients, experts have recommended screening all patients for malnutrition by using a valid nutrition screening tool. If the patient is found to be at risk of malnutrition, practitioners must confirm with a more extensive nutritional assessment tool such as the Patient Generated Subjective Global Assessment tool (PG-SGA), and then initiate an individualized nutrition care plan.[9] The PG-SGA is a version of Subjective Global Assessment (SGA) designed for the nutritional assessment of oncology patients and is dependent on infor-

Corresponding Author: Prof Michelle Miller, Nutrition and Dietetics, School of Health Sciences, Flinders University, GPO Box 2100, Adelaide, SA, 5001, Australia.
Tel/Fax: +61 8 8204 6406 / +61 8 7221 8845
Email: michelle.miller@flinders.edu.au;
nutrition.dietetics@flinders.edu.au
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APPENDIX 1.5: AUTHOR CONTRIBUTIONS

This chapter is a co-authored publication.

Sharma Y, Thompson C, Kaambwa B, Shahi R, Hakendorf P, Miller M. Investigation of the benefits of early nutrition screening with telehealth follow up in elderly acute medical admissions. *Quarterly Journal of Medicine*. 2017;110(10):639-647. doi: 10.1093/qjmed/hcx095.

YS was involved in study design, recruitment, statistical analysis, data interpretation and wrote the manuscript. MM, BK, RS and CT were involved in study design and analysis. PH provided statistical input. YS, MM, BK and CT critically reviewed final manuscript before submission

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Original Paper

ORIGINAL PAPER

Investigation of the benefits of early malnutrition screening with telehealth follow up in elderly acute medical admissions

Y. Sharma[1], C. H. Thompson[2], B. Kaambwa[3], R. Shahi[4], P. Hakendorf[5] and M. Miller[6]

From the [1]Department of General Medicine, Flinders Medical Centre, South Australia, School of Medicine, Flinders University, Adelaide, South Australia 5042, [2]Discipline of Medicine, University of Adelaide, Adelaide, South Australia 5005, [3]Department of Health Economics, Flinders University, Adelaide, South Australia 5042, [4]Faculty of Medicine, Health and Nursing, Monash University, Melbourne, Australia 3800, [5]Department of Clinical Epidemiology, Flinders Medical Centre, Adelaide, South Australia 5042 and [6]Department of Nutrition & Dietetics, Flinders University, Adelaide, South Australia 5042

Address correspondence to Dr Y. Sharma, Department of General Medicine, Flinders Medical Centre and School of Medicine, Flinders University, Flinders Drive, Bedford Park, Adelaide, South Australia 5042. email: Yogesh.Sharma@sa.gov.au

Summary

Background: The benefit of providing early nutrition intervention and its continuation post-discharge in older hospitalized patients is unclear. This study examined efficacy of such an intervention in older patients discharged from acute care.
Methods: In this randomized controlled trial, 148 malnourished patients were randomized to receive either a nutrition intervention for 3 months or usual care. Intervention included an individualized nutrition care plan plus monthly post-discharge telehealth follow-up whereas control patients received intervention only upon referral by their treating clinicians. Nutrition status was determined by the Patient Generated Subjective Global Assessment (PG-SGA) tool. Clinical outcomes included changes in length of hospital stay, complications during hospitalization, Quality of life (QoL), mortality and re-admission rate.
Results: Fifty-four males and 94 females (mean age, 81.8 years) were included. Both groups significantly improved PG-SGA scores from baseline. There was no between-group differences in the change in PG-SGA scores and final PG-SGA scores were similar at 3 months 6.9 (95% CI 5.6–8.3) vs. 5.8 (95% CI 4.8–6.9) ($P = 0.09$), in control and intervention groups, respectively. Median total length of hospital stay was 6 days shorter in the intervention group (11.4 (IQR 16.6) vs. 5.4 (IQR 8.1) ($P = 0.01$). There was no significant difference in complication rate during hospitalization, QoL and mortality at 3-months or readmission rate at 1, 3 or 6 months following hospital discharge.
Conclusion: In older malnourished inpatients, an early and extended nutrition intervention showed a trend towards improved nutrition status and significantly reduced length of hospital stay.

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APPENDIX 1.6: AUTHOR CONTRIBUTIONS

This chapter is a co-authored publication.

Sharma Y, Thompson C, Miller M, Shahi R, Hakendorf P, Horwood C, Kaambwa B. Economic evaluation of an extended nutritional intervention in older Australian hospitalized patients: a randomized controlled trial. *BMC Geriatrics* 2018. 18:41. doi: 10.1186/s12877-018-0736-0.

YS was involved in study design, data collection, statistical analysis, data interpretation and wrote the manuscript. MM, CT and BK were involved in study design and data interpretation. BK was involved in economic analysis. RS was involved in data collection and analysis. PH and CH provided statistical input. YS, BK, CT and MM critically reviewed manuscript for final submission.

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BMC Geriatrics

RESEARCH ARTICLE Open Access

Economic evaluation of an extended nutritional intervention in older Australian hospitalized patients: a randomized controlled trial

Yogesh Sharma[1,2*], Campbell Thompson[3], Michelle Miller[4], Rashmi Shahi[5], Paul Hakendorf[6], Chris Horwood[6] and Billingsley Kaambwa[7]

Abstract

Background: Prevalence of malnutrition in older hospitalized patients is 30%. Malnutrition is associated with poor clinical outcomes in terms of high morbidity and mortality and is costly for hospitals. Extended nutrition interventions improve clinical outcomes but limited studies have investigated whether these interventions are cost-effective.

Methods: In this randomized controlled trial, 148 malnourished general medical patients ≥60 years were recruited and randomized to receive either an extended nutritional intervention or usual care. Nutrition intervention was individualized and started with 24 h of admission and was continued for 3 months post-discharge with a monthly telephone call whereas control patients received usual care. Nutrition status was confirmed by Patient generated subjective global assessment (PG-SGA) and health-related quality of life (HRQoL) was measured using EuroQoL 5D (EQ-5D-5 L) questionnaire at admission and at 3-months follow-up. A cost-effectiveness analysis was conducted for the primary outcome (incremental costs per unit improvement in PG-SGA) while a cost-utility analysis (CUA) was undertaken for the secondary outcome (incremental costs per quality adjusted life year (QALY) gained).

Results: Nutrition status and HRQoL improved in intervention patients. Mean per included patient Australian Medicare costs were lower in intervention group compared to control arm (by $907) but these differences were not statistically significant (95% CI: -$2956 to $4854). The main drivers of higher costs in the control group were higher inpatient ($13,882 versus $13,134) and drug ($838 versus $601) costs. After adjusting outcomes for baseline differences and repeated measures, the intervention was more effective than the control with patients in this arm reporting QALYs gained that were higher by 0.0050 QALYs gained per patient (95% CI: -0.0079 to 0.0199). The probability of the intervention being cost-effective at willingness to pay values as low as $1000 per unit improvement in PG-SGA was > 98% while it was 78% at a willingness to pay $50,000 per QALY gained.

Conclusion: This health economic analysis suggests that the use of extended nutritional intervention in older general medical patients is likely to be cost-effective in the Australian health care setting in terms of both primary and secondary outcomes.

Trial registration: ACTRN No. 12614000833662. Registered 6 August 2014.

Keywords: Malnutrition, Economic evaluation, Health related quality of life, Quality adjusted life years, Older patients

* Correspondence: Yogesh.Sharma@sa.gov.au
[1]Department of General Medicine, Flinders Medical Centre, Adelaide, South Australia, Australia
[2]College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia
Full list of author information is available at the end of the article

APPENDIX 1.7: LIST OF PUBLICATIONS ARISING FROM THIS CANDIDATURE

Peer Reviewed Journal Articles:

Sharma Y, Miller M, Shahi R, Hakendorf, P, Horwood C, Thompson, C. Malnutrition screening in acutely unwell elderly inpatients. *Br J Nurs.* 2016;25(18)**:**1006-1014.

Sharma Y, Thompson C, Shahi R, Hakendorf P, Miller M. Malnutrition in acutely unwell hospitalized elderly – “The skeletons are still rattling in the hospital closet”. *J Nutr. 2017*;1-6. doi:10.1007/s12603-017-0903-6.

Sharma Y, Thompson C, Kaambwa B, Shahi R, Miller M. Validity of the Malnutrition Universal Screening Tool in Australian hospitalized acutely unwell elderly patients. *Asia Pac J Clin Nutr.* 2017;26:994-1000. doi: 10.6133/apjcn.022017.15.

Sharma Y, Thompson C, Kaambwa B, Shahi R, Hakendorf P, Miller M. Investigation of the benefits of early malnutrition screening with telehealth follow up in elderly acute medical admissions. *QJM –an International Journal of Medicine* 2017.110(10):639-647. doi: 10.1093/qjmed/hcx095.

Sharma Y, Miller M, Kaambwa B, Shahi R, Hakendorf, P, Horwood, C, Thompson C. Malnutrition and its association with readmission and death within 7 days and within 8 to 180 days post-discharge in older patients: a prospective observational study. *BMJ open* 2017.7(11):e018443. doi: 10.1136/bmjopen-2017-018443.

Sharma Y, Thompson C, Miller M, Shahi R, Hakendorf P, Horwood, C, Kaambwa B. Economic evaluation of an extended nutritional intervention in older Australian hospitalized patients: a randomized controlled trial. *BMC Geriatrics.* 2018;18:41. doi: 10.1186/s12877-018-0736-0.

Miller M, Thomas J, Suen, J, De Sheng O, **Sharma Y**. Evaluating photographs as a replacement for the in-person physical examination of the scored Patient-Generated Subjective Global Assessment in elderly hospital patients. *J Acad Nutr Diet.* 2018;118(5):896-903. doi: 10.1016/j.jand.2017.10.010.

APPENDIX 1.8: LIST OF CONFERENCE PRESENTATIONS ARISING FROM THIS CANDIDATURE

1. **Sharma Y**. Malnutrition Screening in General Medicine - Findings from the FMC malnutrition study. Paper presented at: *South Australian Association of Internal Medicine (SAAIM) Workshop.* Adelaide, Australia. 6th April 2016.

2. **Sharma Y**. Extended Nutrition intervention in older malnourished patients discharged from acute care- results of a randomized clinical trial. Paper presented at: *South Australian Association of Internal Medicine (SAAIM) Workshop.* Adelaide, Australia. 6th April 2017.

3. **Sharma Y.** Malnutrition in older patients discharged from acute care-does intervention really matters? Paper presented at *Flinders Health Research Week. Adelaide, Australia.*4-8 September 2017.

4. **Sharma Y.** Investigation into the Clinical benefits of early nutrition screening with telehealth follow up in older patients discharged from acute care- results of a randomized controlled trial. Paper presented at *IMSANZ17-Internal Medical Society of Australia and New Zealand Annual Scientific Meeting*. Hobart, Australia. 14-16 September 2017.

5. **Sharma Y**, Thompson C, Kaambwa B, Shahi R, Hakendorf P, Horwood C, Roberts S, Miller M. Validity of Malnutrition Universal Screening Tool against a reference standard in acutely unwell older General Medical patients. Poster session presented at: *IMSANZ17 Internal Medical Society of Australia and New Zealand Annual Scientific Meeting.* Hobart, Australia 14-16 September 2017.

6. **Sharma Y,** Thompson C, Kaambwa B, Shahi R, Roberts S, Miller M.
Clinical Benefits of early and extended nutritional intervention in older patients discharged from acute care- A Randomized Clinical Trial. Poster session presented at *AuSPEN Collaboration in Clinical Nutrition 'Evidence-based nutrition for improving patient outcomes'*. Gold Coast, Australia. 16-18 November 2017.

7. **Sharma Y**. Admission Nutritional status as a predictor of Post-discharge Clinical outcomes in older hospitalized patients-A prospective observational study. Paper presented at: *IMSANZ18-Transitioning through diversity.* Tauranga, New Zealand. 7-9 March 2018.

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