In critically ill patients, should nutrition support prescription be individualised to their mortality risk and nutritional status?

by

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Thesis summary

Optimising nutritional status is traditionally associated with aggressive nutrition support designed to provide higher energy and protein intakes. However, in the critical care arena, this issue has become controversial. While several studies demonstrated that higher intakes resulted in lower mortality and infection risk, others showed otherwise. In an effort to identify patients who would derive the most benefit from higher energy and protein intakes, a systematic approach was undertaken with the aim of developing a prognostic model, namely the Global Index of Mortality Probability in the Severely ill (GLIMPSE). This work hypothesized that the integration of key factors such as baseline nutritional status and disease severity could better: 1) prognosticate mortality, and 2) identify patients who would derive the most benefit from aggressive nutrition support in the critical care setting.

To identify nutrition assessment tools that have good prognostic validity for worsened clinical outcomes in critically ill patients, two systematic reviews and an original study were conducted. The first systematic review [1] coupled with an original study [2] concluded that the 7-point Subjective Global Assessment (7-point SGA) has good prognostic validity but that this was not the case for the thickness of the adductor pollicis muscle [3].

To identify tools that quantify disease severity, two original studies were conducted. The first study concluded that the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) has limited prognostic accuracy and that more predictors are required to improve performance [4]. The second study showed that the modified Nutrition Risk in Critically Ill score (mNUTRIC) is a valid disease severity score with consistent and robust mortality prognostic value [5].

The above key findings led to the development of GLIMPSE, in which baseline nutritional status (measured by the 7-point SGA) and disease severity (measured by mNUTRIC) were integrated into a logistic model, and a robust validation study demonstrated that GLIMPSE has good discrimination and calibration accuracy for 28-day mortality.

However, GLIMPSE was unable to identify patients who would benefit from aggressive nutrition support as high-energy and protein intakes are positive and inversely associated with 28-day mortality in patients with identical mortality risk. In other words, in malnourished and severely ill patients, aggressive nutrition support was associated with higher mortality risk in some patients whereas the converse was observed in others, and GLIMPSE was unable to differentiate between them.

A review of recent evidence suggests that energy and protein metabolism during the early phase of critical illness differ across patients, and this determines how aggressive nutrition support can affect clinical outcomes. Some literature also claims that aggressive nutrition support provided at the later phase of critical illness may be more effective. Taken together, in critically ill patients with high mortality risk, it appears that it is not so much "who" requires aggressive nutrition support as "when" it should be provided.

In conclusion, it takes more than baseline nutritional status and disease severity to determine energy and protein needs in the early phase of critical illness. More work is needed to elucidate the complex interactions between metabolic processes during the early phase of critical illness so that individualised nutrition therapy can be provided in order to bring about the best clinical outcomes.

Declaration

I certify that this thesis 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 and belief, it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed: ……

Date: 11th July 2019 ……

Acknowledgement

My dream since 2006 materialised this year with the completion of this thesis. It has been a rollercoaster ride over five years, with many ups and downs. This thesis and associated publications are the result of hard work, long hours, and a passion for improving patient care. Being an external PhD student, there were spells of solitude, but I have been truly blessed to have had constant reminders from family and friends to focus on the greater goal ahead. As this ride comes to a conclusion, I can truly say it has been an enthralling journey, which has enriched my life as a researcher. I would like to take the opportunity to thank all those who made this possible.

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All generous giving and every perfect gift is from above,
coming down from the Father of lights,
with whom there is no variation or the slightest hint of change.
James 1:17

Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II

ARDS: Acute Respiratory Distress Syndrome

ASPEN: American Society of Parenteral and Enteral Nutrition

ENS: Exclusive Nutrition Support

ESPEN: European Society of Parenteral and Enteral Nutrition

GLIMPSE: Global Index of Mortality Probability in the Severely Ill

HD: High Dependency

ICU: Intensive Care Unit

mNUTRIC: Modified Nutrition Risk in Critically Ill

NRS-2002: Nutrition Risk Screening – 2002

NTIS: Non-Thyroidal Illness Syndrome

SGA: Subjective Global Assessment

SOFA: Sequential Organ Failure Assessment

Overview of the thesis structure

This thesis consists of eight chapters, seven of which contain material already published, and one ready to be submitted to an internationally-refereed journal (Table 1). The final chapter outlines the original contribution to knowledge, discusses the strengths and limitations of the thesis, and proposes future directions for research.

Chapter One explains the basis for including baseline nutritional status in the prognostication of poor clinical outcomes in critically ill patients. This was achieved via a systematic review that established the prevalence of malnutrition in intensive care units (ICU) and identified nutrition assessment tools that have good prognostic validity for poor clinical outcomes in the critically ill.

Chapter Two explores the possibility of including a surrogate nutrition assessment tool (i.e., thickness of the adductor pollicis muscle) to predict poor clinical outcomes in the critically ill. This was achieved via a systematic review that determined the validity and reliability of this assessment tool in identifying malnutrition risk among adults in the hospital setting. More importantly, the review evaluated the prognostic value of this tool for poor outcomes in critically ill patients.

Chapter Three summarises the limitations of the systematic review embedded in Chapter One. It also describes an original study performed to address the identified limitations and consequently provides a more valid estimate of the association between malnutrition and poor clinical outcomes in critically ill patients (i.e., 28-day mortality and ICU length-of-stay). As a result, baseline nutritional status was selected as a candidate predictor in the prognostication of poor outcomes in critically ill patients.

Chapter Four describes the intricacies involved in measuring disease severity. It also outlines the statistical approaches used to evaluate disease severity prognostic models. In the absence of local studies employing established statistical methods to validate a widely-used

prognostic model (APACHE II), Chapter Four also contains an original study that aimed to determine the prognostic performance of APACHE II in a mixed ICU in Singapore.

Chapter Five tests the hypothesis whereby a combination of baseline nutritional status and disease severity can better predict 28-day mortality via an original study. This chapter forms the basis of developing a prognostic model that integrates the above predictors to better predict mortality.

Chapter Six explores the modifying effects of nutrition support on the predicted mortality of critically ill patients. Results reported in this chapter helped to guide the development of a prognostic model that integrates baseline nutritional status and disease severity to identify patients who would derive the most benefits from aggressive nutrition support.

Chapter Seven outlines the methods used to develop prognostic models. Thereafter, it describes an original study that aimed to develop a prognostic model (GLIMPSE) designed to identify patients who would derive the most benefits from aggressive nutrition support. This chapter also critically appraises the methods used to develop GLIMPSE, and examines the validity of GLIMPSE in identifying patients who would derive the most benefits from aggressive nutrition support.

Chapter Eight outlines the original contribution to knowledge, and discusses implications for practice and future research directions.

Table 1: Summary of publications contributing to this thesis

Chapter	Full citation	Status	Impact Factor (2018)	SCImago quartile ranking (2018)
1	Lew CCH, Yandell R, Fraser RJ, Chua AP, Chong MFF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: A systematic review. JPEN J Parenter Enteral Nutr. 2017;41(5):744-58.	Published	4.109	1
2	Lew CCH, Ong F, Miller M. Validity of the adductor pollicis muscle as a component of nutritional screening in the hospital setting: a systematic review. Clin Nutr ESPEN. 2016;16:1-7.	Published	-	3
3	Lew CCH, Wong GJY, Cheung KP, Chua AP, Chong MFF, Miller M. Association between malnutrition and 28-day mortality and intensive care length-of-stay in the critically ill: A prospective cohort study. Nutrients. 2017;10(1):10.	Published	4.171	1
4	Lew CCH, Wong GJY, Tan CK, Miller M. Performance of the Acute Physiology and Chronic Health Evaluation II (APACHE II) in the prediction of hospital mortality in a mixed ICU in Singapore. PoSH 2018.	Published	-	4
5	Lew CCH, Cheung KP, Chong MFF, Chua AP, Fraser RJL, Miller M. Combining two commonly adopted nutrition instruments in the critical care setting is superior to administering either one alone. JPEN J Parenter Enteral Nutr. 2018;42(5):872-6.	Published	4.109	1
6	Lew CCH, Wong GJY, Cheung KP, Fraser RJ, Chua AP, Chong MFF, et al. When timing and dose of nutrition support were examined, the modified Nutrition Risk in Critically Ill (mNUTRIC) score did not differentiate high-risk patients who would derive the most benefit from nutrition support: A prospective cohort study. Ann Intensive Care. 2018;8(1):98.	Published	3.931	1
7	Lew CCH, Wong GJY, Cheung KP, et al. The association between nutritional adequacy and 28-day mortality in the critically ill is not modified by their baseline nutritional status and disease severity. Crit Care. 2019;23(1).	Published	6.959	1

Background

This section provides an overview of the research background, questions, setting, and methodology.

Background of the Research

Metabolic irregularities, heightened inflammation, and anabolic resistance during critical illness contribute to complexity in how nutrient utilisation affects clinical outcomes in critically ill patients [6]. Since a majority of critically ill patients require non-volitional nutrition support and the amount of nutrients prescribed is entirely determined by the clinician, it is vital that regimes provide nutrients in amounts that minimise the risk of mortality and morbidity.

According to a recent international survey that included 17,154 patients from 923 ICUs, the mean percentage of energy and protein requirements (derived mostly from predictive equations or weight-based formulas) met via nutrition support were 56% and 52%, respectively [7]. Since most critically ill patients do not meet their estimated energy and protein requirements, it is generally believed that aggressive nutrition support, which often translates to early high-energy and protein intakes, will elicit optimum clinical outcomes in the critically ill [8]. For the purpose of this thesis, aggressive nutrition support will be synonymous with early high-energy and protein intakes.

At the initial phase of this research programme, some observational studies [9, 10] and randomised control trials (RCT) [11-14] challenged the general assumption that meeting the measured or estimated energy requirements of critically ill patients will result in the best clinical outcome [8]. Overall, they suggested that underfeeding (energy intake < energy requirement) is either beneficial [11, 14] or harmless [12, 13]. In contrast, other studies continue to suggest that full-feeding (energy intake = energy requirement) is associated with reduced mortality and morbidity risk [15-20].

Findings of observational studies

The inconsistent results in the observational studies [9, 10, 15, 16] were well explained in a multi-institutional audit that included 7,872 patients from 353 ICUs in 33 countries [21]. Heyland et al. [21] showed that studies that associate full-feeding with increased adjusted odds of hospital mortality were influenced by their choice of sample restriction and statistical analysis.

Sample restriction – In a nested cohort study (n = 523), Arabi et al. [9] demonstrated that underfeeding (< 64.6% of energy goal) was associated with lower odds of hospital mortality. However, Heyland et al. [21] argued that such a result was due to the inclusion of patients with short ICU length-of-stay. These patients tend to have better clinical outcomes, and underfeeding is merely circumstantial since they would have less time to achieve the prescribed energy goal [21]. By testing the effects of both including and excluding patients with short ICU length-of-stay in the audit, Heyland et al. [21] showed that Arabi et al.'s observation was due to the inclusion of patients with short ICU length-of-stay, and excluding them demonstrated that underfeeding was associated with higher mortality risk.

Statistical analysis – Based on a prospective cohort study (n = 187), Krishnan et al. [10] concluded that full-feeding (> 66.6% of energy goal) was associated with higher odds of hospital mortality, whereas meeting 33% to 65% of the energy goal was associated with the lowest mortality risk. However, Heyland et al. [21] argued that such observations were mainly due to the method used to calculate the percentage of the energy goal achieved. Ideally, this should be derived from dividing the amount of energy received by the number of days on exclusive nutrition support (ENS) [21]. That is, the denominator should not be ICU length-of-stay since this would include a period when patients are on oral feeding, and energy intake would be considered zero. In the study conducted by Krishnan et al. [10], ICU length-of-stay was used as the denominator. Consequently, the percentage of energy goal achieved may be underestimated.

By imposing the aforementioned sample restriction and statistical analysis, Heyland et al. [21] demonstrated that full-feeding was associated with lower odds of 60-day mortality, and

meeting > 85% of the energy goal was associated with the lowest mortality risk. However, despite the robust findings of observational studies [15, 16, 21], results are limited to association rather than causation since no amount of statistical adjustment can account for residual confounders. Therefore, evidence from RCTs is needed to establish causality.

Findings of randomised controlled trials

At the initial period of this research programme, five RCTs [11-13, 18, 20] compared the impact of underfeeding and full-feeding on mortality outcomes. Collectively, neither treatment resulted in lower mortality except for Arabi et al. [11], where underfeeding lead to lower hospital mortality (12.5% absolute risk reduction, p-value: 0.04), whereas Singer et al. [18] demonstrated that full-feeding resulted in a trend towards lower hospital mortality (17.6% absolute risk reduction, p-value: 0.058) but also to significantly longer duration of mechanical ventilation (5.6 days, p-value: 0.03) and a trend towards higher absolute risk of ventilator-associated pneumonia (13.9%, p-value: 0.08).

The need to identify an optimal energy intake that results in lower mortality is reflected by a large number of subsequent RCTs aimed at answering this question [22] and especially by the sheer number of meta-analyses, seven of which have been published to date [22-28]. These meta-analyses demonstrated that neither underfeeding nor full-feeding affects mortality outcomes, but this conclusion must be seen in the light of the poor quality of evidence provided by the primary studies.

Limitations of randomised controlled trials and meta-analyses of randomised controlled trials

These conflicting results among RCTs are likely due to the heterogeneous nature of the studies. For example, the energy requirements of patients were quantified differently in the RCTs, with some authors using indirect calorimetry [17, 18, 29] while others used a variety of predictive equations. More importantly, there is no clear definition of underfeeding or full feeding. In the RCTs, underfed patients received 7% to 81% while fully-fed patients received 28% to 106% of the energy goals [18, 30]. Therefore, what was deemed underfeeding in some

studies [31, 32] turned out to be the same amount of energy given to patients in the full-feeding arm of other studies [33, 34]. This severely complicates the interpretation of results, and it is no surprise that a conclusion could not be reached in the meta-analyses.

Knowledge Gaps

Baseline nutritional status – A common limitation of these RCTs (and therefore of the meta-analyses) is the lack of baseline nutrition assessment. In a retrospective analysis of 128 RCTs not specifically conducted with critically ill patients, Kondrup et al. [35] concluded that patients at-risk of malnutrition were more likely to benefit from nutrition support. Based on this conclusion, it is conceptually possible that malnourished patients require more energy to attenuate the deleterious effects of critical illness as compared to well-nourished patients. Therefore, the differing baseline nutritional status of the subjects may have confounded the results of the RCTs [23].

Since baseline nutritional status can influence the effects of under- or full-feeding, it is an important parameter to measure. However, the ideal nutrition assessment tool that would both be reliable and provide good mortality prognostic value in critically ill patients remains to be identified [36]. On a related note, a bedside nutrition parameter (i.e., thickness of the adductor pollicis muscle) has garnered attention in the literature as it was demonstrated to have strong prognostic value for mortality in critically ill patients [37]. However, its validity as a nutrition parameter and external prognostic validity requires further evaluation.

Baseline disease severity – Apart from baseline nutritional status, patients' baseline disease severity may also influence how they respond to nutrition support [38]. Disease severity is often quantified by prognostic models, and in the context of critical care, mortality outcomes are often the dependent variable. Prognostic models quantify mortality risk via a composite of predictors (with mathematical functions), and one of such prognostic models is the Acute Physiology and Chronic Health Evaluation II (APACHE II) [39]. APACHE II was developed in the United States more than 30 years ago, and its prognostic validity in Singapore remains questionable since it has never been validated locally with established statistical methods. Despite this, Ng Teng Fong General Hospital (NTFGH) as well as other public hospitals in

Singapore continue to use APACHE II to quantify disease severity. This is of great concern as a Korean study carried out in 2013 showed that APACHE II overestimated mortality risk by up to 60% [40]. The inaccuracy of APACHE II was also clearly demonstrated in some large RCTs [14, 17-19], where similar APACHE II scores resulted in vastly different mortality rates (e.g., studies with APACHE II scores of 22 had mortality rates ranging from 6% to 21%).

Another mortality prognostic model is the Nutrition Risk in the Critically Ill (NUTRIC) Score [38]. This score uses six components – age, APACHE II, Sequential Organ Failure Assessment (SOFA), number of comorbidities, days in hospital before admission to ICU, and interleukin-6 concentrations – to quantify mortality risk in which a score of 0 to 5 and 6 to 10 is classified as low-NUTRIC and high-NUTRIC, respectively. However, the score was subsequently modified to exclude interleukin-6 concentrations [modified-NUTRIC (mNUTRIC)] as this parameter is rarely measured outside of research settings, and a score of 0 to 5 and 6 to 9 is classified as low- and high-mNUTRIC, respectively [41]. However, for unclear reasons, these cut-offs were modified, and scores of 0 to 4 and 5 to 9 are now considered indicative of low and high-mNUTRIC, respectively [42]. Nevertheless, the mNUTRIC scores were purported to identify patients who would derive the most benefit from aggressive nutrition support. That is, patients with high-mNUTRIC scores and receiving full-feeding had reduced odds of 28-day mortality, while the same was not observed in patients with low-mNUTRIC scores [38, 41]. The utility of the mNUTRIC score as a nutrition assessment tool is however questionable because the score has not been prospectively evaluated at the initial period of this research project. Additionally, the applicability of this score in Singapore remains unclear since there is a paucity of local validation data.

Taken together, it is plausible that a combination of baseline nutritional status (well- versus malnourished) and disease severity can influence how full- versus underfeeding of energy and protein may modify mortality outcomes in critically ill patients. Two approaches could be used to examine the above hypothesis.

One approach would be to develop a prognostic model that accurately quantifies the mortality risk of critically ill patients. Such a model could be used to evaluate the presence of any interactions between baseline risk factors (nutritional status and disease severity), energy

and protein intakes, and mortality outcomes. If an interaction exists, this may suggest that the amount of energy and protein administered can modify mortality outcomes in critically ill patients.

An alternative approach would be to conduct a multicentred RCT. This is the best approach to testing the hypothesis because it would optimally control for unknown confounders (if a large number of subjects from multiple centres are recruited) and minimise bias (if the RCT is well-designed). A four-by-two factorial RCT would be required to examine the effects of full- and underfeeding energy and protein (four factors) in well- and malnourished patients (two factors). However, this approach has not been adopted, as there may be insufficient time to recruit a large number of patients into eight treatment arms in a single-centre study. In addition, the present research programme did not have the necessary human resources (e.g., research coordinator, biostatistician) and treatment cost (enteral and parenteral formulas). Therefore, a prognostic model was built instead.

Although conducting an RCT will optimally test the hypothesis, development of a prognostic model that accurately accounts for both baseline nutritional status and disease severity may be useful in informing future RCTs. In the context of RCTs, prognostic models can be used to ensure that outcome predictors are well-balanced across treatment and control groups in order to better quantify the effect size of the treatment. This is important as Royston et al. [43] demonstrated that baseline imbalance of outcome predictors in RCTs may nullify the effects of treatment (type 2 error). Furthermore, even when baseline characteristics are well-balanced, adjustment of prognostic factors may increase the power of the study [44]. In the clinical setting, prognostic models may aid in the practice of stratified medicine in which subgroups of patients with distinct risk characteristics (e.g., malnourished and with high disease severity) can be identified to receive a specific treatment (e.g., aggressive nutrition support) [45]. For example, lipid-lowering medications are not given only to all individuals with hyperlipidaemia. Instead, they are prescribed to individuals with a composite of risk characteristics (e.g., age, family history, and comorbidities) quantified by established prognostic models [45].

Given the multifaceted role of prognostic models in research and clinical settings, this research programme aimed to develop a prognostic model that accounts for both nutritional status and disease severity (Figure 1). It is hypothesized that such a prognostic model can better: 1) prognosticate mortality, and 2) identify patients who would derive the most benefit from aggressive nutrition support in the critical care setting.

Research Questions

In a nutshell, the development of a prognostic model involves four steps. Firstly, identify a host of candidate predictors and study their association with the outcome of interest. Candidate predictors can range from demographics, medical history, physical examination, and disease severity. Essentially, any variable with a significant association with the outcome can be a candidate predictor, and this includes those that may not be causal (e.g., tumour markers) [46]. Secondly, develop a model by assigning relative weights to all important predictors via regression analysis. Thirdly, determine the prognostic performance of the model, and lastly, perform internal validation and, if necessary, adjust for overfitting and optimism [47].

A conceptual framework and systematic approach were adopted in order to develop a novel prognostic model that would include both baseline nutritional status and disease severity (Figure 1). Seven research questions were formulated and empirically investigated. Questions 1 to 5 sought to identify important predictors of mortality among critically ill patients, whereas Question 6 sought to determine if aggressive nutrition support can modify mortality outcomes, and Question 7 aimed to develop and validate a novel prognostic model that accounts for both nutritional status and disease severity. The seven research questions were:

1) Which nutrition assessment tool has the best prognostic value for clinical outcomes in the ICU?

2) What is the validity of the thickness of the adductor pollicis muscle as a surrogate assessment of nutritional status and its prognostic validity for worsened clinical outcomes?

3) Is malnutrition associated with worsened clinical outcomes in the ICU in Singapore?
4) What is the prognostic validity of the APACHE II for mortality in Singapore?

5) What is the association between nutritional status and disease severity in critically ill patients?
6) What is the applicability of the mNUTRIC in Singapore? and

7) What is the validity of a new prognostic model (Global Index of Mortality Probability in the Severely Ill – GLIMPSE) that combines both nutritional status and disease severity?

Research Setting

The 35-bed ICU at NTFGH functions as a closed unit providing support to medical, surgical, neurological, trauma, and cardiac patients. The unit also functions as a High-Dependency (HD) unit that enables patient status to be interchanged between ICU-status and HD-status without the need for transfers. Patients who are mechanically ventilated and require support for two or more organ systems are classified as "ICU-status" and downgraded to HD-status once they are extubated from mechanical ventilation. Regardless of the level of care (ICU-/HD-status), all patients in the unit are treated by the same physicians and allied health professionals. The only difference between ICU- and HD-status is the ratio of nursing staff to patient, which changes from 1:1 to 1:2, respectively.

All patients in the ICU are automatically referred to a dietitian, who provides services from 8:30 am to 6 pm Monday to Friday, and 8:30 am to 12:30 pm on Saturday. Over this duration, dietitians perform nutrition assessment and prescribe and evaluate enteral and/or parenteral nutrition support regiments of patients within 48 hours of admission.

Overview of Methodology and Timeline

Several study designs can be used to develop prognostic models. In this research programme, a prospective cohort study design was adopted as it is considered the best study design for prognostic model development. A prospective cohort study is also the ideal design for studying prognosis since it provides the best data quality given the higher likelihood of optimal documentation of predictors and outcomes [46]. However, it may suffer from indication bias since treatments are often not standardised in observational studies [47]. In contrast to the prospective cohort design, retrospective cohort studies use existing patient data either routinely measured or collected for other reasons in order to develop the prognostic model. Although this study design allows for a more extended period of follow-up, such an advantage is at the expense of poorer data quality, in part due to missing data or errors in routine documentation [46]. A case-control study design was not (and should not be) used because cases and controls are sampled from a population of unknown size. Consequently, the incidence of the outcome of interest cannot be accurately quantified, and the downstream effect is the inability to quantify absolute risk, relative risk, or hazard ratios [46].

This research programme started when the current NTFGH campus was under construction, and all staff were temporarily housed at Alexandra Hospital. Therefore, from September 2013 to July 2015, all research activities were focused on obtaining ethical approval from the local Institute Review Board (Domain Specific Review Board) and conducting systematic reviews (Chapters 1 and 2) to identify candidate nutritional parameters for GLIMPSE.

Data collection started in August 2015 after NTFGH went officially into operation on its new campus in July 2015. A detailed description of the methods used to answer the seven research questions listed above will be outlined in the respective chapters as the methods required to answer each question differ. Briefly, all information was prospectively recorded in the electronic medical record and periodically retrieved. The main categories of data collected were: 1) prognostic parameters; 2) energy and protein intakes; and 3) clinical outcomes such as 28-day mortality, hospital mortality, and ICU length-of-stay. However, the acquisition of energy and protein intakes was only completed in June 2017 as this required extensive data

input and computation. Therefore, analyses of the modifying effects of energy and protein intakes were only possible at a later phase of the research programme.

The seven research questions will be answered in the following chapters. Each chapter will begin with either a literature review or a systematic review highlighting knowledge gaps and followed by an original study designed to address the identified gaps.

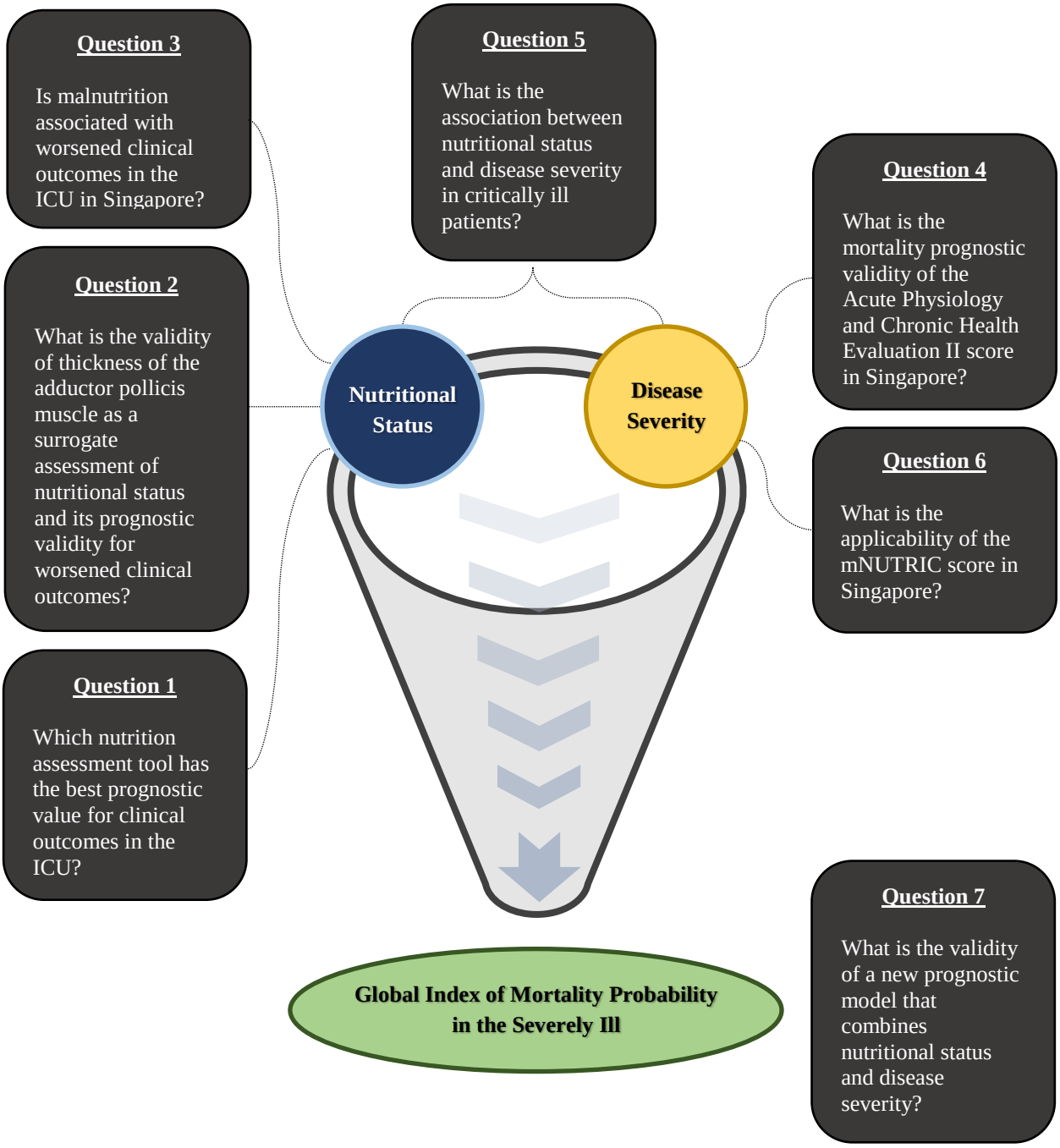


Figure 1: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients

Chapter 1: Which nutrition assessment tool has the best prognostic value for clinical outcomes in the ICU?

1.1. Contribution to the overall research objective

The overall objective of this research programme was to develop a novel prognostic model (GLIMPSE). It was hypothesized that a combination of baseline nutritional status and disease severity can better: 1) prognosticate mortality, and 2) identify patients who would derive the most benefit from aggressive nutrition support in the critical care setting. To test this hypothesis, we must first identify a nutrition assessment tool that can accurately and reliably classify the baseline nutritional status of the critically ill. In addition, the tool must have strong prognostic validity for clinical outcomes such as mortality, length-of-stay, and infection risk.

Nutrition assessment is often confused with nutrition screening in the literature, and these terms are often erroneously used interchangeably. This should not be the case since they serve different purposes. According to the American Society of Parenteral and Enteral Nutrition (ASPEN), screening is "a process to identify an individual who is malnourished or who is at risk of malnutrition to determine if a detailed nutrition assessment is indicated" [36]. While the focus of ASPEN is to identify individuals who require further nutrition assessment, the focal point of screening as defined by the European Society of Parenteral and Enteral Nutrition (ESPEN) is to prognose outcomes due to existing nutritional factors and whether nutritional intervention can positively modify outcomes [35]. Despite these differences, both societies concur on three points. First, nutrition screening should be the first step in the nutrition care process and be conducted on all hospitalised patients. Second, nutrition screening tools should have high sensitivity to identify all at-risk patients. Lastly, patients identified to be at risk of malnutrition should receive a detailed nutrition assessment to determine the most appropriate nutrition intervention and evaluation [48, 49]. Nutrition assessment entails gathering more in-depth information and the performance of a nutrition-focused physical examination or anthropometry to diagnose malnutrition [48, 49]. Taken together, nutrition screening identifies individuals at risk of malnutrition and determine those who may benefit

from nutrition intervention whereas nutrition assessment is used to confirm and diagnose malnutrition.

There are myriad nutrition screening and assessment tools, but their applicability in the critical care setting remains unclear. Therefore, a systematic review was carried out in August 2014 to identify valid nutrition assessment tools suitable for use in this research programme. The systematic review was submitted for publication in July 2015 and accepted in December 2015. Following the completion of the review, there were new developments in the definition of malnutrition as well as new studies in the literature that evaluated the association between malnutrition and the clinical outcomes in critically ill patients. To keep this chapter up-to-date and preserve the integrity of the published systematic review as much as possible, pertinent new information will be added below, and footnotes will be used to indicate sections added to the published manuscript.

The following section contains material from:

Lew CCH, Yandell R, Fraser RJ, Chua AP, Chong MFF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. JPEN J Parenter Enteral Nutr. 2017;41(5):744-58.

Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 75%
- Writing and editing: 80%

I personally made a major contribution to the conception of the manuscript, design of the systematic review, and acquisition, analysis, and interpretation of the studies included in the systematic review; I also drafted the manuscript and revised it according to the recommendations provided by my co-authors and the peer reviewers.

1.2. Introduction[†]

Malnutrition has been shown to be independently associated with higher mortality risk, longer hospital length-of-stay, and increased cost of hospitalisation [50, 51]. However, the association between malnutrition and adverse clinical outcomes in the ICU setting is less clear. Nevertheless, given that critically ill patients are often in a heightened pro-inflammatory state (which can itself significantly worsen nutritional status) [49], the effects of malnutrition are likely to be magnified in the ICU. Therefore, it is of clinical importance to examine the association between malnutrition and ICU clinical outcomes.

However, it is challenging to demonstrate an association between malnutrition and adverse clinical outcomes in the ICU as the diagnosis of malnutrition may have been inappropriate in some studies. For instance, low levels of serum albumin were previously regarded as a biochemical indicator of nutritional status and were associated with an increased risk of both morbidity and mortality in the ICU [52, 53]. However, it is now recognized that serum albumin concentrations could also be reflective of disease severity [54]. In other studies, screening as opposed to assessment tools has been used to determine nutritional state [55, 56]. Conceptually, this may confuse the issue as the purposes of nutrition screening and assessment are different. Nutrition screening determines the risk of malnutrition, whereas nutrition assessment is diagnostic of malnutrition [57]. Since all nutrition screening tools have some degree of misclassification bias, studies where nutrition screening tools were used to evaluate the association between malnutrition and ICU clinical outcomes are likely to have uncertain validity.

To rigorously assess the association between malnutrition and clinical outcomes in the ICU, studies require the use of validated nutrition assessment tools. The Subjective Global Assessment (SGA) [58], Mini Nutritional Assessment [59], and Malnutrition Clinical Characteristics [49] are validated nutrition assessment tools recommended by the Academy of Nutrition and Dietetics and ASPEN [36, 49]. *In 2015 (after the submission and publication of*

[†] Content of Sections 1.2 to 1.6 is similar to an original published article. To keep the thesis up-to-date, new information in the form of italicised texts was added to the published systematic review.

this article [1]), the ESPEN published a consensus statement on Diagnostic Criteria for Malnutrition [48]. A detailed comparison of the four nutrition assessment tools [48, 49, 58, 59] reveals considerable differences in the components and criteria used to diagnose malnutrition (Table 1).

Subjective Global Assessment

The SGA was established by Detsky et al. [58] in 1987 to assess nutritional status and predict clinical outcomes such as hospital mortality, incidence of infection, use of antibiotics, and length-of-stay within a surgical population. It uses a composite of eight components (weight history, dietary changes, gastrointestinal symptoms, functional capacity, degree of metabolic stress, loss of muscle mass, loss of subcutaneous fat, and fluid accumulation) to diagnose malnutrition.

Malnutrition Clinical Characteristics

At face value, the Malnutrition Clinical Characteristics [49] is similar to the SGA [58] as they share six similar components [60]. However, the Malnutrition Clinical Characteristics excludes "gastrointestinal symptoms" (a component of SGA), and in the assessment of functional status, "degree of mobility" in the SGA was replaced with handgrip strength in the Malnutrition Clinical Characteristics. In addition, the Malnutrition Clinical Characteristics is relatively more objective than the SGA because components such as "weight loss" and "energy intake" have specific classification criteria to differentiate their aetiology (based on the level of inflammatory insult) and degree of malnutrition [60].

Diagnostic Criteria for Malnutrition

The Diagnostic Criteria for Malnutrition [48] has three major differences when compared to the other three nutrition assessment tools. Firstly, it uses the least number of criteria to diagnose malnutrition. Secondly, all criteria are objective measurements. Lastly, it dichotomises nutritional status into well- or malnourished states whereas the other assessment tools [49, 58, 59] have various gradings of malnutrition.

Mini Nutritional Assessment

The Mini Nutritional Assessment was developed in 1994 to specifically assess the nutritional status of elderly populations [59]. Compared to the SGA [58], the Malnutrition Clinical Characteristics, [49] and the Diagnostic Criteria for Malnutrition [48], the Mini Nutritional Assessment uses the most components to diagnose malnutrition, and it is the only nutrition assessment tool that uses a scoring system to classify individuals into well-nourished or malnourished states [59].

The Global Leadership Initiative on Malnutrition (GLIM)

Given the confusion caused by the multiple approaches used to diagnose malnutrition, a Global Leadership Initiative on Malnutrition (GLIM) led by the four largest global Parenteral and Enteral Nutrition Societies (ASPEN, ESPEN, Parenteral and Enteral Nutrition Society of Asia, and Latin American Federation of Parenteral and Enteral Nutrition) was formed to reach a global consensus on a Diagnostic Criteria for Malnutrition in the clinical settings [61]. Since 2016, several face-to-face meetings were held to shortlist diagnostic criteria commonly used to define malnutrition, and in the February 2017, the group shortlisted five criteria: 1) nonvolitional weight loss; 2) low body mass index; 3) reduced muscle mass; 4) reduced food intake or assimilation; and 5) disease burden/inflammation [61]. These five criteria were further divided into phenotypic (Criteria 1 to 3) and aetiologic groups (Criteria 4 and 5), and a consensus scheme for malnutrition diagnosis was proposed in September 2018 [62]. According to the group, the diagnosis of malnutrition must include at least one phenotypic criteria coupled with at least one etiologic criteria. The group also proposed a specific threshold for severity grading of malnutrition (moderate versus severe) using the phenotypic criteria, and emphasised that clinicians should use the etiologic criteria to guide appropriate intervention and evaluation [62]. However, since this new set of diagnostic criteria has not been validated, the SGA, Malnutrition Clinical Characteristics, Diagnostic Criteria for Malnutrition, and Mini Nutritional Assessment will be deemed to be validated assessment tools in this thesis.

This systematic review aimed to examine the association between malnutrition (diagnosed by the SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics,

and Diagnostic Criteria for Malnutrition) and clinical outcomes in the ICU. For the sake of completeness, this review also aimed to evaluate the results of studies that utilised nutrition screening tools as they are widely used in the ICU setting, and their predictive validity specific to clinical outcomes in the ICU have not been addressed in previous reviews [63]. In addition, in view of the paucity of data in the literature, the prevalence of malnutrition in the ICU is also reported.

Table 2: Aim of systematic review summarised by the PICO framework

P	**Population**	Patients admitted to the intensive care unit who were > 18 years old and not pregnant.
I	**Intervention/ Prognostic factor/ Exposure**	Malnutrition diagnosed by the Subjective Global Assessment, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and/or Diagnostic Criteria for Malnutrition.
C	**Comparison**	Well-nourished patients classified by the Subjective Global Assessment, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and/or Diagnostic Criteria for Malnutrition.
O	**Outcome**	All clinical outcomes reported in the primary studies.

Table 3: Comparison of criteria used to diagnose malnutrition among the four established nutrition assessment tools*

Parameters	Mini Nutritional Assessment	Subjective Global Assessment	Malnutrition Clinical Characteristics	Diagnostic criteria of malnutrition
Energy intake	• Over the last three months	• Over a self-defined period	• Over a period of one week to three months and above	• No
Weight History	• Over the last three months	• Over the last two weeks and six months	• Over a period of one week to one year	• Over the last three months to indefinite time
Muscle store	• Mid-arm circumference • Calf circumference	• Deltoids • Quadriceps	• Deltoids, quadriceps, temporalis, pectoralis, interosseous muscles, latissimus dorsi, trapezius, gastrocnemius	• Measured by the fat-free mass index [64]
Subcutaneous fat store	• No	• Triceps • Fat overlying the ribs	• Triceps • Fat overlying the ribs • Orbital	• No
Fluid accumulation	• No	• Oedema at the ankle, sacral and/or ascites	• Oedema at extremities, vulvar/scrotal oedema or ascites	• No
Functional status	• Mobility over a self-defined period	• Mobility over a self-defined period	• Level of hand grip strength	• No

* This is a new piece of information added to the published systematic review [1].

Table 2: Comparison of criteria used to diagnose malnutrition among the four establish nutrition assessment tools (cont.)*

Parameters	Mini Nutritional Assessment	Subjective Global Assessment	Malnutrition Clinical Characteristics	Diagnostic criteria of malnutrition
Severity of Illness	• Psychological stress or acute disease over the last three months • Neuropsychological problems	• Level of metabolic demand associated with admission diagnosis	• Classified by degree of inflammation, i.e., acute versus chronic illness, and absence of inflammation	• No
Body mass Index	• Yes	• No	• No	• Yes
Others	• Place of dwelling • More than three prescription drugs and pressure ulcers • Number of full meals in a day and mode of feeding • Daily intake of protein-rich food, fruits or vegetables, and fluids • Self-perception of nutritional status and health status	• Gastrointestinal symptoms that lasted more than two weeks	• Nil	• Nil

* This is a new piece of information added to the published systematic review [1].

Table 2: Comparison of criteria used to diagnose malnutrition among the four establish nutrition assessment tools (cont.)*

Parameters	Mini Nutritional Assessment	Subjective Global Assessment	Malnutrition Clinical Characteristics	Diagnostic criteria of malnutrition
Method of diagnosing malnutrition	• Each of 18 domains carries a score • Score ≥ 24: well-nourished • Score 17 to 23.5: at risk of malnutrition Score < 17: malnourished	• Each domain carries a brief descriptor to differentiate the degree of malnutrition • Assessor utilises all information to classify patients' nutritional status into: 1) Well-nourished 2) Mildly-moderately malnourished 3) Severely malnourished	• Having two or more of the six characteristics is diagnosed as malnutrition • The severity of malnutrition depends on the criteria set for each characteristic • Nutritional status is classified as moderately or severely malnourished	• Having one of the following is diagnosed as malnutrition: 1) Body mass index of <18.5 kg/m^2, or 2) Weight loss with either: a) Reduced body mass index of < 20 kg/m^2 in patients aged < 70 years or < 22 kg/m^2 in patients aged ≥ 70 years, or b) Low fat-free mass index of < 15 and < 17 kg/m^2 in females and males, respectively

* This is a new piece of information added to the published systematic review [1].

1.3 Methods

Details of the protocol for the published systematic review were registered on PROSPERO (Registration number: CRD42014014152). Reporting of the review is consistent with the PRISMA statement, a globally acceptable set of guidelines for quality reporting.

Eligibility criteria

All published case-control and cohort studies were eligible for inclusion in the review, and no restriction was imposed on publication date. Data were considered from patients admitted to the ICU who were > 18 years old and not pregnant. In addition, there was no restriction on the length of follow-up. All studies in which the clinical outcomes of patients in the ICU were determined based on the results of their nutrition screening or nutrition assessment tools (i.e., not at risk of malnutrition versus at risk of malnutrition or well-nourished versus malnourished) were included in the review.

Information sources and search methods

To identify relevant articles, a search strategy was developed with reference to the eligibility criteria. Free text terms and broad search terms (MeSH in PubMed, the Cochrane Library of Databases, and CINAHL Headings in CINAHL) were used. As nutrition screening and assessment tools are often used interchangeably in studies, synonyms for "malnutrition" and "nutritional status" were combined with synonyms for "screening" and "assessment" to ensure that all types of nutrition screening and assessment tools were identified [65]. Results were then combined with synonyms for "intensive care unit" to identify all nutrition screening and assessment tools used in the ICU. Appropriate exclusion terms were applied to include only adults and suitable publication types. Based on three studies, which consistently demonstrated no evidence of bias against the use of English language restrictions, the literature search was limited to articles written in English [66-68]. In addition, a "human" limit was applied, where possible. This search strategy was appropriately adapted to the electronic databases listed in the Appendix-1 to ensure consistency across all searches. Pubmed, CINAHL, Scopus, and the Cochrane Library were searched systematically on 1 August 2014.

In addition to electronic databases, the reference lists in the articles included in this systematic review were hand-searched along with the Tables of Contents of Critical Care Medicine, the Journal of Parenteral and Enteral Nutrition, and Nutrition in Clinical Practice from inception to August 2014 to identify other relevant articles. These journals were chosen as they had the highest number of relevant articles in accordance with the search strategy on Scopus.

Lastly, an additional search was performed on 30 April 2018 to keep this systematic review up-to-date. Search terms such as "Subjective Global Assessment," "Mini Nutritional Assessment," "Malnutrition Clinical Characteristics," or "Diagnostic Criteria of Malnutrition" were combined with synonyms for "intensive care unit" to identify new studies that determined the association between malnutrition (diagnosed by the four validated nutrition assessment tools) and clinical outcomes. Identical exclusion criteria to those described above were imposed during the literature search, and the date range was limited to 2014-2018.

Study selection

After duplicates were removed, two reviewers (Rosalie Yandell and I) independently screened the titles and abstracts, and studies that were clearly not aligned with the aims of the review were excluded. Full-text versions of all potentially relevant studies were obtained for further evaluation. *For the recent literature search (2014-2018), only one reviewer (myself) performed the screening.*

As the review aimed to determine the association between premorbid malnutrition and clinical outcomes, premorbid malnutrition was restricted to malnutrition that existed as a comorbidity on admission to the ICU. Studies with nutrition screening and/or assessment conducted before or within 48 hours of ICU admission were included to minimize reverse causality bias. Only studies that used nutrition assessment tools and/or screening tools were included. Articles that reported the prevalence of malnutrition *(determined by the SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and DSC),* all forms of mortality measures (e.g., ICU mortality and hospital mortality), length-of-stay (e.g., ICU

length-of-stay and hospital length-of-stay), and/or incidence of infections were also included in the review. Articles that reported other relevant clinical outcomes (e.g., post-operation complications and ICU readmission) were also included. Any articles that measured the prognostic value of individual biochemical markers or anthropometric measurements were excluded. In addition, articles that did not report the prevalence of malnutrition, relevant clinical outcomes, and/or results specific to patients in the ICU were excluded. Articles where the clinical outcomes between at-risk and not-at-risk patients for malnutrition and between well-nourished and malnourished patients were not compared were also excluded. In cases of disagreement, both reviewers sought consensus through discussion. If consensus could not be reached, a third reviewer's (Michelle Miller) opinion was sought to resolve the issue. The PRISMA flow diagram was used to summarize the article selection process (Figure 1).

Data extraction

A data extraction sheet was developed and piloted on five randomly selected articles and then refined accordingly. One reviewer (myself) extracted the required data and the second reviewer (Rosalie Yandell) checked the extracted data. Disagreements were resolved by discussion. If no consensus was reached, a third reviewer's (Michelle Miller) opinion was sought. Five authors [37, 55, 69-71] were contacted for further information, and four responded [37, 69-71]. Extracted data were grouped into six categories, as follows: 1) study design, patient characteristics (age, severity of disease, and medical versus surgical ICU admission), and selection criteria; 2) type, timing, and assessors of nutrition screening and/or assessment; 3) overall rate of all mortality measures, risk estimates, and/or p-values for differences in mortality rates between well- and malnourished patients and patients at-risk and not-at-risk of malnutrition; 4) overall average hospital and/or ICU length-of-stay, risk estimates of prolonged length-of-stay, and/or p-values for differences in length-of-stay between well- and malnourished patients and patients at-risk and not-at-risk of malnutrition; 5) incidence of infections and risk estimates or p-values for differences between well- and malnourished patients and patients at-risk and not-at-risk of malnutrition; and 6) other clinical outcomes such as ICU readmission rates, discharge location, wound healing rates, pressure ulcer prevalence, and incidence of organ rejection between well- and malnourished patients and patients at-risk and not-at-risk of malnutrition. Prevalence of malnutrition was based on the nutrition

assessment tools (*SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and/or DSC*).

Study appraisal and synthesis

A guide that is frequently cited in critical appraisal tools was used to ascertain the prognostic validity of the studies [72]. Among the eight criteria in the guide, reviewers (Rosalie Yandell and I) independently appraised the studies against four of the criteria that are specific to the assessment of risk of bias. Disagreements were resolved by discussion, and a third reviewer's (Michelle Miller) opinion was sought if no consensus was reached. In the absence of widely accepted cut-offs classifying level of bias, studies with low risk of bias were defined as those that met at least three of the four criteria in this review. As this review aimed to determine the independent association between nutritional status and clinical outcomes, one of these criteria had to include the statistical adjustment of important prognostic factors.

Statistical pooling was not performed as there was a limited number of studies with low risk of bias, and outcome measures were either inconsistent (e.g., ICU versus hospital mortality) or expressed differently (e.g., mortality expressed as odds ratio, hazard ratio, or rate). Results of the review were weighted towards the consistency of evidence among studies with low risk of bias.

1.4 Results

The flow chart for article selection is provided in Figure 2. In brief, the literature search initially generated 1,628 articles, from which 460 duplicates were excluded. These included a study by Lomivorotov et al. [73] that had identical methodology and similar subject characteristics to another larger study [69]. Based on the title and abstract selection process, 57 articles were shortlisted for full-text review. From this, a total of 20 studies were identified for inclusion after the addition of one article identified by hand searching (Figure 2). *The recent literature search (2014-2018) identified five studies [74-78], but of these, only four [74-77] used validated nutrition assessment tools to quantify the prevalence of malnutrition and/or*

establish the association between malnutrition and clinical outcomes. Therefore, a total of 24 articles were identified.

Seventeen studies recruited a heterogeneous group of patients [37, 55, 69-71, 74-77, 79-87], three recruited elderly patients [88-90], two recruited post-liver-transplant patients [91, 92] and two more cardiac surgery patients [56, 69], and one recruited patients with acute kidney injury [93]. Nineteen articles [37, 55, 56, 69-71, 74, 75, 77, 81, 83, 86-93] reported relevant clinical outcomes, of which eight had low risk of bias [37, 69, 75, 81, 87, 88, 90, 92] and were used to evaluate the association between malnutrition and ICU clinical outcomes (Table 3).

All 25 studies were prospective cohort studies except for Bector et al. [74] and Vallejo et al. [76], which used a retrospective approach to gathering data. The follow-up duration ranged from the entire ICU admission period to one-year post-discharge (Table 4). In approximately half of the studies, the clinician who carried out the nutrition screening and assessment was not identified [37, 56, 69, 80, 82, 83, 85, 87, 89, 91-93]. Where this parameter was reported, screening and assessment were performed by one or more dieticians in *seven studies [71, 74, 75, 79, 84, 86, 88]*; *physicians in four [70, 76, 77, 81]*, nurses in one [90], and a combination of physicians, nurses, and dietician in the final study [55]. About 60% of the studies recruited patients predominantly from medical ICUs [37, 55, 70, 74-77, 81-84, 86, 88, 89], and two studies [87, 93] from surgical ICUs. In the other nine studies, the proportion of patients recruited from the medical or surgical ICUs was not stated [56, 69, 71, 79, 80, 85, 89, 91, 92]. The Acute Physiology and Chronic Health Evaluation II (APACHE II) [39] was used in most of the studies to quantify disease severity, ranging from *11 to 25 [37, 55, 70, 71, 74-77, 81, 82, 84, 86-90, 93]*. Beside APACHE II, other scoring systems used included the Simplified Acute Physiology Score II, APACHE IV, the European System for Cardiac Operative Risk Evaluation (EuroSCORE), the Child-Pugh Score, the Model for End-Stage Liver Disease (MELD), and the SOFA score.

The mortality rate in ICUs ranged from 11.9% to 47.5%, and in hospitals from 2.5% to 46.1%. The 28-day and 1-year mortality rate ranged from 30.3% to 69.6% and 6.4% to 46.8%, respectively. The mean ICU length-of-stay was 0.7 to 28.5 days, and the mean hospital

length-of-stay ranged from 6.6 to 30.1 days. Infection was reported as incidence or episodes per patient in three studies [56, 69, 92]. Other clinical outcomes are summarised in Table 4. *Of the 25 studies, 20 used validated nutrition assessment tools (SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and/or DSC) to diagnose malnutrition and reported malnutrition prevalence. The prevalence of malnutrition in studies that recruited a heterogeneous group of critically ill patients ranged from 13.9% to 78.1%.* Table 5 summarizes the prevalence of malnutrition in other groups of patients. Two studies concurrently measured the prevalence of malnutrition in the general ward and the ICU. Penie [85] reported that the malnutrition prevalence was 54.8% in the ICU and 41.2% in the general ward. Peterson et al. [82] reported that ICU patients had higher odds of malnutrition compared to medical patients in the general ward (OR: 1.6; 95% CI: 1.1, 2.3; p-value: 0.02).

Nutrition Assessment Tools

Subjective Global Assessment – *A total of 13 studies used the SGA to diagnose malnutrition [37, 69-71, 74, 77, 81, 86-88, 91-93]* and measured its association with relevant clinical outcomes. However, only five had a low risk of bias [37, 69, 81, 88, 92], with most demonstrating that malnutrition was associated with higher hospital mortality and longer ICU length-of-stay. Malnutrition was also independently associated with higher incidence of infections (4.5 versus 0.6 episodes per patient, adjusted p-value: 0.0001) [92], higher risk of ICU readmission (adjusted odds ratio: 2.27; 95% CI: 1.08, 4.80; p-value: < 0.05) [81], and higher percentage of patients being discharged to nursing facilities [88]. Sheean et al. [88] compared the percentage of well- and malnourished elderly patients discharged back to their own homes as opposed to nursing facilities. The percentage of malnourished elderly patients discharged home was 28.6% lower than for their well-nourished counterparts (adjusted p-value: 0.001). However, malnutrition diagnosed by the SGA was not independently associated with ICU mortality [37]. Malnutrition was also not independently associated with wound healing, acute graft rejection, or failure in patients following liver transplantation [92].

Mini Nutritional Assessment – In two studies, the Mini Nutritional Assessment was used to diagnose malnutrition, and both studies showed a low risk of bias [69, 88]. Except for post-operative complications (adjusted odds ratio: 1.60; 95% CI: 1.10, 2.20; p-value: < 0.01)

[69], malnutrition diagnosed by the Mini Nutritional Assessment was not independently associated with any other clinical outcomes.

Malnutrition Classification Criteria – One recent study used the Malnutrition Clinical Characteristics and showed a significant dose-dependent association between malnutrition and hospital mortality [75]. This is the only study that scored low in all domains of the risk-of-bias assessment.

Diagnostic Criteria for Malnutrition – One study used both the SGA and DSM to measure the prevalence of malnutrition in ICUs, but the association between malnutrition and clinical outcomes was not reported. There was considerable discordance between the SGA and the Diagnostic Criteria for Malnutrition as malnutrition prevalence quantified by the SGA was 74.1% whereas it was 13.9% when the Diagnostic Criteria for Malnutrition was used with the same cohort [76].

Nutrition Screening Tools

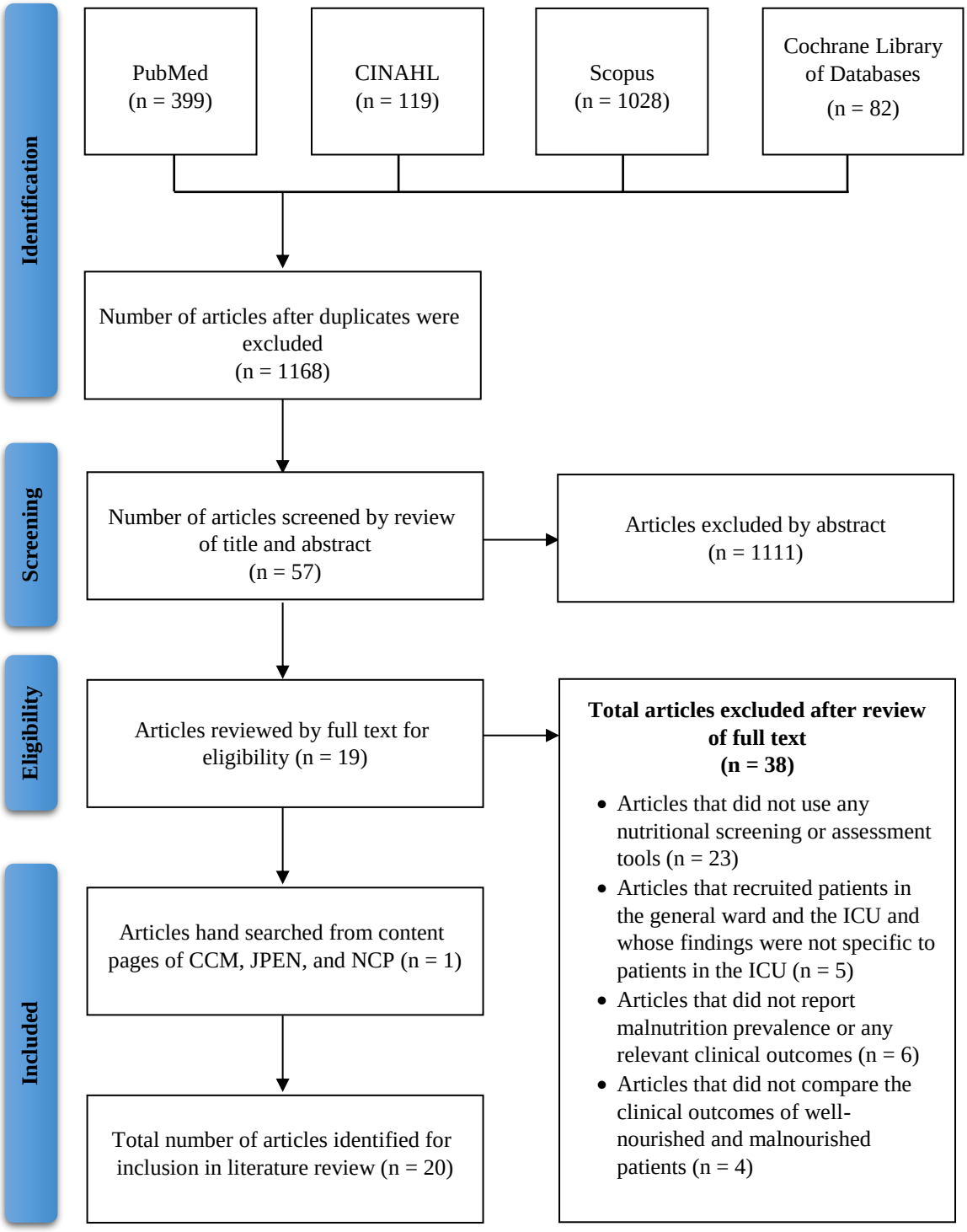
Ten nutrition screening tools were identified (Table 6) [35, 38, 94-101]. However, the prognostic values of only five such tools are reported in the literature (Nutritional Risk Screening – NRS–2002 [35], the Malnutrition Universal Screening Tool (MUST) [94], the Mini Nutritional Assessment-Short Form [100], the Prognostic Inflammatory and Nutritional Index [98], and the Short Nutritional Assessment Questionnaire [99]).

Nutrition Risk Screening 2002 – Four studies used the NRS-2002 to identify patients at risk of malnutrition [55, 69, 88, 89]. Two studies [69, 88] had a low risk of bias, one of which demonstrated malnutrition risk to be independently associated with both greater hospital mortality (adjusted p-value: 0.03) and a higher percentage of patient discharge to nursing facilities (as opposed to their own homes) [88]. The association between malnutrition risk and ICU length-of-stay was unclear as Lomivorotov et al. [69] demonstrated that patients at risk of malnutrition were more likely to stay more than two days in the ICU (adjusted OR: 1.80; 95% CI: 1.10, 3.20; p-value: 0.03). However, this was not replicated in the study by Sheean et al. [88] (adjusted p-value: 0.23). An increased risk of malnutrition was not associated with hospital

length-of-stay (adjusted p-value: 0.08) [88] or postoperative complications (adjusted OR: 1.30; 95% CI: 0.70, 2.30; p-value: 0.34) [69].

Malnutrition Universal Screening Tool – Malnutrition risk was quantified using the MUST in three studies [56, 69, 90]. Studies with low risk of bias showed that malnutrition risk determined by the MUST was independently associated with one-year post-discharge mortality (adjusted OR: 12.5; 95% CI: 2.08, 100; p-value: 0.01) *[this was reported as 0.08 (95% CI: 0.01, 0.48) [90], but for the purpose of consistency, the odds ratio are reversed in this chapter]*. No association was observed for postoperative complication (adjusted OR: 1.30; 95% CI: 0.90, 2.00; p-value: 0.11) or ICU length-of-stay (adjusted OR: 1.20; 95% CI: 0.90, 2.00; p-value: 0.33) [69].

Other nutrition screening tools - The Mini Nutritional Assessment-Short Form and the Prognostic Inflammatory and Nutritional Index were used in one study each [83, 88], and the Short Nutritional Assessment Questionnaire was used in two studies [56, 69]. Malnutrition risk determined by the Mini Nutritional Assessment-Short Form was independently associated with higher hospital mortality (adjusted p-value: < 0.01) [88]. Regardless of the risk of bias, the Prognostic Inflammatory and Nutritional Index and the Short Nutritional Assessment Questionnaire were not associated with any clinical outcomes [56, 69, 83].



CCM: Critical Care Medicine; **JPEN:** Journal of Parenteral and Enteral Nutrition; **NCP:** Nutrition in Clinical Practice

Figure 2: Summary of each stage of search methods and number of articles retrieved

Table 4: Critical appraisal of risk of bias

Author	Subjects were representative and recruited at the same time	Follow-up was sufficient and complete	Outcome criteria were either objective or blinded	Important prognostic factors were adjusted	Risk of Bias
Sungurtekin et al. [70]	+	+*	±	–	Possible
Küçükardali et al. [55]	+	–	±	–	Possible
Sheean et al. [86]	+	+	±	–	Possible
Caporossi et al. [37]	+*	+*	±	±	Low
Coltman et al. [71]	+	+*	±	–	Possible
Fontes et al. [81]	+	+	±	+	Low
Schlossmacher et al. [83]	+	+	±	-	Possible
Terekeci et al. [89]	+	+	±	–	Possible
Sheean et al. [88]	+	+	±	±	Low
Tripathy et al. [90]	+	+	±	+	Low
van Venrooij et al. [56]	–	+	±	–	Possible
Lomivorotov et al. [69]	+	+*	±	+	Low
De Luis Román et al. [91]	+	+	±	–	Possible
Merli et al. [92]	+	+	±	+	Low
Guimaraes et al. [93]	+	+	±	–	Possible
Studies published after the systematic review					
Bector et al. [74]	–	+	+	–	Possible
Verghese et al. [77]	–	+	–	+	Possible
Ceniccola et al. [75]	+	+	+	+	Low
Gattermann Pereira et al. [87]	–	+	±	+	Possible

* Information was not available in the manuscript and clarification was sought from the author. +: Met criteria; –: Did not meet criteria; ±L Unclear

Table 5: Summary of studies included in the systematic review

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Sungurtekin et al. [70]	124 (55/45)	56 (NA)	APACHE II: 25 (NA)*	SGA	Moderate: 26.6 Severe: 11.3	Total: ICU: 23.4 Well-nourished: ICU: 14.3 Malnourished: ICU: 38.3 p-value: < 0.05	- - -	- - -
Küçükardali et al. [55]	342 (100/0)	67 (NA)	APACHE II: 19 (NA)*	NRS-2002	Moderate & Severe: 39.4	Total: Hosp: 26.9 Well-nourished: Hosp: 10.6 Malnourished: Hosp: 51.8 p-value: 0.02	Hosp: 6.6* Hosp: 6.4 Hosp: 7.9 p-value: < 0.05	- - -
Sheean et al. [86]	49 (100/0)	56 (NA)	APACHE II: 24 (NA) APACHE IV: 80 (NA)	SGA	Moderate & Severe: 49.0	Total: - Well-nourished: - Malnourished: -	ICU: 10.8 * ICU: 11.1 ICU: 10.5 p-value: 0.76	- - -
Caporossi et al. [37]	246 (61/39)	62 {NA}	APACHE II: 18 {NA} (range: 5-37)	SGA	Moderate: 53.7 Severe: 24.4	Total: ICU: 20.3 Well-nourished: ICU: 5.9 Malnourished: ICU: 24.5 Adj-OR: 2.00 (95% CI: 0.50, 7.60), p-value: 0.28	ICU: 9.0 - - Adj-OR: 21.00 (95% CI: 2.80, 157.70), p-value: < 0.01	- - -
Coltman et al. [71]	294 (NA)	59 (NA)	APACHE II: 13 (6.2)	SGA	Moderate & Severe: 37.8	Total: Hosp: 7.1 Well-nourished: Hosp: 4.4 Malnourished: Hosp: 11.7 OR: 2.90 (95% CI: 1.16, 7.24), p-value: 0.02 †	ICU: 4.3, Hosp: 8.5 ICU: 3.7, Hosp: 6.9 ICU: 5.4, Hosp: 9.9	- - -

Table 4: Summary of studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Fontes et al. [81]	185 (63/37)	62 (NA)	APACHE II: 14 {NA}	SGA	Moderate: 41.6 Severe: 12.4	Total: Hosp: 33.0 Well-nourished: - Malnourished: - Adj-OR: 8.12 (95% CI: 2.94, 22.42), p-value: < 0.05	- - -	- - - Adj-OR of malnourished patient readmitted to the ICU: 2.27 (95% CI: 1.08, 4.80), p-value < 0.05
Sheean et al. [88]	260 (57/43)	74 (NA)*	APACHE II: 12 (NA)*	SGA	Moderate: 21.6 Severe: 1.6	Total: Hosp: 6.2 Well-nourished: Hosp: 4.8‡ Malnourished: Hosp: 23.0‡ Adj. p-value: < 0.01§	ICU: 3.0, Hosp: 8.8 ICU: 2.7, Hosp: 8.0 ICU: 4.1, Hosp: 11.3 ICU Adj. p-value: 0.11‡ Hosp Adj. p-value: 0.08‡	Disch. Home: 69.2% Disch. Home: 76.1% Disch. Home: 47.5% Adj. p-value: < 0.01 ‡
				MNA	Moderate: 24.4 Severe: 10.0	Total: Hosp: 6.2 Well-nourished: Hosp: 6.1‡ Malnourished: Hosp: 16.7‡ Adj. p-value: 0.09§	ICU: 3.0, Hosp: 8.8 ICU:2.7, Hosp: 7.8 ICU:3.7, Hosp: 10.8 ICU Adj. p-value: 0.17‡ Hosp Adj. p-value: 0.07‡	Disch. Home: 69.2% Disch. Home: 76.2% Disch. Home: 56.7% Adj. p-value: 0.19 ‡
				MNA-SF	Moderate: 20.0 Severe: 5.8	Total: Hosp: 6.2 Well-nourished: Hosp: 5.3‡ Malnourished: Hosp: 21.7‡ Adj. p-value: < 0.01§	ICU: 3.0, Hosp: 8.8 ICU:2.7, Hosp: 8.2 ICU:4.1, Hosp: 10.6 ICU Adj. p-value: 0.06‡ Hosp Adj. p-value: 0.18‡	Disch. Home: 69.2% Disch. Home: 76.8% Disch. Home: 47.8% Adj. p-value: 0.19‡
				NRS-2002	Mild: 10.6 Moderate: 4.9 Severe: 15.0	Total: Hosp: 6.2 Well-nourished: Hosp: 5.8‡ Malnourished: Hosp: 19.5‡ Adj. p-value: 0.03§	ICU: 3.0, Hosp: 8.8 ICU:2.8, Hosp: 8.0 ICU:3.8, Hosp: 11.1 ICU Adj. p-value: 0.23‡ Hosp Adj. p-value: 0.08‡	Disch. Home: 69.2% Disch. Home: 74.9% Disch. Home: 53.2 Adj. p-value: 0.01‡

Table 4: Summary of the studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Tripathy et al. [90]	109 (NA)	75. (NA)	APACHE II: 19 (6.5)	MUST	Moderate: 20.2 Severe: 47.7	Total: 28-day PD: 30.3 Well-nourished: 28-day PD: 17.1 Malnourished: 28-day PD: 37.8 OR: 2.94 (95% CI: 1.10, 8.00), p-value: 0.03† Total: 1-year PD: 46.8 Well-nourished: 1-year PD: 25.5 Malnourished: 1-year PD: 74.5 Adj-OR: 0.01 (95% CI: 0.01, 0.60), p-value: 0.01 Total: ICU: 11.9 Well-nourished: ICU: - Malnourished: ICU: -	ICU: 7.1 - - - - - - - - -	- - - - - - - - - -
van Venrooij et al. [56]	325 (NA)	66 (NA)	Euro-SCORE (%) 0-2: 27.4 3-5: 33.5 ≥ 6: 39.1	MUST SNAQ	Moderate & Severe: 20.9 Moderate & Severe: 7.5	Total: Hosp: 2.5 Well-nourished: - Malnourished: - p-value: > 0.05 Total: Hosp: 2.5 Well-nourished: - Malnourished: - p-value: > 0.05	ICU > 2: 36%, Hosp>7: 33% - - p-value: >0.05 ICU > 2: 36%, Hosp > 7: 33% - - p-value: > 0.05	- - - - - -
Schlossmacher et al. [83]	83 (100/0)	64 (NA)	SAPS II: 65 (21.9)	PINI	Mean score: 118.5	Total: ICU: 19.3 Well-nourished: - Malnourished: - p-value: 0.491	ICU: 28.5 - -	- - -

Table 4: Summary of the studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Lomivorotov et al. [69]	1193 (NA)	6 (NA)*	Logistic Euro SCORE: 3.0 - 4.4 {NA}	SGA	Moderate: 4.6 Severe: 0.4	Total: Hosp: 2.8 Well-nourished: - Malnourished: -	- - - Adj-OR for > 2 days of ICU stay: 2.00 (95% CI 1.10, 3.70), p-value: 0.02	- - -
				MNA	Moderate: 19.1 Severe: 0.9	Total: Hosp: 2.8 Well-nourished: - Malnourished: -	- - - Adj-OR for > 2 days of ICU stay: 1.40 (95% CI 0.70, 2.30), p-value: 0.07	- - - Adj-OR for POC: 1.60 (95% CI 1.10, 2.20), p-value: < 0.01
				SNAQ	Moderate: 6.9 Severe: 8.9	Total: Hosp: 2.8 Well-nourished: - Malnourished: -	- - -	- - - Adj-OR for POC: 1.30 (95% CI 0.90, 2.00), p-value: 0.11
				NRS-2002	Moderate & Severe: 7.0	Total: Hosp: 2.8 Well-nourished: - Malnourished: -	- - - Adj-OR for > 2 days of ICU stay: 1.80 (95% CI 1.10, 3.20), p-value: 0.03	- - - Adj-OR for POC: 1.30 (95% CI 0.70, 2.30), p-value: 0.34
				MUST	Moderate: 8.6 Severe: 8.3	Total: Hosp: 2.8 Well-nourished: - Malnourished: -	- - - Adj-OR for > 2 days of ICU stay: 1.20 (95% CI 0.90, 2.00), p-value: 0.33	- - - Adj-OR for POC: 1.30 (95% CI 0.90, 2.00), p-value: 0.11

Table 4: Summary of the studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Guimaraes et al. [93]	56 (45/55)	58 (NA)	APACHE II: 21 (6.1) SOFA: 9 (NA)	SGA	Moderate: 67.0 Severe: 15.0	Total: 28-day: 69.6 Well-nourished: 28-day: 60.0 Malnourished: 28-day: 71.1 p-value: 0.46	- - -	- - -
De Luis Román et al. [91]	31 (NA)	56 (NA)	Child Pugh stage: (%) A = 9.7 B = 25.8 C = 64.5	SGA	NA	Total: 1-year: 6.4 Well-nourished: - Malnourished: - p-value: > 0.05	ICU: 0.7, Hosp: 22.4 - -	Incidence of acute organ rejection: 9.5%. Nutritional status did not influence the rate of acute organ rejection.
				MNA	NA	Total: 1-year: 6.4 Well-nourished: - Malnourished: - p-value: > 0.05	ICU: 0.7, Hosp: 22.4 - -	
Merli et al. [92]	38 (NA)	52 (NA)*	MELD: 15.4 (NA)* Child-Pugh: 8.8 (NA)*	SGA	Moderate & Severe: 52.6	Hosp: 5.3 Total: Hosp: 0.0 Well-nourished: Hosp: 10.0 Malnourished: p-value: 0.10	ICU: 12.9[a], Hosp: 30.1[a] ICU: 5.0, Hosp: 18.0 ICU: 20.0, Hosp: 41.0 Adj-HR for ICU: 0.18, p-value: < 0.01 Adj-HR for Hosp: 0.20, p-value: < 0.01	Delayed WH: 15.8% Delayed WH: 5.0% Delayed WH: 25.0% p-value: 0.08
Banks et al. [79]	62 (NA)	NA	NA	SGA	Moderate & Severe: 32.2	Total: NA Well-nourished: NA Malnourished: NA	NA NA NA	NA NA NA
Chakravarty et al. [80]	500 (NA)	59 (NA)	NA	SGA	Moderate & Severe: 65.6	Total: NA Well-nourished: NA Malnourished NA	NA NA NA	NA NA NA

Table 4: Summary of the studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)		Mortality (%)		Length-of-stay (days)	Others
Penie [85]	73 (NA)	NA	NA	SGA	Moderate & Severe:	54.8	Total: Well-nourished: Malnourished	NA NA NA	NA NA NA	NA NA NA
Terekeci et al. [89]	142 (100/0)	70 (NA)	APACHE II: 19 (NA)*	NRS-2002	Mean score:	4.4	Total: Well-nourished: Malnourished:	- - -	- - -	- NU: 3.6, UD: 3.6 NU: 6.4, UD: 5.9 NU p-value: < 0.05 UD p-value: < 0.05
Peterson et al. [82]	50 (52/48)	59 (NA)	APACHE II: 22 (NA)	SGA	Moderate & Severe:	44.0	Total: Well-nourished: Malnourished:	NA NA NA	ICU: 9.0, Hosp: 18.5 NA NA	NA NA NA
Sheean et al. [86]	57 (100/0)	50 (NA)	APACHE II: 24 (10)	SGA	Moderate & Severe:	50.8	Total: Well-nourished: Malnourished	NA NA NA	NA NA NA	NA NA NA

Table 4: Summary of the studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Studies published after the systematic review								
Bector et al. [74]	57 (100/0)	60 (NA)	APACHE II: 21 (NA)*	SGA	Moderate: 19.0 Severe: 16.0	Total: ICU: 24.6 Well-nourished: ICU: 10.8 Malnourished: ICU: 50.0 p-value: 0.004	ICU: NA ICU: NA ICU: NA p-value: >0.05	NA
Vallejo et al. [76]	1053 (53/47)	59 (NA)	APACHE II: NA	SGA DCM	Moderate: 50.9 Severe: 23.2 Present: 13.9	Total: - Well-nourished: - Malnourished: -	- - -	NA
Ceniccola et al. [75]	327 (58/42)	53 (NA)	APACHE II: 19 (NA)	MCC	Moderate: 15.6 Severe: 14.1	Total: Hosp: 46.1 Well-nourished: Hosp: 34.8 Malnourished: Hosp: 64.3 Adj-OR for MM: 2.4 (95% CI: 1.3, 4.3) Adj-OR for SM: 3.3 (95% CI: 1.5, 7.7)	- - -	NA
Gattermann Pereira et al. [87]	76 (0/100)	60 (16)	APACHE II: 11 {7.0, 14.0}	SGA	Moderate: 38.2 Severe: 22.4	Total: Hosp: 18.2 Well-nourished: Hosp: 3.3 Malnourished: Hosp: 28.3 p-value: 0.005 Adj-HR: 2.97 (95% CI: 0.37, 23.59), p-value: 0.304	ICU: 3.0, Hosp: 30.5 ICU: 2.5, Hosp: 20.5 ICU: 4.7*, Hosp: 39.3* Adj-RR for ICU ≥ 3: 1.40, p-value: 0.102 Adj-RR for Hosp ≥ 31: 2.57, p-value: 0.003	NA

Table 4: Summary of the studies included in the systematic review (cont.)

Authors	n (m/s)	Age (yrs)	Severity Score	Tool	Malnutrition (%)	Mortality (%)	Length-of-stay (days)	Others
Verghese et al. [77]	200 (100/0)	NA	APACHE II: NA	SGA	Moderate: 48.5 Severe: 6.5	Total: ICU: 47.5 Well-nourished: ICU: 28.9 Malnourished: ICU: 62.7 Adj-OR for MM: 3.5 (95% CI: 1.7, 7.3) Adj-OR for SM: 11.1 (95% CI: 2.3, 54.7)	ICU: 8.6 ICU: NA ICU: NA p-value: 0.041	NA

Values are means (standard deviation). Median {interquartile range} or percentages unless otherwise stated. Age and severity scores are rounded to the nearest 10**. Adj**: Adjusted; **Adj-HR**: Adjusted hazard ratio; **Adj-OR**: Adjusted odds ratio; **APACHE II/IV:** Acute physiology and chronic health evaluation II/IV; **CI**: Confidence interval; **Disch**: Discharged; **DCM:** Diagnostic criteria for malnutrition**; EuroSCORE:** European system for cardiac operative risk evaluation; **Hosp**: Hospital; **ICU**: Intensive care unit; **IR:** Interquartile range; **m/s**: percentage of medical ICU/surgical ICU patients; **MCC:** Malnutrition classification criteria; **MELD:** Model for end-stage liver disease; **MM:** Moderate malnutrition; **MNA**: Mini nutritional assessment; **MNA-SF**: Mini nutritional assessment short form; **MUST**: Malnutrition universal screening tool; **NA**: Not available; **NRS-2002**: Nutritional risk screening 2002; **NSC**: Nutritional status classification in the department of veterans affairs; **NU**: Mean NRS-2002 score of patients with newly developed pressure ulcers; **op**: Operation; **OR**: Odds ratio; **PINI:** Prognostic inflammatory and nutrition index; **Post-op**: Post-operation; **POC**: Post operation complication; **SAPS II:** Simplified acute physiology score II; **SD:** Standard deviation; **SGA**: Subjective global assessment; **SM:** Severe malnutrition; **SNAQ**: Short nutritional assessment questionnaire; **SOFA:** Sequential organ failure assessment score; **UD**: Mean NRS-2002 score of patients with pressure ulcers at discharge; **WH**: Wound healing; ***:** approximation; †: self-calculated from the values provided, ‡: Hospice and death combined, §: adjusted for APACHE II only.

Table 6: Prevalence of malnutrition

Types of patients in ICU	Prevalence of malnutrition
Heterogeneous group [37, 55, 70, 71, 74-77, 79-82, 84-87]	13.9% - 78.1%
Elderly [88]	23.2% - 34.4%
Cardiac surgery [69]	5.0% - 20.0%
Liver transplantation [91, 92]	52.6%
Acute kidney injury [93]	82.0%

Table 7: Nutrition screening tools used in ICU

Instrument	Diet Related and/or Gastrointestinal Symptoms	Anthropometry and/or Physical Assessment	Severity of Illness	Others
Nutritional Risk Screening – 2002 [35]	Diet history over the last week	Weight loss in previous three months and BMI	Diagnosis	Age
Malnutrition Universal Screening Tool [94]	Diet history over the last five days	Percentage of weight loss in the previous three to six months and BMI	Presence of acute disease	
Nutritional Status Classification Scheme [97]	Current nutritional intake and appetite, gastrointestinal symptoms, and chewing and swallowing problems	Percentage of weight loss over the last two weeks to six months and percentage of ideal body weight	Diagnosis, levels of serum albumin, and lymphocyte count	
Instant Nutrition Assessment [101]			Levels of serum albumin and lymphocyte count	
Maastricht Index [96]		Percentage ideal body weight	Levels of serum albumin, prealbumin, and lymphocyte count	
Mini Nutritional Assessment – Short Form [100]	Diet history over the last three months	Weight history in the previous three months, BMI, and calf circumference	Psychological stress or acute disease in the past three months	Mobility and neuropsychological problems
Nutrition Risk in Critically Ill Score [38]			APACHE II, SOFA, number of comorbidities, and levels of IL6	Age, duration of hospitalization before admission to ICU

Table 6: Nutrition screening tools used in the intensive care unit (cont.)

Instrument	Diet Related and/or Gastrointestinal Symptoms	Anthropometry and/or Physical Assessment	Severity of Illness	Others
Prognostic Inflammatory and Nutritional Index [98]			Levels of serum albumin, prealbumin, C-reactive protein, and α1-acid glycoprotein	
Prognostic Nutritional Index [95]		Triceps skin fold	Levels of serum albumin and transferrin and skin Sensitivity	
Short Nutritional Assessment Questionnaire [99]	Appetite over the last month and use of nutritional supplement or tube feeding as a source of nutrition in the previous month	Amount of weight loss over the last one month and six months		

APACHE II: Acute physiology and chronic health evaluation II; **BMI:** Body mass index; **IL6:** Interleukin; **SOFA:** Sequential organ failure assessment

1.5 Discussion

This is the first systematic review to demonstrate an association between malnutrition and clinical outcomes in the ICU using validated nutrition assessment tools. Although malnutrition has previously been reported to prolong hospital length-of-stay and to increase the risk of infection and mortality in patients in the ICU [102-105], these associations have often been extrapolated from studies of patients who are not admitted to the ICU [101, 106, 107]. Where studies have been conducted on patients in the ICU and these associations have been observed [52, 53], the strength of these associations is weakened by the methods used to arrive at a diagnosis of malnutrition.

Overall there appears to be a clear independent association between malnutrition *(diagnosed by the SGA and the Malnutrition Clinical Characteristics)* and higher hospital mortality, but this association is not universal as exemplified by the study conducted by Merli et al. [92]. It is unclear if the lack of association in that study reflects the small sample size (n=38), very low mortality rate (5.3%), or patient characteristics (liver transplantation). The association between malnutrition and ICU mortality is also less consistent. Sungurtekin et al. [70] and Caporossi et al. [37] showed that ICU mortality in malnourished patients were higher than their counterparts, but Caporossi et al. [37] did not find an association after statistical adjustment for possible confounders. To better demonstrate the association between malnutrition and mortality risk, studies should assess these relationships in a dose-dependent manner. The SGA classifies nutritional status into three categories: well-nourished, mildly to moderately malnourished, and severely malnourished. Since mortality risk is assessed on a continuum, using three categories may better demonstrate the association between malnutrition and mortality risk. *This method of analysis was implemented in a recent study conducted by Verghese et al. [77] in which a significant dose-dependent association between malnutrition (diagnosed by the SGA) and ICU mortality was demonstrated. However, given its possible risk of bias, more studies are needed to confirm the association between malnutrition and ICU mortality.*

Malnutrition has been associated with extended hospital [69, 92] and ICU length-of-stay [69] in patients after surgery. This could result from the increased incidence of infections associated with malnutrition [92]. Although malnutrition in elderly patients was not associated with increased duration of hospital or ICU length-of-stay, this most probably reflects confounders in baseline variables (such as age, body mass index, and admission diagnosis) that were not amenable to statistical adjustment in the multivariable model [88]. Consistent with this, Lim et al. [51] have shown hospital length-of-stay to be significantly higher in malnourished patients in general wards, following adjustment for possible confounders.

With respect to the predictive value of the four validated nutrition assessment tools (SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and Diagnostic Criteria for Malnutrition) in the ICU, the SGA appears to have the most consistent predictive value, even if this can be attributed to the paucity of studies that used the Mini Nutritional Assessment and Malnutrition Clinical Characteristics, and to the absence of studies that used the Diagnostic Criteria for Malnutrition to determine the association between malnutrition and clinical outcomes in critically ill patients. The SGA and the Diagnostic Criteria for Malnutrition were developed to both assess nutritional status and predict clinical outcomes [58, 61], whereas the Mini Nutritional Assessment and the Malnutrition Clinical Characteristics were developed solely to assess nutritional status [49, 59]. That said, the SGA and the Malnutrition Clinical Characteristics use very similar components to diagnose malnutrition. Thus, as would be anticipated, the SGA and the Malnutrition Clinical Characteristics have been shown to have better predictive value compared to the Mini Nutritional Assessment. The results of this review are in agreement with a recent systematic review that evaluated the criterion, construct and predictive validity of nutrition screening and assessment tools used mostly in general wards [65]. As van Bokhorst-de van der Schueren et al. [65] concluded, the SGA had good predictive validity, especially for hospital mortality, length-of-stay, and complications.

The SGA includes professional judgment regarding the severity of loss of muscle mass and subcutaneous fat (Table 2). The association between loss of muscle mass and clinical outcomes has been determined [37, 108, 109]. When adjusted for all possible confounders, loss of muscle mass (measured by surrogates such as thickness of the adductor pollicis muscle [37],

bio-impedance analysis [109], level of serum creatinine [108], and mid-arm muscle circumference [110]) consistently demonstrates a positive association with poorer clinical outcomes. In addition, a large-scale study conducted recently demonstrated that the loss of subcutaneous fat assessed by the SGA was independently associated with hospital mortality [110]. The above could be possible reasons for the better prognostic value of the SGA. Since the SGA was also demonstrated to be a reliable tool [84], it is recommended as the better nutrition assessment tool in the ICU. *Nevertheless, it is important to recognise that the SGA is not without its limitations since Sheean et al. [111] demonstrated that sarcopenia was present in 50% to 60% of patients classified as well-nourished by the SGA.*

The association between malnutrition risk and clinical outcomes in the ICU is less clear. This could result from misclassification bias caused by the varying discriminative ability of the nutrition screening tools in identifying malnourished patients. Nevertheless, the NRS-2002 and MUST appear to have better predictive value among the nutrition screening tools. This may reflect similarity in the components included in both screening tools, i.e., short-term weight loss, body mass index, and weight loss over the last three months (Table 6). The results of the current review concur with those in a recent systematic review, where the NRS-2002 and MUST were shown to have better predictive value than other screening tools [65]. In addition, the NRS-2002 and MUST were also shown to have fair to good validity in another comprehensive review [63]. Interestingly, the review also revealed that the Malnutrition Screening Tool (MST) is the only screening tool with consistent evidence for both validity and reliability. However, the MST cannot be evaluated in the current review as it is not used in the eligible studies.

Although the strengths of this systematic review include a comprehensive literature search and stringent criteria for the risk of bias, there were some limitations. Firstly, it was beyond the scope of this review to comment on the causal effects of malnutrition on clinical outcomes in the ICU because the evidence was limited to observational cohort studies. Secondly, *most studies (except Ceniccola et al. [75])* did not satisfy all four criteria for risk of bias since the nutritional status of the subjects was not blinded to the treating physician or other members of the treating team. Although it is recognized that performing blinding is challenging, the lack of concealment may introduce significant biases. Future studies should

explore innovative ways of blinding. Alternatively, studies using a retrospective case review method might be particularly useful to validate these results. Thirdly, the review was only able to assess the validity and prognostic value of the *SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics and Diagnostic Criteria for Malnutrition* as well as the various nutrition screening tools reported in the literature. It is likely that other nutrition screening tools are used in the ICU setting. Lastly, the impact of malnutrition could not be quantified via a meta-analysis because of heterogeneity in outcome measures. Future studies should report outcomes in the form of risk estimates with adjustment of all important prognostic factors. In addition, it is proposed that receiver operating characteristic be carried out as the area under the receiver operating characteristic curve could be used to determine the clinical utility of nutritional status as a variable for prognostication.

Future Research and Policy Implications

In this review, the prevalence of malnutrition varied widely, and this may be due in part to the choice of nutrition assessment tool used to diagnose malnutrition. For example, there was considerable discordance between the SGA and the Diagnostic Criteria for Malnutrition in the study conducted by Vallejo et al. [76]. In the same cohort of patients, malnutrition prevalence quantified by the SGA was 74.1% whereas it was 13.9% when the Diagnostic Criteria for Malnutrition was used [76]. This is clear evidence of the need for a set of universal malnutrition diagnostic criteria. Since a consensus scheme for diagnosing malnutrition in adults was proposed recently, future studies should use this scheme to measure and report malnutrition prevalence.

Nevertheless, it is important for individual ICUs to determine the local prevalence of malnutrition to guide their screening and assessment policy. In cases where the prevalence of malnutrition is high (e.g., 80%), resources should be focused on nutrition assessment. On the other hand, efforts should be directed towards nutrition screening when the prevalence of malnutrition is lower (e.g., 40%) [112]. Future studies should compare the cost-effectiveness of nutrition screening and assessment across a range of malnutrition prevalence in the ICU as these require different amount of resources.

This review demonstrated that malnutrition is predictive of mortality outcomes. Existing mortality prognostic models such as the APACHE II [39] and Simplified Acute Physiology Score III [113, 114] generally use conventional predictors such as physiological variables, medical history, admission diagnosis, and/or medical treatment to predict mortality. Since this review demonstrated that nutritional status has independent prognostic value, future models should include nutritional status when prognosticating mortality.

Using appropriate nutrition screening and assessment tools will help identify effective strategies that reduce the negative impact of malnutrition. Previous studies that tested the effects of different amount, type, and composition of macro- and micronutrient have had mixed results [115]. In the studies, biochemical markers of nutritional status failed to demonstrate consistent improvement in clinical outcomes. The common limitation in those studies is the lack of valid baseline nutrition assessment for randomisation and/or stratification of analysis. It is plausible that the efficacy of treatment is dependent on the baseline nutritional status of the subjects. Therefore, future studies should include valid nutrition assessment at baseline.

1.6 Conclusion

Considering the evidence presented in the systematic review of published and more recent studies, there is a strong suggestion that malnutrition (diagnosed by validated nutrition assessment tools) is associated with poorer clinical outcomes such as hospital mortality and ICU length-of-stay. Among the four assessment tools (SGA, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and Diagnostic Criteria for Malnutrition), the SGA appears to have the most consistent prognostic validity in the critical care setting. Since the new Diagnostic Criteria for Malnutrition proposed by the Global Leadership Initiative on Malnutrition group has not been validated in the ICU and the Malnutrition Clinical Characteristics and the Diagnostic Criteria for Malnutrition were conceived after the initiation of this research programme, the SGA was adopted as the nutrition assessment tool for this research programme and the official assessment tool in NTFGH. In addition, the evidence provided by the published systematic review was used to support a new nutrition assessment policy in which all patients admitted into the ICU of NTFGH will have their nutritional status assessed by a dietitian, using the SGA, within 48 hours of ICU admission.

Findings in this chapter suggest that nutritional status should be included in the prognostication of mortality in critically ill patients. This is the first step towards developing a model that combines baseline nutritional status and disease severity to better predict mortality and identify patients who would derive the most benefit from aggressive nutrition support in the ICU. However, it can be challenging to determine the nutritional status of critically ill patients as they frequently are unable to provide adequate information for a comprehensive nutrition assessment. Therefore, a surrogate measure of nutritional status will be examined in the next chapter in the hope to fill this gap.

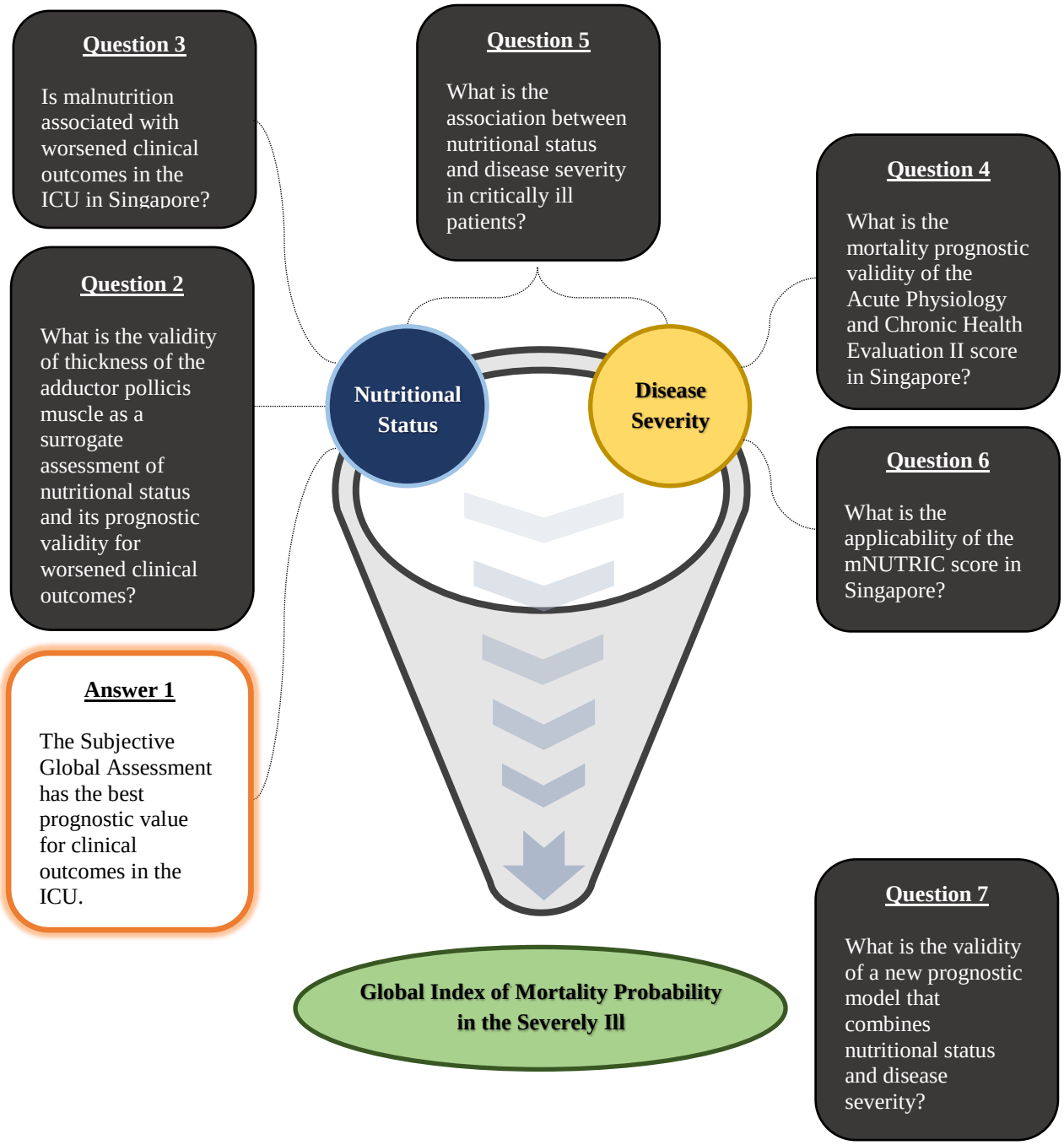


Figure 3: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 1

Chapter 2: Validity of the thickness of the adductor pollicis muscle as a surrogate assessment of nutritional status and its prognostic validity for worsened clinical outcomes

2.1. Contribution to the overall research objective

The SGA uses information such as weight and diet history, gastrointestinal symptoms, functional capacity, degree of metabolic stress, loss of muscle mass and subcutaneous fat, and fluid accumulation to comprehensively assess the nutritional status of patients. However, its applicability in the critical care setting may be limited as critically ill patients may not be able to provide essential information such as weight and diet history at the initial stage of ICU admission. Therefore, it may be advantageous to include another nutrition parameter in GLIMPSE.

The thickness of the adductor pollicis muscle may be a promising nutrition parameter to be included in GLIMPSE. It may be used as a surrogate assessment of nutritional status in the ICU since it is an objective bedside assessment that does not require any information from patients or their caregivers. However, it must demonstrate good agreement with the SGA before it can be included as a predictor in GLIMPSE. Therefore, a systematic review was conducted in May 2015 to determine the validity and reliability of the thickness of the adductor pollicis muscle in identifying malnutrition risk. The manuscript was submitted in August 2016 and accepted in the same month.

To keep this chapter up-to-date, evidence provided by studies published after the systematic review is also included in this chapter. In addition to being a valid and reliable nutrition parameter, the thickness of the adductor pollicis muscle must also be associated with poorer clinical outcomes in order to be included as a predictor in GLIMPSE. Therefore, the prognostic validity of the thickness of the adductor pollicis muscle will also be reviewed in this chapter.

The following section contains material from:

Lew CCH, Ong F, Miller M. Validity of the adductor pollicis muscle as a component of nutritional screening in the hospital setting: a systematic review. Clin Nutr ESPEN. 2016;16:1-7.

Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 75%
- Writing and editing: 95%

I made a major contribution to the conception of the manuscript, design of the systematic review, and acquisition, analysis, and interpretation of the studies included in the systematic review; I also drafted the manuscript and revised it accordingly to the recommendations provided by my co-authors and the peer reviewers.

2.2. Introduction[†]

Loss of muscle mass is one of the hallmarks of malnutrition [48, 49]. There are several ways of measuring loss of muscle mass in the clinical setting, namely bio-impedance analysis, physical examination, and anthropometry. The accuracy of bio-impedance analysis is variable, especially in the clinical setting as several conditions that are highly prevalent in the hospital (e.g. oedema, hypoalbuminemia, and some medications) can confound the results [116]. Concerning physical examination and anthropometry, where accuracy is skill-dependent, anthropometry may have an advantage over physical examination as it is relatively more objective in measuring muscle loss.

In the clinical setting, anthropometry for the measurement of muscle loss is commonly quantified by the mid-arm muscle area [117]. However, it is an indirect measurement of muscle

[†] The content of Sections 2.2 to 2.6 is similar to an original published article. To keep this thesis up-to-date, new information in the form of italicised text was added to the published systematic review.

mass as both the areas of subcutaneous fat and bone in the mid-arm region are adjusted in the calculation of muscle mass. This has been shown to over-estimate muscle mass by up to 25% [118]. In contrast, the thickness of the adductor pollicis muscle is the only muscle that can be directly measured with a calliper [119].

The adductor pollicis muscle is located between the thumb and index finger. It is easily accessible and can be directly measured because it is anatomically well-defined, flat in shape, and has a minimal amount of subcutaneous fat surrounding it [119]. Studies suggest that the thickness of the adductor pollicis muscle is a good surrogate measurement for total muscle mass [117, 120]. Therefore, the thickness of the adductor pollicis muscle could potentially be used in combination with other conventional nutritional parameters as part of nutritional screening if it can independently discriminate well- and malnourished patients at the bivariate level [121]. Therefore, this chapter primarily aims to determine the validity and reliability of the thickness of the adductor pollicis muscle in identifying malnutrition risk among adults in the hospital setting via a systematic review. *The secondary aim is to evaluate the prognostic value of the thickness of the adductor pollicis muscle for poorer outcomes in critically ill patients.*

Table 8: Aim of systematic review summarised by the PICO framework

P	**Population**	Primary aim: adult patients (>18 years old) who are not pregnant, and had their thickness of the adductor pollicis muscle measured along with nutritional status established by the Subjective Global Assessment and/or the Mini-nutritional Assessment. Secondary aim: studies that reported the association between the thickness of the adductor pollicis muscle and clinical outcomes in adult critically ill patients (>18 years old) who are not pregnant.
I	**Intervention/ Prognostic factor/ Exposure**	Patients who had thier thickness of the adductor pollicis muscle classifed as "low" in the primary studies.
C	**Comparison**	Patients who had thier thickness of the adductor pollicis muscle classifed as "normal" in the primary studies.
O	**Outcome**	Primary aim: agreement between the classification of the thickness of the adductor pollicis muscle and nutritional status. Secondary aim: all clinical outcomes reported in the primary studies.

2.3. Methods

Protocol and registration

The protocol *of the published systematic review* is registered on PROSPERO (Registration number: CRD42015023261).

Eligibility criteria

Since measurement of the thickness of the adductor pollicis muscle is relatively new, a broad set of eligibility criteria was developed to maximise the possibility of gathering all relevant articles. *For the primary aims, all case-control, cohort, and cross-sectional studies were eligible. For the secondary aim, only case-control and cohort studies were included because the cross-sectional study design may not be suitable for determining the prognostic validity of the thickness of the adductor pollicis muscle. In addition, all studies that measured the thickness of the adductor pollicis muscle along with either nutritional status or clinical outcomes of the critically ill were included. No restriction was imposed on publication date or language.*

Information sources and search methods

For the primary aims, a search strategy was developed with reference to the eligibility criteria, and three electronic databases, namely PubMed, CINAHL, and Scopus were systematically searched on 2 May 2015. To maximize the possibility of gathering all relevant studies, both free text terms and broad search terms (MeSH in PubMed and CINAHL Headings in CINAHL) were used. Synonyms for "malnutrition" and "nutritional status" were combined with synonyms for "screening" and "assessment" to identify all tools used to measure nutritional status [58]. Results of the latter were combined with all articles that included measurements of the adductor pollicis muscle. This search strategy was adapted to all three electronic databases to ensure consistency (Appendix-2). To further ensure that all relevant articles were identified, the reference lists of the articles that were included in this systematic review were hand-searched. *For the secondary aim, search terms such as "adductor pollicis"*

and synonyms for "intensive care unit" were combined in PubMed, and a hand search was performed on the reference lists of the articles included in the review. These were carried out in order to identify all studies that measured the thickness of the adductor pollicis muscle in critically ill patients.

Study selection

For the primary aims, there was a manageable number of articles following removal of duplicates. Therefore, instead of screening titles and abstracts, two reviewers (Fangyi Ong and I) assessed the relevance of the studies independently by evaluating the full-text versions of the articles. In all cases of disagreement, consensus was sought through discussion. *A similar method was adopted for the secondary aim, but only one reviewer (myself) performed the screening and assessment of article relevancy.*

This review focused on the thickness of the adductor pollicis muscle measured in a hospital setting. Therefore, only studies that recruited adults (>18 years old) and non-pregnant patients in the hospital were included. Articles that used electrical stimulation of the ulnar nerve to evaluate the strength of contraction and maximum rate of slackness of the adductor pollicis muscle were excluded. This method is not feasible in clinical practice as it requires specialised equipment, and the procedure is painful for the patient. Instead, articles that measured the thickness of the adductor pollicis muscle along with a valid nutrition assessment tool (SGA [58] and/or the Mini-nutritional Assessment [59]) were included in the review. In addition, articles included used appropriate statistical methods to evaluate the validity of the thickness of the adductor pollicis muscle in differentiating well- and malnourished patients. According to Jones [121], variables that could potentially be included as part of nutritional screening should minimally be able to differentiate well- and malnourished individuals at a bivariate level. Therefore, only studies that compared the mean or median of the thickness of the adductor pollicis muscle between well- and malnourished patients, reported discriminative statistics and/or agreement statistics were included. The PRISMA flow diagram was used to summarise the article selection processes (Figure 4). *For the secondary aims, the study selection criteria were largely similar to those described above except that all subjects had to be ICU patients and the thickness of the adductor pollicis muscle had to be measured within*

48 hours of ICU admission. In addition, the study had to report the association between the thickness of the adductor pollicis muscle and all forms of mortality measures (e.g., ICU mortality and hospital mortality) or length-of-stay (e.g., ICU length-of-stay and/or hospital-length-of-stay).

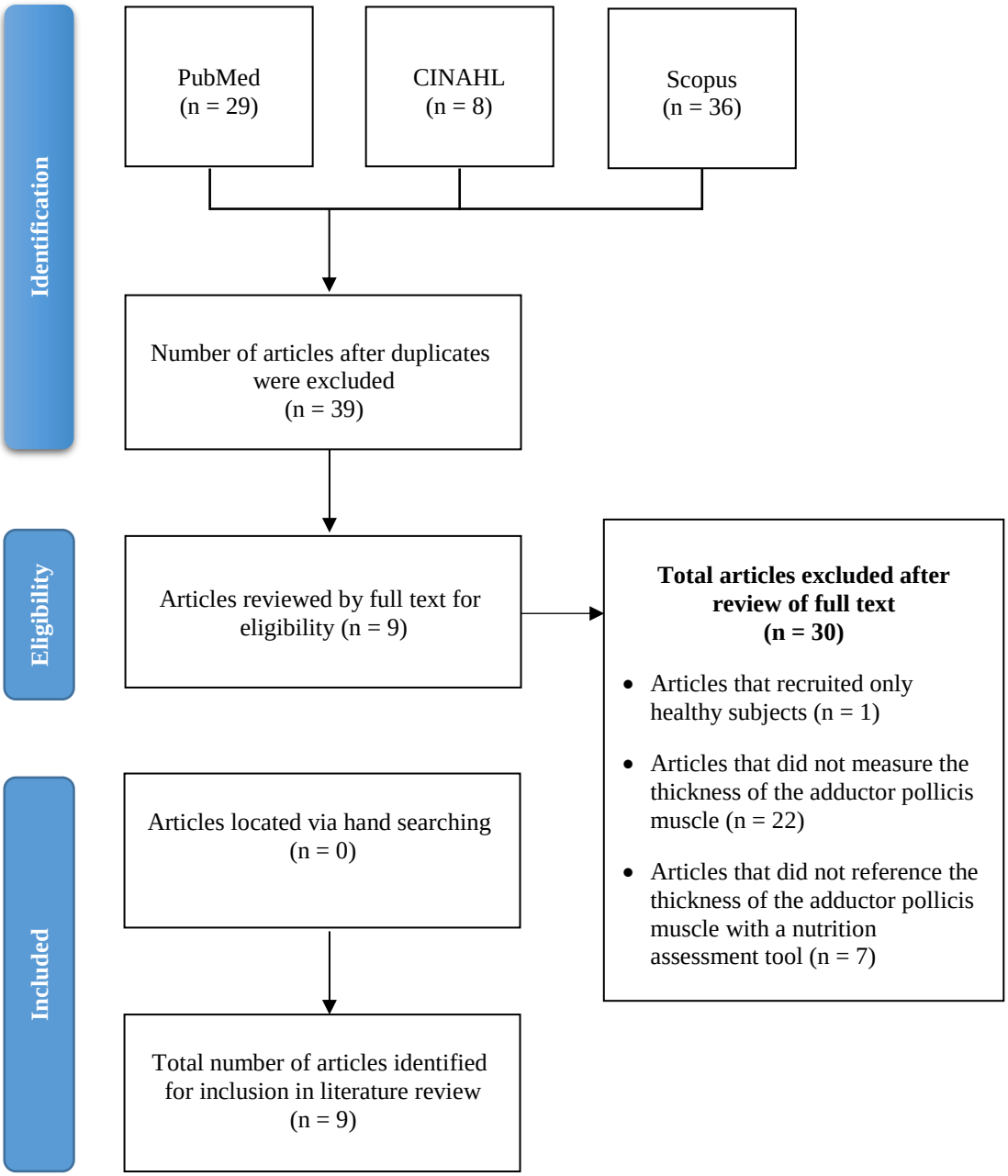


Figure 4: Summary of each stage of search methods and number of articles retrieved, excluded, and included in this systematic review

Data extraction

Data were extracted and grouped into *five* categories, as follows: 1) study design, country, patient characteristics (age and primary diagnosis); 2) timing and assessor of the thickness of the adductor pollicis muscle and nutrition assessment; 3) prevalence of malnutrition determined by nutrition assessment; 4) descriptive statistics (mean, standard deviation, median, and inter-quartile range), bivariate statistics (one-way analysis of variance and correlation), discriminative statistics (sensitivity, specificity, and area under the receiver operative characteristics curve [ROC]), multivariable analysis, agreement statistics (kappa), and reliability statistics (intra- and inter-assessor error), *and 5) clinical outcomes (thickness of the adductor pollicis muscle of survivors versus non-survivors, ICU-, and/or hospital length-of-stay.* Five authors were contacted for further information, and all of them responded [37, 122-125]. One reviewer (myself) extracted the required data, and the second reviewer (Fangyi Ong) checked the extracted data. Disagreements were resolved by discussion. If no consensus was reached, the opinion of a third reviewer (Michelle Miller) was sought.

Study appraisal and synthesis

For the primary aims, an evidence-based quality assessment tool, i.e., Quality Assessment of Diagnostic Accuracy Studies – II (QUADAS-II) [126], with high construct validity, interrater reliability, and internal consistency was used to evaluate the diagnostic validity of the studies included in this review. Essentially, it is a checklist of seven items that assess the risk of bias in four main domains (patient selection, index test, reference test, and patient flow). The tool also assesses the applicability of the diagnostic studies with reference to the review question. Each domain was scored as "low risk," "high risk," or "unclear risk" according to the detailed scoring criteria outlined by Whiting et al. [126]. The critical appraisal was independently performed by two reviewers (Fangyi Ong and I), and any disagreement between the two reviewers was resolved by discussion, or the opinion of a third reviewer (Michelle Miller) was sought if no consensus was reached.

For the secondary aim, the risk of bias in included studies was assessed with the same critical appraisal tool used in Chapter 1. Similarly, studies with low risk of bias were defined

as those having important prognostic factors statistically adjusted and meeting two of the remaining three criteria outlined by Laupacis et al. [72].

No meta-analysis was performed as measurements of the thickness of the adductor pollicis muscle were reported in means and medians. In addition, discriminative statistics were not pooled as the thickness of the adductor pollicis muscle cut-off points for malnutrition used were different: while Bragagnolo et al. [127] used cut-off values derived from their study, Gonzalez et al. [125] used cut-off values derived previously from a group of well-nourished subjects [119]. Similarly, agreement statistics were not pooled as the thickness of the adductor pollicis muscle cut-off points for malnutrition were different: while Nunes et al. [128] used cut-off values derived from Lameu et al. [129], Maurício et al. [122] and Silva et al. [124] used cut-off values derived from Gonzalez et al. [119].

2.4. Results

For the primary aims, the literature search generated 73 articles. Upon removal of duplicates and studies that did not meet the eligibility criteria, nine studies were included in the review. The flow chart of the selection process is provided in Figure 4. *Following publication of the systematic review, two more studies were published, resulting in 11 studies being reviewed for the primary aims. For the secondary aims, PubMed located 18 articles, of which four were relevant, and one additional article was identified via hand search. Hence, five articles were used to evaluate the prognostic validity of the thickness of the adductor pollicis muscle. Since three of these articles were identical to those used to achieve the primary aims, a total of 13 original articles are reviewed in this chapter.*

Of the 13 studies, 10 were carried out in Brazil, and the others were carried out in Portugal [130], Iran [131], and Singapore [132]. All studies were written up in English except for two written in Portuguese [127, 128]. They were all cross-sectional studies except for five studies, which were prospective cohort studies [37, 127, 131-133]. Most of the studies recruited medical patients, i.e., those with cancer [134, 135], critical illness [37, 131-133, 136], or liver [128] and renal diseases [123], as well as a group of heterogeneous inpatients [130]. The other three studies recruited surgical patients [125, 127, 134]. The mean or median age of the

subjects were 50 to 69 years old. Malnutrition was diagnosed by the SGA [37, 122-125, 127, 128, 133, 134, 136] or the Patient-Generated Subjective Global Assessment [130], and the prevalence of malnutrition in the inpatient setting ranged from 31.6% [125] to 88.5% [127] and was 6.7% [128] in the outpatient setting (Table 7).

All studies had some risk of bias (Table 8). In the domain of Index Test, both the SGA and the thickness of the adductor pollicis muscle measurements were carried out in a non-blinded fashion. In the domain of Reference Standard, two studies had partial verification bias because the SGA was not performed on all the patients and the rationale was not reported [124, 125]. There were applicability concerns in three studies. Silva et al. [124] and Nunes et al. [128] did not provide details on the methods used to perform the SGA and/or the thickness of the adductor pollicis muscle measurements, and Pereira et al. [123] and Silva et al. [124] did not report the type of calliper used.

Table 9: Summary of the validity of the thickness of the adductor pollicis muscle in differentiating nutritional status

Authors	n	Age (yrs)	Measurement details	Malnutrition prevalence	Bivariate/Multivariable statistics	Discriminative statistics	Agreement statistics
Bragagnolo et al. [127]	87	53.8 (15.4)	TAPM and SGA measured within 48 h of admission, by NSP	SGA-A: 11.5% SGA-B: 29.9% SGA-C: 58.6% DTAPM: 62.8% NDTAPM: 65.9%	Mean DTAPM and NDTAPM of SGA-A was significantly higher than SGA-B, p-value: < 0.001 Mean DTAPM and NDTAPM of SGA-B was significantly higher than SGA-C, p-value: 0.05	<u>Sensitivity</u> DTAPM: 72.4% NDTAPM: 77.3% <u>Specificity</u> DTAPM: 100.0% NDTAPM: 100.0% <u>ROC</u> DTAPM: 0.93 (95% CI: 0.86, 0.99) NDTAPM: 0.92 (95% CI: 0.85, 0.98)	NA
Bragagnolo et al. [134]	90	53.0 (16.0)	TAPM and SGA measured within 24 h of admission, by NSP	SGA-A: 14.4% SGA-B: 32.2% SGA-C: 53.3% TAPM: NA	<u>Multi-linear regression</u> Compared to SGA-B and SGA-C, DTAPM and NDTAPM were 4.7 mm thicker in SGA-A, p < 0.001	NA	NA
Caporossi et al. [37]	246	62 {NA}	NA	SGA-A: 21.9% SGA-B: 53.7% SGA-C: 24.4% TAPM: NA	<u>TAPM of right hand (mm)</u> SGA-A: 17.2 (5.4) SGA-B: 16.8 (5.7) SGA-C: 12.9 (5.3)* <u>TAPM of left hand (mm)</u> SGA-A: 15.8 (4.6) SGA-B: 15.9 (5.9) SGA-C: 12.3 (5.5)*	NA	NA

Table 7: Summary of the validity of the thickness of the adductor pollicis muscle in differentiating nutritional status (cont.)

Authors	n	Age (yrs)	Measurement details	Malnutrition Prevalence	Bivariate/Multivariable statistics	Discriminative statistics	Agreement statistics
Nunes et al. [128]	119	56.3 (12.0)	TAPM and SGA measured at outpatient visit, by NSP	SGA-A: NA SGA-B and SGA-C: 6.7% TAPM: 14.3%	NA	NA	Kappa: 0.25
Maurício et al. [122]	70	60.4 (14.3)	TAPM and SGA measured before radio-/chemotherapy by dietitians (number NA)	SGA-A: 30.0% SGA-B: 24.3% SGA-C: 45.7% TAPM: 13.3%	TAPM (mm) SGA-A: 24.3 (4.2) † SGA-B: 22.5 (6.5) SGA-C: 20.0 (5.1)	NA	Kappa: 0.04, p-value: < 0.05
Pereira et al. [123]	73	52.3 (17.0)	TAPM and SGA measured after haemodialysis, by two trained nutritionists	SGA-A: 52.0% SGA-B: 46.6% SGA-C: 1.4% TAPM: NA	No difference in the number of patients with TAPM lower or higher than 10 mm in each SGA category, p-value: 0.55	NA	NA
Silva et al. [124]	43	NA	TAPM and SGA measured before radio-/chemotherapy, by dietitians (number NA)	SGA-A: 13.9% SGA-B: 13.9% SGA-C: 72.2% TAPM: 44.2%	TAPM (mm) SGA-A: 21.0 {NA} SGA-B: 21.5 {NA} SGA-C: 16.5 {NA}‡	NA	Kappa: < 0.20

Table 7: Summary of the validity of the thickness of the adductor pollicis muscle in differentiating nutritional status (cont.)

Authors	n	Age (yrs)	Measurement details	Malnutrition prevalence	Bivariate/Multivariable statistics	Discriminative statistics	Agreement statistics
Gonzalez et al. [125]	361	49.6 (17.8)	TAPM and SGA measured by trained personnel (number and timing NA)	SGA-A: 68.4% SGA-B: 24.1% SGA-C: 7.5% TAPM: NA	DTAPM (Male) (mm) SGA-A: 26.0 {25.0, 28.0}† SGA-B: 19.5 {16.5, 22.0} SGA-C: 18.0 {15.0, 20.0} DTAPM (Female) (mm) SGA-A: 23.0 {21.0, 25.0}† SGA-B: 18.0 {16.0, 20.0} SGA-C: 17.0 {15.0, 18.0} NDTAPM (Male) (mm) SGA-A: 25.0 {24.0, 28.0}† SGA-B: 18.5 {15.5, 20.0} SGA-C: 16.0 {15.0, 20.0} NDTAPM (Female) (mm) SGA-A: 22.0 {20.0, 25.0}† SGA-B: 18.0 {16.0, 20.0} SGA-C: 16.0 {12.0, 18.0} Correlation with SGA DTAPM: r = -0.61, p-value: < 0.05 NDTAPM: r = -0.60, p-value: < 0.05 Multivariate linear regression DTAPM and NDTAPM of SGA-B and -C were 4.59 mm and 4.56 mm, and 6.51 mm and 6.14 mm thinner than SGA-A respectively, p-value: <0.001	Sensitivity DTAPM: 34.9% NDTAPM: 37.7% Specificity DTAPM: 98.7% NDTAPM: 97.8%	NA

Table 7: Summary of the validity of the thickness of the adductor pollicis muscle in differentiating nutritional status (cont.)

Authors	n	Age (yrs)	Measurement details	Malnutrition prevalence	Bivariate/Multivariable statistics	Discriminative statistics	Agreement statistics
Guerra et al. [130]	688	58 (21)	TAPM and SGA measured within 72 h of admission by two trained nutritionists	PG-SGA-A: 52.1% PG-SGA-B: 24.1% PG-SGA-C: 23.8% TAPM: NA	Correlation between TAPM and SGA r = -0.194, p-value: 0.001	NA	NA
New studies published after the systematic review							
Karst et al. [136]	83	68.7 (12.5)	TAPM and SGA measured within 48 h of admission by a nutritionist	SGA-A: 62.7% SGA-B: 20.5% SGA-C: 16.9% TAPM: 33.7%	NA	ROC with TAPM of < 6.5 mm as cut-off for malnutrition 0.82 (95% CI: 0.73, 0.91)	NA
Pereira et al. [133]	59	60.1 (17.4)	TAPM and SGA measured within 48 h by NSP	SGA-A: 40.7% SGA-B: 35.6% SGA-C: 23.7% TAPM: 79.7%	SGA-A: 15.7 (3.9) SGA-B: 14.5 (3.2) SGA-C: 13.4 (4.5) p-value: 0.203 Multivariable regression referencing 5th percentile for age and sex of an established reference range [119] Adj-RR: 2.0 (95% CI: 0.9, 4.7)	ROC with TAPM treated as a continuous variable: 0.61 (95% CI: 0.46, 0.76)	Kappa between SGA and TAPM 0.238 p-value: 0.04

Values are means (standard deviation) ot median {interquartile range} unless stated; * p-value: 0.001 SGA-C compared to SGA-A and SGA-B; † p-value: < 0.05 SGA-A compared to SGA-B and SGA-C; ‡ p-value: < 0.05 SGA-C compared to SGA-B; **Adj-RR:** Adjusted relative risk, **DTAPM:** Dominant thickness of the adductor pollicis muscle; **h:** hour; **NA:** Not available; **NDTAPM:** Non-dominant thickness of the adductor pollicis muscle; **NSP:** Non-specific personnel; **PG-SGA:** Patient-generated subjective global assessment; **ROC:** area under the receiver operating characteristics curve; **SGA:** Subjective global assessment; **TAPM:** Thickness of the adductor pollicis muscle

Table 10: Assessment of methodological risk of bias based on QUADAS-II

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference Standard	Flow and timing	Patient selection	Index test	Reference standard
Bragagnolo et al. [127]	+	–	+	+	+	+	+
Bragagnolo et al. [134]	+	–	+	+	+	+	+
Caporossi et al. [37]	+	–	+	+	+	+	+
Nunes et al. [128]	+	–	+	+	+	–	+
Maurício et al. [122]	+	–	+	+	+	+	+
Pereira et al. [123]	+	–	+	+	+	–	+
Silva et al. [124]	+	–	–	+	+	–	–
Gonzalez et al. [125]	+	–	–	+	+	+	+
Guerra et al. [130]	+	–	+	+	+	+	+
New studies published after the systematic review							
Karst et al. [136]	+	–	+	+	+	+	+
Pereira et al. [133]	+	–	+	+	+	+	+

+ Low risk – High risk

The procedures used to measure the thickness of the adductor pollicis muscle were similar in seven studies [122-125, 127, 130, 134]. Measurements were taken while subjects were seated, elbows bent at a 90-degree angle and hands resting on the knees. However, four studies had to modify the procedure to take into account limitations in critically ill patients [37, 131-133]. Measurements were taken while these subjects were in a supine position, elbows bent at a 90-degree angle and hands lying on the upper abdomen. Although the procedures were mostly similar, the recorded measurements were derived differently. Most studies used the mean of *two or* three consecutive measurements [37, 123, 125, 127, 130-134, 136] while other studies used the highest value of three measurements [122, 124]. Nunes et al. [128] did not report how the recorded measurements were derived. Callipers used to measure the thickness of the adductor pollicis muscle were also different across the studies. The Cescorf calliper was used in *five studies* [37, 127, 128, 134, 136], the Lange calliper in *three studies [122, 125, 133], Caliper [131], Holtian [132]* and the Harpenden calliper in one study [130]. Pereira et al. [123] and Silva et al. [124] did not report the type of calliper used.

Intra- and inter-assessor reliability of the thickness of the adductor pollicis muscle measurements was not reported in all the studies. *Furthermore, the clinicians who carried out the measurements of the adductor pollicis muscle were not identified in more than half of the studies [37, 125, 127, 128, 132-134]. When specified, measurements were performed by nutritionists [123, 130, 136], students [131] or dietitians [122, 124].*

Validity and reliability of the thickness of the adductor pollicis muscle in identifying malnutrition risk

The difference in the thickness of the adductor pollicis muscle between well- and malnourished patients was determined mostly by bivariate analyses. One-way analysis of variance was used in several studies, and this showed mixed results (Table 7) [37, 122, 124, 125, 127, 133]. Only Bragagnolo et al. [127] demonstrated that the thickness of the adductor pollicis muscle was significantly higher in patients with better nutritional status (SGA-A > SGA-B > SGA-C). However, this result was not observed in other studies [37, 122, 124, 125, 133]. Gonzalez et al. [125] demonstrated that the adductor pollicis muscle of well-nourished patients (SGA-A) was significantly thicker than in malnourished patients (SGA-B and SGA-C

combined). On the other hand, Maurício et al. [122], Caporossi et al. [37], and Silva et al. [124] demonstrated that the adductor pollicis muscle of both well- and mildly-moderately malnourished patients (SGA-A and SGA-B combined) were significantly thicker than severely malnourished patients (SGA-C). Other bivariate analyses quantified the correlation and agreement (kappa) between the thickness of the adductor pollicis muscle and nutritional status diagnosed by the SGA [122-125, 128, 130, 133]. Correlation analyses showed mixed results as Gonzalez et al. [125] found moderate negative correlation whereas Pereira et al. [123] and Guerra et al. [130] found either no correlation or weak negative correlation between the SGA and the thickness of the adductor pollicis muscle. Kappa analyses were performed in *four studies*, and agreement between the thickness of the adductor pollicis muscle and SGA was consistently poor (with kappa ranging from 0.04-0.25) [122, 124, 128, 133].

Multilinear regression analysis was used in two studies to determine the difference in the thickness of the adductor pollicis muscle between well- and malnourished patients. Both studies showed that the thickness of the adductor pollicis muscle of well-nourished patients were thicker than that of their malnourished counterparts [125, 134]. After adjusting for sex, age, and/or weight, the adductor pollicis muscle of the dominant and non-dominant hands in well-nourished patients were at least 4.6 mm thicker than in malnourished patients [125, 134]. *However, a recent study using multivariable analysis (adjusted for sex) revealed that a measurement of the thickness of the adductor pollicis muscle below the 5th percentile of established reference [119] was not associated with a higher risk of malnutrition [133]*.

Only four studies used discriminative statistics [125, 127, 133, 136] (i.e., ROC, sensitivity and specificity analyses), and these generally showed that the thickness of the adductor pollicis muscle could differentiate well-nourished patients from malnourished patients (combination of mildly-moderately and severely malnourished) except for Pereira et al. [133], in which the ROC curve showed only moderate discrimination (ROC AUC: 0.61). The specificity of the thickness of the adductor pollicis muscle in discriminating well-nourished patients from malnourished patients was high (Table 7) [125, 127]. However, the cut-off values used in both studies were different.

There were vast variations in the cut-off values used to define nutritional status. Nunes et al. [128] used cut-off values provided by Lameu et al. [129] whereas Maurício et al. [122], Silva et al. [124] and Gonzalez et al. [125] used cut-off values provided by Gonzalez et al. [119]. Other studies self-defined their cut-off values using the ROC analysis with the SGA as the criterion standard [127], or the 10^{th} percentile [37], 50^{th} [123] percentile, or one standard deviation below the mean [137] of the thickness of the adductor pollicis muscle measurements of recruited subjects. Table 9 summarises the cut-off values used in the studies included in the review.

Table 11: Thickness of the adductor pollicis muscle cut-off values used to define malnutrition risk

Authors	Method used to determine the TAPM cut-off value to define malnutrition risk	DTAPM (mm)			NDTAPM (mm)		
		Male	Female	All	Male	Female	All
Bragagnolo et al. [127]	Receiver Operative Characteristics	NA	NA	13.4	NA	NA	13.1
Bragagnolo et al. [134]	NA	NA	NA	NA	NA	NA	NA
Caporossi et al. [37]	10th percentile of subjects' TAPM	NA	NA	9.5	NA	NA	8.3
Nunes et al. [128]	Referenced Lameu et al. [129], where 421 healthy subjects aged 18 to 87 were recruited. Mean cut-off values were derived from values that were more than one standard deviation away from the mean and median.	9.5† 11.0‡	8.0† 9.0‡	NA NA	9.5† 11.0‡	8.0† 9.0‡	NA NA
Maurício et al. [122] Silva et al. [124] Gonzalez et al. [125] Pereira et al. [133]	All three studies referenced Gonzalez et al. [119], where 300 healthy subjects aged 18 to 90 were recruited. Cut-off values were derived from the 5th percentile of the subjects' TAPM	20.0§ 23.0¶ 18.0††	16.0§ 17.0¶ 14.0††	NA NA NA	19.0§ 21.0¶ 16.0††	15.0§ 16.0¶ 14.0††	NA NA NA
Pereira et al. [123]	Median of the subjects' TAPM measurements	NA	NA	10‡	NA	NA	10‡
Guerra et al. [130]	NA	NA	NA	NA	NA	NA	NA
Karst et al. [136]	Referenced de Andrade et al. [137], where 99 cardiac surgical patients with a mean age of 50 were recruited. Cut-off value was derived from a value that was one standard deviation below the mean TAPM measurements.	NA	NA	6.5	NA	NA	6.5

† mean; ‡ median; § 18 to 29 years old**;** ¶ 30 to 59 years old**;** †† ≥ 60 years old**; DTAPM:** Dominant thickness of the adductor pollicis muscle**; NA:** Not available; **NDTAPM:** Non-dominant thickness of the adductor pollicis muscle**; TAPM:** Thickness of the adductor pollicis muscle

Prognostic validity of thickness of the adductor pollicis muscle for poorer clinical outcomes in critically ill patients

Six studies investigated the prognostic value of the thickness of the adductor pollicis muscle for worsened clinical outcomes in critically ill patients (Table 10). The number of patients in these studies ranged from 59 to 304, and their mean age, APACHE II scores, and mortality rate ranged from 51 to 69 years, 10 to 21, and 5% to 42%, respectively. All studies had some risk of bias, with Caporossi et al. [37] having the lowest risk and Nematifard et al. [138] the highest.

Bivariate comparison of the thickness of the adductor pollicis muscle between survivors and non-survivors showed inconsistent results. While survivors had significant thicker adductor pollicis muscle in two studies [37, 131, 138], this observation was not made in other studies [132, 133, 136]. In contrast, results of multivariable regressions were more consistent. After adjusting for possible confounders, Caporossi et al. [37] and Ghorabi et al. [131] demonstrated a significant association between low thickness of the adductor pollicis muscle (approximately 9.0 mm) and ICU mortality. Similarly, Nematifard et al. [138] revealed that thickness of the adductor pollicis muscle < 15 mm was associated with hospital mortality.

Studies that sought to determine the association between ICU length-of-stay and thickness of the adductor pollicis muscle had mixed results. Bivariate analyses showed that the variability in adductor pollicis muscle measurements only explained 1.0% to 16% of the variability in ICU length-of-stay [131, 132], and the median ICU length-of-stay between patients with extremely thin adductor pollicis muscle (i.e., 6.5 mm) was not significantly longer than for their counterparts [136]. Although bivariate analyses had consistent findings, multivariable regressions yielded conflicting results. While ICU length-of-stay was not associated with thickness of the adductor pollicis muscle in the study conducted by Caporossi et al. [37], significant association was observed in other studies [131, 133]. The cut-off value used by Ghorabi et al. [131] was 9 mm while that used by Pereira et al. [133] was much higher (ranging from 14.0 mm to 23.0 mm).

Table 12: Summary of association between thickness of the adductor pollicis muscle and poorer clinical outcomes in critically ill patients

Authors	n	Age (yrs)	APACHE II	Tool	Reference criterion	Mortality	Bivariate/ multivariable analysis	ICU Length-of-stay (days)	Risk of bias
Caporossi et al. [37]	246	62 (NA)*	18 (NA)*	Cescorf skinfold calliper	10th percentile of measurements in the study	ICU: 20.3%	Right hand Survivor: 16.7 (6.0) Non-survivor: 14.1 (6.4) p-value: 0.03 Left hand Survivor: 16.1 (6.9) Non-survivor: 13.4 (5.7) p-value: 0.04 Multivariable regression Adj-OR: 6.3 (95% CI: 1.2, 32.6)	Multivariable regression Adj-OR: 1.9 (95% CI: 0.7, 4.8)	a) Low b) Low c) High d) Low
Leong Shu-Fen et al. [132]	229	59.4 (16.0)	NA	Holtian skinfold calliper	Mean of TAPM in survivors and non-survivors	28-day: 20.1%	Right hand Survivor: 20.5 (6.1) Non-survivor: 20.0 (5.3) p-value: 0.62 Left hand Survivor: 20.0 (6.3) Non-survivor: 19.7 (5.0) p-value: 0.77	Correlation of determination Right hand: 3.3% Left hand: 1.0%	a) Low b) Low c) High d) High
Karst et al. [136]	83	68.7 (12.5)	NA	Cescorf skinfold calliper	TAPM of < 6.5 mm {de Andrade, 2005 #12004}	Undefined: 4.8%	Survivors with TAPM above reference criterion: 3.8% Survivors with TAPM below reference criterion: 7.1% p-value: 0.519	> 6.5 mm: 4 {3, 6} < 6.5 mm: 3 {2, 4.8} p-value: 0.183	a) Low b) Low c) High d) High

Table 10: Summary of association between thickness of the adductor pollicis muscle and poorer clinical outcomes in critically ill patients (cont.)

Authors	n	Age (yrs)	APACHE II	Tool	Reference criterion	Mortality	Bivariate/ multivariable analysis	ICU Length-of-stay (days)	Risk of bias
Ghorabi et al. [131]	127	51.3 (20.4)	20.7 (NA)	Caliper skinfold calliper	TAPM < 9 mm	ICU: 42%	Dominant hand Survivor: 16.7 (2.2) Non-survivor: 11.1 (2.0) p-value: 0.05 Multivariable regression Adj-OR: 5.6 (95%CI: 0.02, 0.12) – erroneously reported	Correlation of determination Dominant hand: 16% Multivariable regression for length-of-stay of > 10 days Adj-OR: 11.3 (95%CI: 4.4, 29.1)	a) Unclear b) Low c) High d) Low
Pereira et al. [133]	59	60.0 (17.4)	9.9 (NA)	Lange skinfold calliper	5th percentile for age and sex of established reference range [119]	Hospital: 10.2%	Non-dominant hand Survivor: 14.8 (3.6) Non-survivor: 13.7 (5.7) p-value: 0.487	Multivariable regression for length-of-stay of > 3 days Adj-RR: 2.9 (95%CI: 1.1, 7.8)	a) High b) Low c) High d) Low

Table 10: Summary of association between thickness of the adductor pollicis muscle and poorer clinical outcomes in critically ill patients (cont.)

Authors	n	Age (yrs)	APACHE II	Tool	Reference criterion	Mortality	Bivariate/ multivariable analysis	ICU Length-of-stay (days)	Risk of bias
Nematifard et al. [138]	304	54.7 (18.3)	15.0 (NA)	Caliper skinfold calliper	Median of TAPM measurements (< 15 mm)	Hospital: 31.6%	Dominant hand Survivor: 16.0 {14.0, 18.0} Non-survivor: 13.0 {12.0, 14.0} p-value: 0.001 Multivariable regression Adj-OR: 1.29 (95% CI: 1.21, 1.37) C-statistics TAPM: 0.166 APACHE II: 0.771 TAPM and APACHE II: 0.851	NA	a) High b) High c) High d) Low

Values are means (standard deviation) or median {interquatile range} unless stated. *****: approximation; **a):** Subjects were representative and recruited at the same time; **b):** Follow-up was sufficient and complete; **c):** Outcome criteria were either objective or blinded; **d):** Important prognostic factors were adjusted; **Adj-OR:** Adjusted odds ratio; **APACHE II:** Acute physiology and chronic health evaluation II; **Adj-RR:** Adjusted relative risk determined by Poisson regression; **CI:** Confidence interval; **ICU**: Intensive care unit

2.5. Discussion

This is the first systematic review that evaluated the validity and reliability of the thickness of the adductor pollicis muscle in identifying malnutrition risk *as well as the prognostic validity of the* thickness of the adductor pollicis muscle *for poorer clinical outcomes in critically ill patients. The results showed that the* thickness of the adductor pollicis muscle *has limited validity as a component of nutritional screening and parameter for prognostication of clinical outcomes in critically ill patients.*

Validity and reliability of the thickness of the adductor pollicis muscle in identifying malnutrition risk

Although bivariate and multivariable analyses demonstrated that the thickness of the adductor pollicis muscle among malnourished patients were significantly different from their well-nourished counterparts, such results may be overestimated because some risk of bias was present since the SGA and the thickness of the adductor pollicis muscle were performed in a non-blinded fashion.

Concordance between the thickness of the adductor pollicis muscle and SGA was generally poor. Pereira et al. [133] demonstrated that the thickness of the adductor pollicis muscle had only moderate discriminative ability in identifying malnutrition (ROC: 0.61). When concordance was analysed by kappa statistics, the thickness of the adductor pollicis muscle consistently had poor concordance (ranged from 0.04-0.25) [122, 124, 128, 133]. Only Bragagnolo et al. [127] and Karst et al. [136] showed that the thickness of the adductor pollicis muscle had excellent discrimination (ROC ranged from 0.82 to 0.92). These disparate findings were likely due to differences in the cut-off values used. Since the consensus scheme for diagnosing malnutrition in adults was proposed recently [62], concordance between thickness of the adductor pollicis muscle and the new scheme has not been reported.

Different cut-off values were used to define malnutrition risk (Table 9). Some studies self-derived the cut-off values [37, 123, 127] whereas other studies [122, 124, 125, 128, 136] used cut-off values derived either from healthy populations [119, 129] or from patients [137].

Lameu et al. [129] and Gonzalez et al. [119] measured the thickness of the adductor pollicis muscle of well-nourished and healthy individuals and established cut-off values that define malnutrition risk. However, these cut-off values may have limited generalizability as all of the subjects were monoethnic, i.e., Brazilians. Thickness of the adductor pollicis muscle cut-off value used by Karst et al. [136] was exceptionally low (i.e. < 6.5 mm) when compared to other studies reported in the systematic review (9.5 mm to 23.0 mm in Males, and 8.0 mm to 17.00 mm in Females – Table 9).

The applicability of using thickness of the adductor pollicis muscle as a component of nutritional screening may be limited by the lack of measurement standardization and reliability measurement. The methods and callipers used to measure the thickness of the adductor pollicis muscle varied across studies. The consequence of such differences is demonstrated by the results of Lameu et al. [129] and Gonzalez et al. [119], where cut-off values used to define malnutrition risk were vastly different. Lameu et al. [129] used the Lange calliper and the mean of three measurements, whereas Gonzalez et al. [119] used the Crecorf calliper and the highest value of three measurements. These differences could explain the discrepancies in the results of the studies included in the review. None of the studies reported the reliability of measuring the thickness of the adductor pollicis muscle. Since a clinically useful tool requires both validity and reliability [135], the absence of intra- and inter-reliability data precludes the use of thickness of the adductor pollicis muscle in the hospital setting.

Recent developments in the literature further questioned the validity of the thickness of the adductor pollicis muscle as a surrogate measure of lean body mass. Early studies suggested that the thickness of the adductor pollicis muscle is a useful component of nutrition screening and assessment since it is a good surrogate measure of lean body mass – as evidenced by fair correlation with other anthropometry measurements (body mass index and mid-arm muscle circumference) or bio-impedance analysis [117, 120]. However, the validity of the thickness of the adductor pollicis muscle as a surrogate measure of lean body mass was recently challenged by three studies [139-141]. Unlike previous studies [117, 120], these studies used more accurate measurements of lean body mass, such as predictive equation [142] or dual-energy X-ray absorptiometry [140, 141]. They collectively demonstrated that the thickness of the adductor pollicis muscle only accounted for 12% to 37% of the variability in lean body mass

and concluded that it is a poor surrogate measure for lean body mass [139-141]. More importantly, body weight and the body mass index had significantly higher predictive value for lean body mass, and the addition of the thickness of the adductor pollicis muscle in multivariable analyses increased the accuracy of prediction by only 0.06% to 4% – an amount that is unlikely to have substantial clinical significance.

Prognostic validity of thickness of the adductor pollicis muscle for poorer clinical outcomes in critically ill patients

Six studies investigated the prognostic value of the thickness of the adductor pollicis muscle for worsened clinical outcomes in critically ill patients (Table 10). Collectively, the association between low thickness of the adductor pollicis muscle and mortality yielded conflicting results. While three studies [37, 131, 138] showed that low thickness of the adductor pollicis muscle was associated with higher adjusted odds for ICU mortality, the same was not demonstrated in other studies [132, 133, 136]. The reason for the disparate results is unclear, but it may be attributed to differences in the cut-off value used to define "low thickness of the adductor pollicis muscle."

The association between the thickness of the adductor pollicis muscle and ICU length-of-stay is equivocal. While Ghorabi et al. [131] and Pereira et al. [133] showed inverse association, Caporossi et al. [37] showed no association, and Leong Shu-Fen et al. [132] revealed that the thickness of the adductor pollicis muscle accounted for only up to 3% of the variability in ICU length-of-stay. Thus, it is difficult to interpret the rationale for the conflicting results, and the plausible explanation is likely the differing cut-off value used to define "low thickness of the adductor pollicis muscle."

2.6. Conclusion

Studies included in the published systematic review [1] and the newer studies demonstrated that thickness of the adductor pollicis muscle has poor agreement with the SGA. This may be due to its weak association with lean body mass. Therefore, it must be concluded that thickness of the adductor pollicis muscle plays a limited role in nutrition screening and

assessment. Furthermore, thickness of the adductor pollicis muscle exhibits questionable prognostic value for poorer clinical outcomes in critically ill patients. This may be partly due to the lack of a robust cut-off value that has adequate external validity to define "low thickness of the adductor pollicis muscle". Given the above rationales, thickness of the adductor pollicis muscle was excluded as a candidate predictor for GLIMPSE, leaving the SGA as the only candidate nutrition parameter. The next chapter therefore aims to verify the association between malnutrition diagnosed by the SGA and poorer clinical outcomes in the local setting.

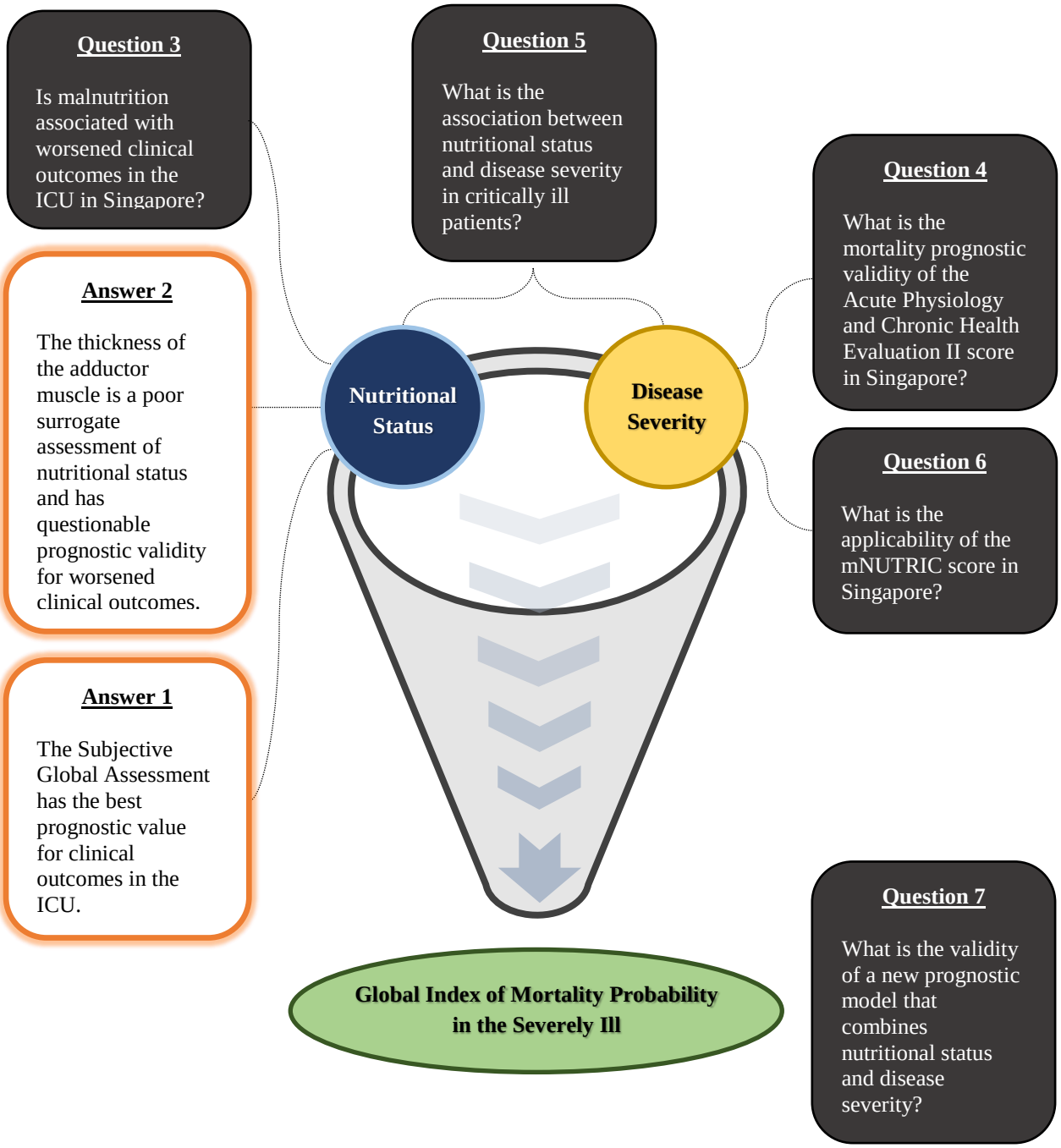


Figure 5: Conceptual Framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 2

Chapter 3: Is malnutrition associated with worsened clinical outcomes in the intensive care unit in Singapore?

3.1. Contribution to the overall research objective

Given the findings of the systematic review in Chapter One, the SGA [58] was adopted as the official nutrition assessment tool in 2014, in which all patients in the ICU at NTFGH receive a nutrition assessment using the SGA within 48 hours of ICU admission. The Malnutrition Clinical Characteristics [49] was not selected as it was not validated at that point in time. Similarly, the Diagnostic Criteria for Malnutrition [48] was not chosen as it was only conceived in 2015.

Malnutrition diagnosed by the SGA was associated with increased ICU length-of-stay [37, 69, 92], ICU re-admission [81], incidence of infection [92], and the risk of hospital mortality [81, 88] in Italy [92], Russia [69], Brazil [37, 81] and the United States [88]. However, the external validity of these associations has not been studied in Singapore, and it is essential to do so because no nutrition assessment tool has been shown to be valid in all settings [65]. More importantly, there were several limitations in the primary studies that weaken the association between malnutrition and worsened clinical outcomes [1]. To develop a prognostic model that includes nutritional status as a predictor from a local cohort of critically ill patients, it is essential to demonstrate a robust relationship between malnutrition and worsened clinical outcomes in the local setting.

Since the SGA is encompassed in the standard nutritional care in NTFGH, it provides a unique opportunity to conduct a prospective cohort study in which all patients can be included to minimise the risk of selection bias. Therefore, a prospective cohort study was conducted in NTFGH, and close attention was given to the study design, in which the limitations identified in Chapter 1 were addressed. However, two outcomes were not measured, namely incidence of infection, and ICU re-admission rate, the former because of the absence of an Infectious Disease Physician to classify infection cases, and the latter because of the technical challenges

involved in defining re-admission status in the medical records. Therefore, in the manuscript submitted on 9 November 2017 and accepted on 19 December, the clinical outcome measures were mortality and ICU length-of-stay.

The following section contains material from:

Lew CCH, Wong GJY, Cheung KP, Chua AP, Chong MFF, Miller M. Association between malnutrition and 28-day mortality and intensive care length-of-stay in the critically ill: a prospective cohort study. Nutrients. 2017;10(1):10.

Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 75%
- Writing and editing: 90%

I made a major contribution to the conception of the manuscript, the design of the research, and acquisition, analysis, and interpretation of the data; I also drafted the manuscript and revised it according to the recommendations provided by my co-authors and the peer reviewers.

3.2. Introduction[†]

Malnutrition within the critical care setting is a global issue, with prevalence in both developing and developed countries as high as 78.1% and 50.8%, respectively [1]. Lew et al. [1] recently conducted a systematic review to determine the association between malnutrition and worsened clinical outcomes in the ICU. Two nutrition assessment and ten nutrition screening tools were identified in the review. The review demonstrated that nutrition risk determined by nutrition screening tools (NRS-2002 [35], MYST [94]) showed inconsistent association with clinical outcomes [1]. In contrast, malnutrition diagnosed by the SGA [58]

[†] The content of Sections 3.2 to 3.6 is similar to an original published article. To keep the thesis up-to-date, new information in the form of italicised texts was added to the published manuscript.

more consistently was associated with increased length-of-stay in the ICU and a higher risk of mortality. Therefore, the systematic review recommended the use of the SGA in the critical care setting [1].

The systematic review also identified possible limitations in the included primary studies. For example, there was a lack of blinding of the treatment team (intensivists and nurses) to the objective of the studies. This may have introduced treatment bias that weakened the validity of the association between malnutrition and worsened clinical outcomes in the ICU [1].

Another evaluation of the primary studies included in the systematic review [1] is the quality of the statistical adjustment as optimal statistical adjustment is essential for a valid quantification of the association between a particular risk factor and the outcome of interest [47]. The primary studies used the APACHE II crude score [39] instead of the predicted mortality risk (PMR) to adjust for mortality risk. This may not be ideal because the PMR better reflects actual mortality risk by factoring both the admission diagnosis and the APACHE II crude score in its derivation [39]. Consequently, the APACHE II crude score of patients with different admission diagnoses can be identical, whereas the PMR may differ due to the difference in mortality associated with the diagnoses [39, 143, 144]. For example, patients with congestive heart failure and an APACHE II score of 23 would have a PMR of 36%. In contrast, the same APACHE II score would translate to a PMR of 64% in patients with sepsis. Therefore, the PMR may be a more appropriate covariate for statistical adjustment of mortality risk than the APACHE II crude score.

In response to the systematic review conducted by Lew et al. [1], which highlighted considerable limitations in the included studies (i.e., the lack of blinding and sub-optimal statistical adjustment), this study aimed to overcome these limitations in an effort to perform a valid determination of the association between malnutrition and 28-day mortality and ICU length-of-stay among critically ill patients. *This includes performing a dose-dependent analysis for a more robust investigation.*

3.3. Materials and Methods

This prospective observational cohort study was conducted in the ICU of Ng Teng Fong General Hospital (Singapore). Between August 2015 and October 2016, consecutive patients admitted to the ICU were screened for eligibility. Patients ≥ 21 years of age with ≥ 24 hours ICU length-of-stay were enrolled, and only data from their first ICU admission within the same hospitalisation were included in the study. The physicians and nurses were blinded to the objective of the study to reduce the risk of selection and treatment biases. The Domain Specific Review Board approved this study (NHG DSRB Ref: 2014/00878), and informed consent was not required since this was an observational study, where no attempt was made to change the standard of care. This study was registered with ClinicalTrials.gov, number NCT03213899, and the reporting of this study followed the TRIPOD statement [145].

Data collection

The ICU contains 35 beds and functions as a closed unit that provides support to both medical and surgical patients. The unit also concurrently functions as an HD Unit as patients' status can be changed between ICU-status and HD-status within the same ICU-/HD bed. Patients are classified as "ICU-status" when mechanically ventilated and requiring support of two or more organ systems. They are downgraded to HD-status once they are extubated from mechanical ventilation. When in HD-status, patients are treated by the same physicians and allied health professionals. The only difference between ICU- and HD-status is the nursing to patient ratio, which changes from 1:1 to 1:2.

All data were prospectively measured and recorded in the electronic medical records. The primary outcomes were 28-day mortality and ICU length-of-stay. For ICU length-of-stay (in days), duration was measured from the date of the first ICU admission to the date of the first change in ICU-status to HD-status or discharge to the general ward. To enable robust statistical adjustments, other parameters known to be covariates for mortality and ICU length-of-stay [38, 146] were also collected (location, length of hospitalization, and presence/absence of vasoactives and cardiopulmonary resuscitation before ICU admission; APACHE II; PMR derived from the APACHE II and admission diagnosis [39]; SOFA [147]; Charlson

Comorbidity Index [148]; length of mechanical ventilation; and ICU and hospital length-of-stay).

Nutrition Assessment

It is part of routine care for all ICU patients to receive nutrition assessment (7-point SGA) within 48 hours of admission to the ICU. Three experienced dietitians performed the 7-point SGA and agreement between the dietitians was previously measured in 68 patients. The weighted kappa was 0.85 (standard error = 0.079, p-value < 0.001), indicating good agreement. Information required for the 7-point SGA was obtained from either the patients or their main caregivers. In cases where nutritional status cannot be determined within the first 48 hours (due to inadequate information), data on nutritional status were considered "missing." This was to minimise reverse causality bias as the study aimed to determine the association between premorbid malnutrition and hospital mortality.

The 7-point SGA [149, 150] is a variant of the SGA [58]. It was used not only to determine the association between malnutrition and hospital mortality and ICU length-of-stay but also to allow a dose-dependent analysis. One key advantage of using the 7-point SGA is the detailed response options that improve standardisation and objectivity in the classification of nutritional status [150]. Similar to the conventional SGA, the 7-point SGA classifies nutritional status into three major categories (well-nourished, mildly-moderately malnourished, and severely malnourished). Specifically, patients with SGA-A7 and SGA-A6 are well-nourished; SGA-B5, SGA-B4 and SGA-B3 are mildly-moderately malnourished; and SGA-C2 and SGA-C1 are severely malnourished. Each 1-point decrease reflects a greater degree of malnutrition, and this increased resolution allowed the association between malnutrition and hospital mortality to be analysed in a dose-dependent manner.

Statistical analysis

Patient characteristics were reported as mean and standard deviation (continuous variables) or counts and percentages (categorical variables) and were compared using Student's t-test or Chi-square tests, as appropriate. Medians and inter-quartile ranges were reported for

variables that deviate from normality, and the Mann-Whitney U-test was used for comparison. The relative risk for the association between malnutrition (SGA-B5 to SGA-C1) and 28-day mortality was quantified using a modified Poisson regression model incorporating the robust sandwich variance [151]. Collinear variables were excluded, and backward elimination of covariates was performed to obtain a parsimonious model. The dose-dependent relationship between the degree of malnutrition and 28-day mortality was quantified using the same Poisson regression with the exception of having nutritional status (SGA-A7 to SGA-C1) analysed as a continuous variable.

To explore the effects of sub-optimal statistical adjustment, two logistic regression models were compared. Model A contained commonly used covariates (age, duration of mechanical ventilation, APACHE II, and duration of stay in the ICU and hospital), while Model B contained all the above covariates but replaced the APACHE II with PMR and included additional covariates associated with ICU clinical outcomes but often not adjusted in other studies (presence/absence of vasoactive drugs and length of hospitalization before ICU admission). The McFadden's pseudo-R2 and Akaike information criterion revealed that Model B performed better, with the McFadden's pseudo-R2 and the Akaike information criterion of Model B being 1.5% higher (43.0% versus 41.5%) and 7 units lower (315 versus 322), respectively, than Model A. Therefore, the statistical adjustment in Model B was superior to Model A.

The association between malnutrition and ICU length-of-stay was determined by a series of simple linear regressions. Only ICU survivors were considered in the analysis to account for the competing risk of death on ICU length-of-stay [152]. Since the simple linear regressions showed that none of the patient characteristics were significantly associated with ICU length-of-stay, a multivariable linear regression was not carried out. Statistical analyses were performed using STATA 14.2 (Stata Corp, College Station, TX, USA) and significance assumed at p-value < 0.05.

3.4. Results

There were 502 eligible patients; however, 63 were excluded as they lacked 7-point SGA data (Figure 6). Excluded patients had significantly shorter length of hospitalization (median: 8.0 days versus 14.0 days), less severe comorbidities (median of Charlson morbidity index: 0.0 versus 1.0), and proportionally fewer of them were admitted from the general wards (7.9% versus 18.7%). Among the remaining 439 patients (medical: 294, surgical: 145), sepsis (23.9%), respiratory (22.1%), neurological (22.1%), and cardiovascular (18.5%) conditions were the most common reasons for ICU admission. The 28-day mortality rate was 28.0% (n = 123), and no patients were lost to follow-up.

Prevalence of malnutrition was 28% (mildly-moderately malnourished: 25% – SGA-B5: 13.4%, SGA-B4: 7.3%, SGA-B3: 4.3%; severely malnourished: 3% – SGA-C2: 2.7%, SGA-C1: 0.2%). Malnourished patients were significantly older and had lower body mass index and higher disease severity as compared to their well-nourished counterparts (Table 11). In addition, the prevalence of malnutrition was highest in patients admitted with sepsis (38.1%) and lowest in patients with neurological conditions (14.4%). Patients with respiratory and cardiovascular conditions had similar prevalence (24.7% and 28.4%, respectively).

Malnutrition was associated with a 33% increased risk of 28-day mortality. The dose-dependent analysis revealed that each 1-point decrease in the 7-point SGA (indicative of a greater degree of malnutrition) was associated with an 8% increase in the risk of 28-day mortality (Table 12).

There were 363 patients who survived their ICU admission, and their median ICU length-of-stay was 2.0 days (IQR: 1.0, 5.0). Simple linear regression did not identify any covariate that was associated with ICU length-of-stay (Table 13).

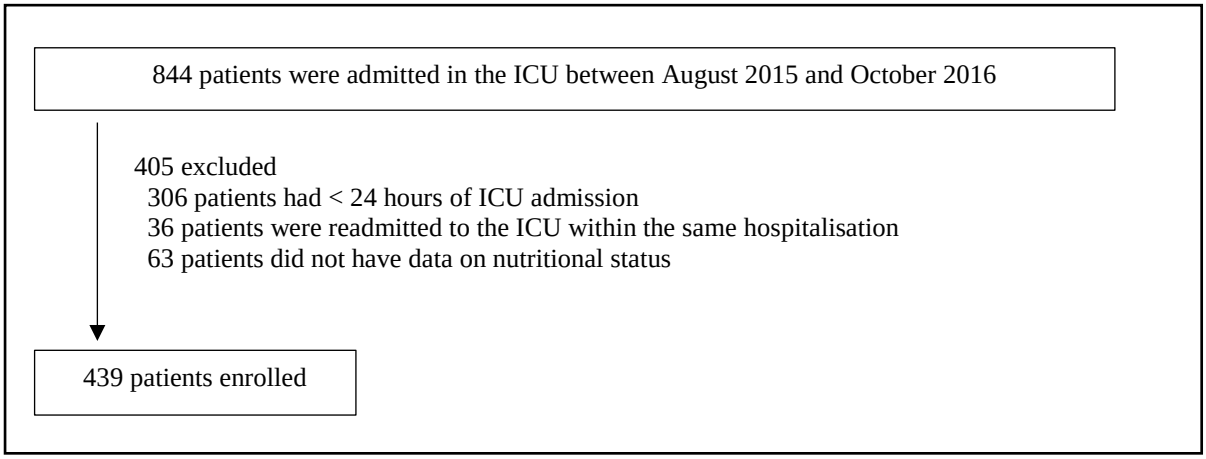


Figure 6: Enrollment of patients

Table 13: Comparison of characteristics between well-nourished and malnourished patients and 28-day survivors and non-survivors

Parameters	Well-nourished (n = 316)	Malnourished (n = 123)	p-value	Survivor (n = 316)	Non-survivor (n = 123)	p-value
Age (years)	59.8 (15.7)	65.6 (15.3)	0.001	59.3 (15.9)	66.8 (14.1)	< 0.001
Male	188 [59.5]	69 [56.1]	0.517	191 [60.4]	67 [54.5]	0.254
BMI (kg/m^2)	26.2 (5.8)	22.6 (5.8)	< 0.001	25.2 (6.0)	25.1 (6.2)	0.960
Location before adm						
ED/HD/OT	263 [83.2]	94 [76.4]	0.100	268 [84.8]	89 [72.4]	0.003
Wards	53 [16.8]	29 [23.6]		48 [15.2]	34 [27.6]	
Type of adm						
No surgery	210 [66.5]	83 [67.5]	0.974	199 [63.0]	94 [76.4]	0.027
Elective surgery	10 [3.2]	4 [3.3]		11 [3.5]	3 [2.4]	
Emergency surgery	96 [30.4]	36 [29.3]		106 [33.5]	26 [21.1]	
Charlson morbidity index	1.0 {0.0, 3.0}	1.0 {1.0, 3.0}	0.054	1.0 {0.0, 3.0}	1.0 {0.0, 3.0}	0.320
LOS before ICU adm (days)	0.0 {0.0, 1.0}	1.0 {0.0, 3.0}	< 0.001	0.0 {0.0, 1.0}	1.0 {0.0, 3.0}	0.008
APACHE II	23.7 (8.0)	26.9 (7.9)	< 0.001	22.6 (7.4)	29.5 (7.7)	< 0.001
SOFA	8.3 (3.6)	9.5 (4.2)	0.009	7.9 (3.5)	10.7 (3.8)	< 0.001
Predicted mortality risk (%) *	47.7 (25.8)	59.7 (24.9)	< 0.001	44.1 (24.2)	68.8 (22.2)	< 0.001
Vasoactives before ICU adm	134 [42.4]	59 [48.0]	0.292	127 [40.2]	66 [53.7]	0.011
CPR before ICU admission	35 [11.1]	18 [14.6]	0.304	17 [5.4]	36 [29.3]	< 0.001
Length of MV (days)	2.0 {1.0, 5.0}	2.0 {1.0, 5.0}	0.734	2.0 {1.0, 4.0}	3.0 {2.0, 6.0}	< 0.001
ICU LOS (days)	2.0 {2.0, 5.0}	3.0 {2.0, 5.0}	0.981	2.0 {1.0, 4.0}	3.0 {2.0, 6.0}	0.001
Hospital LOS (days)	13.0 {6.3, 24.0}	16.0 {9.0, 27.0}	0.120	15.0 {9.0, 33.0}	9.0 {4.0, 16.0}	< 0.001
28-day mortality	72 [22.8]	51 [41.5]	< 0.001			

Table 11: Comparison of characteristics between well-nourished and malnourished patients and 28-day survivors and non-survivors (cont.)

Parameters	Well-nourished (n = 316)	Malnourished (n = 123)	p-value	Survivor (n = 316)	Non-survivor (n = 123)	p-value
Malnutrition				72 [22.8]	51 [41.5]	< 0.001
SGA sub-categories						
SGA-7	217 [68.7]			165 [52.2]	52 [42.3]	
SGA-6	99 [31.3]			79 [25.0]	20 [16.3]	
SGA-5		59 [48.0]		38 [12.0]	21 [17.1]	
SGA-4		32 [26.0]		16 [5.1]	16 [13.0]	
SGA-3		19 [15.4]		9 [2.8]	10 [8.1]	
SGA-2		12 [9.8]		9 [2.8]	3 [2.4]	
SGA-1		1 [0.8]		0 [0.0]	1 [0.2]	

Values are mean (SD), median {interquatile range}, or counts [percentage]

* Derived from the Acute Physiologic and Chronic Health Evaluation II

adm: admission; **APACHE II:** Acute physiology and chronic health evaluation II; **BMI:** Body Mass Index; **CPR:** Cardiopulmonary resuscitation; **ED:** Emergency department; **HD:** High dependency; **ICU:** Intensive Care Unit; **LOS:** Length-of-stay; **MV:** Mechanical ventilation; **OT:** Operation theatre; **SGA:** Subjective Global Assessment; **SOFA:** Sequential Organ Failure Assessment

Table 14: Multivariable analysis of the association between malnutrition and 28-day mortality

Parameters	Risk estimates *		p-value
Malnourished†	Crude RR	1.82 (95% CI: 1.36, 2.44)	< 0.001
	Adj-RR	1.33 (95% CI: 1.05, 1.69)	0.019
Every 1-point decrease in the 7-point SGA‡	Crude RR	1.18 (95% CI: 1.08, 1.30)	< 0.001
	Adj-RR	1.08 (95% CI: 1.00, 1.16)	0.039

***** Adjusted for age; presence/absence of vasoactive drugs and length of hospitalization before admission to the ICU; duration of mechanical ventilation; predicted mortality risk derived from the Acute Physiologic and Chronic Health Evaluation II; and duration of stay in the ICU and hospital

† Reference: Well-nourished (SGA-A7 or SGA-A6)

‡ Every 1-point decrease is indicative of a higher degree of malnutrition

Adj: Adjusted; **RR:** Relative risk; **CI:** Confidence interval; **SGA:** Subjective global assessment

Table 15: Simple linear regression models of association between patient characteristics and length-of-stay in the ICU (measured in days) among patients discharged alive from the ICU

Patient Characteristics (n = 363)	Standardized Beta weight	95% confidence interval	p-value
Age (years)	-0.100 †	-0.105, 0.001	0.057
BMI (kg/m^2)	0.052 †	-0.072, 0.220	0.318
Admitted from the wards	0.005	-2.247, 2.479	0.923
No surgery	-0.200	-1.875, 1.230	0.700
Charlson morbidity index	-0.100 †	-0.870, 0.011	0.056
LOS before ICU admission (days)	0.001 †	-0.180, 0.182	0.063
APACHE II	-0.025 †	-0.140, 0.085	0.632
SOFA	0.031 †	-0.175, 0.324	0.559
Predicted Mortality Risk (%) *	-0.042 †	-0.049, 0.020	0.424
Given vasoactives before ICU admission	0.001	-1.726, 1.745	0.991
Given CPR before ICU admission	0.006	-2.980, 3.364	0.905
Length of MV (days)	0.068 †	-0.213, 5.825	0.068
Malnutrition	-0.015	-2.245, 1.665	0.771

* Derived from the Acute Physiologic and Chronic Health Evaluation II

† Every unit increase

APACHE II: Acute Physiologic and Chronic Health Evaluation II; **BMI:** Body Mass Index, **CPR:** Cardiopulmonary Resuscitation, **ICU:** Intensive Care Unit, **LOS:** Length-of-stay, **MV:** Mechanical Ventilation; **SOFA:** Sequential Organ Failure Assessment

3.5. Discussion

This is the largest study to use a validated nutrition assessment tool in an attempt to demonstrate an association between malnutrition and 28-day mortality and ICU length-of-stay among the critically ill. There was a dose-dependent association between malnutrition and 28-day mortality, but this was not observed for ICU length-of-stay.

The results of this study could not be compared with those in previous studies because either different nutrition assessment tools were used [75] or results were reported in odds ratio [75, 77, 81], hazard ratio [87] or adjusted p-value [88]. Recently, Verghese et al. [77] and Ceniccola et al. [75] similarly demonstrated a dose-dependent relationship in which a greater degree of malnutrition was associated with a higher risk of mortality. However, the magnitude of the associations cannot be compared since different nutrition assessment tools were used to diagnose malnutrition. Nevertheless, the sum of evidence supports a clear positive association between malnutrition and mortality risk. This suggests that nutritional status should be considered along with other conventional prognostic parameters to aid treatment decisions as one of the rationales for limiting life-sustaining treatments in the ICU is poor prognosis.

No significant association was found between malnutrition and ICU length-of-stay. This could be due to two reasons. Firstly, any association between malnutrition (or other parameters such as disease severity) and ICU length-of-stay would be difficult to establish in the context of short ICU length-of-stay. The median ICU length-of-stay in this study was notably shorter than that of a similar cohort in another local tertiary hospital (two versus four to five days) [153]. This could be due to the unique integration of ICU/HD unit in NTFGH, which allows ICU patients to quickly transit to HD care without the need to change location. This is likely a more accurate reflection of the required ICU length-of-stay as compared to other tertiary hospitals, where ICU patients may need to wait for a physical bed in the HD unit before transfer, and this may potentially inflate their ICU length-of-stay. In addition, Sheean et al. [88] did not observe any association between malnutrition and ICU length-of-stay, and this may also be attributed to the relatively short mean ICU length-of-stay (three days). These findings are in contrast with the study by Caporossi et al. [37], where malnutrition was reported to be associated with prolonged ICU admission (mean ICU length-of-stay: nine days). *The*

second plausible reason is related to sub-optimal statistical analyses. Specifically, malnutrition was associated with longer ICU length-of-stay [37, 69, 77] and hospital length-of-stay [87]. However, these results may have limited validity as non-survivors were included in the bivariate analysis. It is necessary to exclude non-survivors when performing such analysis because if malnutrition leads to a faster rate of death (hence shorter length-of-stay), including non-survivors in the analysis will erroneously show a positive association between malnutrition and length-of-stay [152]. In view of these sub-optimal statistical analyses, there is likely no association between malnutrition and ICU length-of-stay. This notion is further verified by Bector et al. [74], which excluded non-survivors and likewise found no association.

Before the systematic review in Chapter 1 was updated with more recent studies, the prevalence of malnutrition among ICUs that admit heterogeneous types of patients was 38 to 78% [1]. This study further widened the range of malnutrition prevalence as 28% of the patients were malnourished. The wide variability calls for studies in individual ICUs to determine their local malnutrition prevalence and identify an appropriate nutrition screening tool (e.g. NRS-2002 [35]) to be used in their respective ICUs. *Until the Global Leadership Initiative on Malnutrition Criteria for the Diagnosis of Malnutrition is validated [62],* these studies may use the SGA as the reference criterion since the validity and reliability of the SGA in the ICU have been well demonstrated [1, 84].

Compared to previous studies, this study has a number of strengths. First, results are more generalizable with the inclusion of both medical and surgical patients. Second, measures were taken to reduce the risk of selection, attrition, treatment, and reverse causality biases. Thirdly, instead of computing the odds ratio, this study expressed the strength of the association between malnutrition and hospital mortality by calculating the adjusted relative risk. This is important as the prevalence of malnutrition was more than 10%, and the use of an odds ratio will result in an overestimation of the association [154].

However, several limitations deserve consideration. Firstly, some patients were excluded from the study due to missing 7-point SGA data. Although they had several characteristics that were significantly different from those patients with 7-point SGA data, these characteristics were either not associated with 28-day mortality and ICU length-of-stay,

or they were adjusted using the multivariable models. Secondly, despite robust statistical adjustments, there remained a possibility of residual confounding in all observational studies. *Thirdly, in patients who were unconscious during nutrition assessment, information such as weight and diet history, gastrointestinal symptoms as well as functional status were obtained from family members. Since the obtained information was not verified by the patients when they are able to communicate, there is potential for misclassification of nutritional status [155]. Lastly, it has been demonstrated that 50% to 60% of well-nourished patients (as classified by the SGA) are in fact sarcopenic, and misclassifications were more common in males and people who are overweight or obese [111]. Therefore, it is possible that some well-nourished patients may be misclassified.*

This study did not measure the extent of nutrition support given to both well- and malnourished patients because such data were still being collected. It is plausible that variations in the degree of nutrition support may modify the association between malnutrition and mortality. The corollary of this view is the following question: Will aggressive nutrition support attenuate the mortality risk of malnourished patients in the ICU?

The optimal nutrition support strategy in the ICU (i.e.. permissive underfeeding vs. meeting estimated energy requirements) remains nebulous, and current evidence from RCTs is mixed [156]. A common limitation among the studies is the lack of baseline nutrition assessment since it is conceptually possible that malnourished patients may require more energy and protein to attenuate the deleterious effects of critical illness as compared to well-nourished patients [35, 115]. Given the clear association between malnutrition and 28-day mortality, future studies that aimed to determine the optimal nutrition support strategy for the critically ill should conduct baseline nutrition assessment to better elucidate how nutritional status can modify the therapeutic effects of different feeding strategies.

3.6. Conclusion

The objective of this research programme was to develop a novel mortality prognostic model (GLIMPSE) that combines baseline nutritional status and disease severity. Chapters One and Three demonstrated a clear association between baseline nutritional status and

increased mortality risk. Therefore, nutritional status (as measured by the SGA) will be included as a candidate predictor for GLIMPSE. Having established the nutrition parameter to be included in GLIMPSE, the next chapter aims to examine how disease severity can be measured in the ICU.

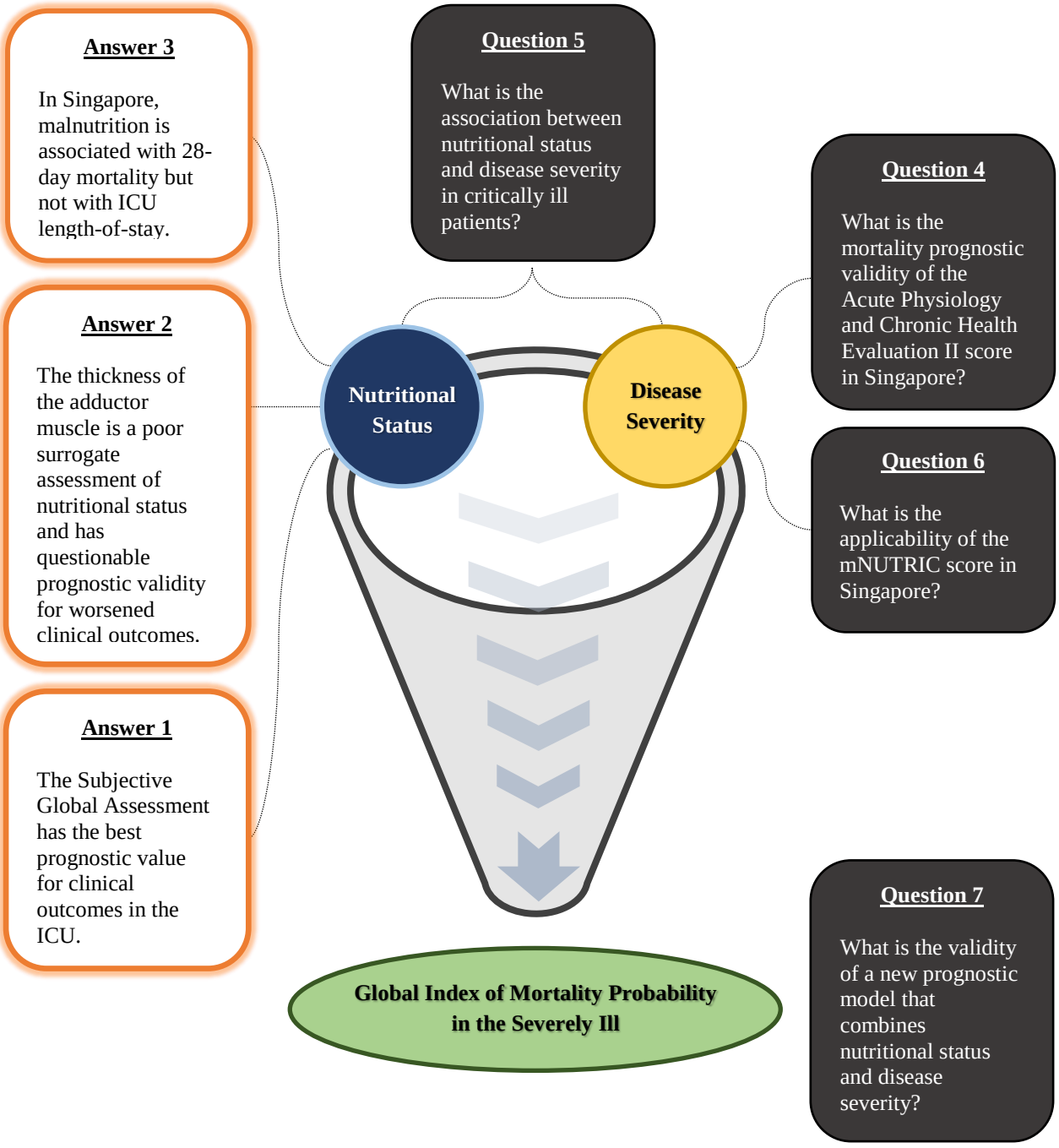


Figure 7: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 3

Chapter 4: What is the mortality prognostic validity of the Acute Physiology and Chronic Health Evaluation score in Singapore?

4.1 Contribution to the overall research objective

Prognostication provides the possible outcomes of medical condition(s) to facilitate healthcare providers, patients, and their caregivers in making decisions on further management, testing, and initiation and cessation of treatment [47]. In the ICU, the outcomes of interest are often the risk of mortality. This can be quantified subjectively based on the physician's experience or via objective prognostic models. The first objective prognostic model (Therapeutic Intervention Scoring System – TISS) was developed in 1974. The TISS estimates the level of nursing care required by an ICU patient, and hence indirectly quantifies the level of disease severity [157]. However, it was the conception of the Acute Physiology and Chronic Health Evaluation (APACHE) [158] that paved the way for the development of more sophisticated models that directly quantify the risk of mortality and other ICU clinical outcomes (such as complications or length-of-stay).

To date, there are three groups of prognostic models: 1) APACHE [159], APACHE II [39], APACHE III [160], and APACHE IV [161]; 2) Simplified Acute Physiology Score [162], Simplified Acute Physiology Score II [163], and Simplified Acute Physiology Score III [113, 114]; and 3) Mortality Probability Model [164], Mortality Probability Model II [165], and Mortality Probability Model III [166]. These models convert predictors (physiological parameters, medical history, and/or admission diagnosis) into numerical scores, and their sum is used to reflect disease severity and mortality risk (the higher the score, the higher the disease severity and mortality risk).

Despite the myriad newer prognostic models such as APACHE IV, Simplified Acute Physiology Score III, and Mortality Probability Model III, APACHE II remains widely used in

the literature as well as in practice [167]. This is likely because APACHE II scores tally without difficulty, and this allows for comparative consistency due to its long history of use. In Singapore, all ICUs in public hospitals use APACHE II to quantify disease severity for quality assessment. However, APACHE II has other applications in areas such as research, supporting treatment decisions, and the provision of prognosis to patients and surrogate decision makers. Since APACHE II is not conventionally used in the field of Dietetics, this Chapter aims to establish a more in-depth understanding of the APACHE II in terms of its applications. In addition, since all the applications of APACHE II depend on its mortality prognostic accuracy, this chapter also aims to summarize the prognostic performance of APACHE II as reported in the literature and include an original study that quantifies the mortality prognostic validity of APACHE II in NTFGH. This is important as this research programme sets out to develop a prognostic model (GLIMPSE) that includes disease severity as one of its predictors. Thus, the validity of the inclusion of APACHE II in GLIMPSE warrants a thorough examination of its prognostic validity in Singapore.

4.2 Introduction

4.2.1 Applications of APACHE II

Quality assessment

ICUs admit patients with the most critical conditions and provide treatments to compensate for the failure of one or more vital organs. These intensive treatments require a substantial amount of resources in the form of staff, consumables, and equipment. In the United States, it was estimated that the cost of one day of ICU-stay is about three times the cost of the general ward (USD 3,518 versus 1,153), and the annual cost of intensive care medicine was estimated to be about USD 81.7 billion [168]. Given the high cost, hospital administrators are particularly interested in assessing the quality of care and in setting benchmarks to optimise cost-effectiveness. The importance of quality assessment is highlighted by the Solucient study, which concluded that about 30,000 deaths could be prevented and USD 1.5 billion saved annually if all ICUs in the United States were operating as efficiently as top-performing units [169].

Hospital administrators usually assess performance by comparing mortality outcomes within or between hospitals as mortality rate reflects important characteristics associated with good clinical practices (use of best practices, accurate diagnosis and timely therapies) [170]. However, there is a need for mortality adjustments since some hospitals inherently admit patients with higher disease severity and thus have higher mortality rates than others. Therefore, prognostic models such as APACHE II play an essential role in the adjustment of disease severity.

Parallel to improvements in prognostic model development (such as the use of multivariable logistic regression to select predictors) have been advances in the methods used to assess prognostic accuracy. First generation models measured prognostic accuracy by discriminative statistics, which quantify the ability of a prognostic model in distinguishing discrete outcomes (death or survival). For instance, a discriminative prognostic model will systematically estimate higher survival probabilities in survivors in comparison to non-survivors. Discrimination is usually measured by the area under the Receiver Operating Characteristic curve (ROC), in which "perfect," "excellent," "very good," "good," "moderate," and "poor" discrimination are defined as ROC of 1.00, 0.90 – 0.99, 0.80 – 0.89, 0.70 – 0.79, 0.60 – 0.69, and < 0.60, respectively [171]. In addition to discrimination, subsequent prognostic models have started to report calibration accuracy. In contrast to discrimination, which focuses on distinguishing discrete outcomes, calibration quantifies the accuracy of risk prediction across the continuum of mortality risk. For example, if a well-calibrated prognostic model estimates the mortality risk of three groups of patients to be 30%, 50%, and 70%, respectively, their actual mortality rates would be very close to those percentages. Calibration is usually measured by the Hosmer-Lemeshow C and H test (with accurate calibration defined as p-value > 0.05) [172], the calibration curve, and the standardised mortality ratio (SMR) [173].

The SMR is a mortality index that is widely used to measure the quality of care. It consists of the ratio of observed versus predicted hospital mortality (estimated by prognostic models). Discordance between observed and predicted mortality rates reflects quality gaps (e.g., inappropriate ICU discharge and/or lack of skills, equipment, or care in the general ward) [170]. Most ICUs aim to keep the SMR below 1.0 as this indicates an overall good performance. The prognostic model used to predict mortality risk must have good calibration

at all risk levels of mortality, for two reasons. Firstly, if mortality risks among low- or high-risk patients are over-estimated, the performance of the ICU will be artificially inflated. The opposite happens when the predicted mortality risk is under-estimated (see Table 14) [170]. Secondly, it is best practice to stratify the SMR calculation by low-, medium- and high-risk patients as the proportion of high-risk patients within a cohort will disproportionately affect the aggregated SMR [170]. As seen in Table 15, both ICU-A and ICU-B performed equally well in all three groups of patients. However, the aggregated SMR of ICU-B appeared to be worse as it contained a larger proportion of high-risk patients. The disproportional weight contributed by high-risk patients is also highlighted in the case of ICU-C, where poor performance in low-risk patients (SMR: 2.00) was masked by good performance in high-risk patients, resulting in an aggregated SMR of 0.98.

Table 16: Calculation of Standard Mortality Ratio (SMR)

No.	Status	Predicted mortality				
		Accurate	Over-estimation		Underestimation	
		All patients	Low-risk group	High-risk group	Low-risk group	High-risk group
Patient 1	Survived	10%	20%	10%	10%	10%
Patient 2	Survived	20%	30%	20%	10%	20%
Patient 3	Survived	20%	30%	20%	15%	20%
Patient 4	Survived	30%	40%	30%	20%	30%
Patient 5	Survived	30%	40%	30%	25%	30%
Patient 6	Demised	60%	60%	75%	60%	50%
Patient 7	Demised	70%	70%	80%	70%	60%
Patient 8	Demised	80%	80%	85%	80%	70%
Patient 9	Demised	90%	90%	95%	90%	80%
Patient 10	Demised	90%	90%	95%	90%	80%
Observed mortality		50%	50%	50%	50%	50%
Mean predicted mortality		50%	55%	53%	47%	45%
SMR		1.00	0.91	0.93	1.06	1.11

SMR: Standardised mortality rate

Table 17: Three hypothetical ICUs, ICU-A, and ICU-B have similar performance within risk groups but different aggregated SMR, and ICU-C had poor performance in low-risk patients but good overall aggregated SMR

Examples	Low-risk patients	Medium-risk patients	High-risk patients	Total patients
ICU-A				
No. of patients	700	250	50	1000
No. of observed deaths	70	75	45	190
No. of predicted deaths	140	75	30	245
Percentage of observed mortality	10%	30%	90%	19.0%
Percentage of predicted mortality	20%	30%	60%	24.5%
SMR	0.50	1.00	1.50	0.78
ICU-B				
No. of patients	400	200	400	1000
No. of observed deaths	40	60	360	460
No. of predicted deaths	80	60	240	380
Percentage of observed mortality	10%	30%	90%	46.0%
Percentage of predicted mortality	20%	30%	60%	38.0%
SMR	0.50	1.00	1.50	1.21
ICU-C				
No. of patients	400	200	400	1000
No. of observed deaths	40	40	360	440
No. of predicted deaths	20	40	390	450
Percentage of observed mortality	10%%	20%	90%	44%
Percentage of predicted mortality	5%%	20%	98%	45%
SMR	2.00	1.00	0.92	0.98

ICU: Intensive care unit, **SMR:** Standardised mortality rate

Research

Disease severity has a substantial impact on outcomes in the ICU. Therefore, researchers quantify disease severity using prognostic models and handle its confounding effects at the design or analytical stage of research.

When conducting RCTs, researchers use prognostic models to quantify baseline disease severity and ensure that it is similar in both treatment and control groups. This is especially important today as the number of multicentre RCTs grows, and this entails having a wide variety of case-mix and disease severity across different centres. Compared to RCTs, retrospective and prospective observational studies usually recruit a more heterogeneous group of patients. In this respect, prognostic models are especially useful as statistical

adjustment of disease severity can be carried out to determine the independent association between the variables and outcomes in question. Statistical analysis can also be stratified by disease severity to identify variability in treatment effects.

However, some caveats are in order regarding the use of prognostic models to adjust for disease severity. For example, evidence from recent multicentre RCTs demonstrated that APACHE II does not accurately predict mortality risk as studies with similar APACHE II scores had vastly different mean ICU mortality rate (see Table 16). This is attributed to the effect of admission diagnosis of patients on their mortality risk (see Figure 8). Therefore, the differences in mean ICU mortality rate between RCTs are likely due to a differing case-mix. However, this has a minimal impact to the internal validity of the RCTs since randomisation ensures a good balance of case-mix and prognostic scores between the treatment and control groups, as demonstrated in the study conducted by Harvey et al. [174].

Table 18: Mean APACHE II score and ICU mortality of recent RCTs

Studies	Mean APACHE II	Mean ICU mortality
Casaer et al. [14]	22	6%
Singer et al. [18]	22	21%
Doig et al. [19]	21	13%
Doig et al. [19]	22	6%
Harvey et al. [174]	20	28%
Arabi et al. [33]	21	18%

APACHE II: Acute physiologic and chronic health evaluation II, **ICU:** Intensive care unit, **RCTs:** Randomised controlled trials

The effects of differing case-mix may have a more substantial impact on observational studies as instead of adjusting for predicted mortality risk (which is a function of both prognostic score and diagnosis), some observational studies merely used the crude APACHE II scores to adjust for disease severity [21, 175, 176]. This may limit the interpretation of these studies since patients with identical APACHE II scores can have vastly different mortality risk (see Figure 8). Nevertheless, prognostic models need to be accurate when quantifying disease severity and mortality risk because inaccuracies will result in erroneous findings in both RCTs and observational studies.

	Patient A	**Patient B**
Admission diagnosis	Asthma	Haemorrhagic stroke
APACHE II Score	30	30
Surgery status	No	Yes

Mortality prediction formula in APACHE II

Ln (risk/1-risk) = -3.517 + (APACHE II score X 0.146) + (0.603 if emergency surgery) + diagnostic weight*

Predicted mortality risk of patient A:
-3.517 + (30 X 0.146) + (-2.108) = -1.245
Exponential of -1.245 = 0.288
Therefore, if (risk/1-risk) = 0.288, then risk = 0.288 / 1.288 = 0.223
Patient A has 22.3% of predicted mortality risk

Predicted mortality risk of patient B"
-3.517 + (30 X 0.146) + 0.603 + (-0.788) = 0.679
Exponential of 0.679 = 1.972
Therefore, if (risk/1-risk) = 1.972, then risk = 1.972 / 2.972 = 0.66
Patient B has 66.4% of predicted mortality risk

* diagnostic weights published in the study conducted by Knaus et al. [39]

Figure 8: Calculation of predicted mortality risk of patients in accordance with APACHE II score and admission diagnosis

4.2.2 Applications of APACHE II: Treatment decisions

Life-sustaining treatments in the ICU can be costly, including parenteral nutrition and continuous haemodialysis. In the United States, the typical cost of compounded parenteral nutrition is USD 239 per day, and the entire duration of such treatment costs about USD 1,681 [177]. In Singapore, this cost was estimated to be USD 340 and 3,090, respectively [178]. In the case of continuous haemodialysis, it was estimated that such treatment costs USD 474 per day, and the typical cost of the entire treatment is USD 8,052 [179]. Given the high cost of parenteral nutrition and continuous haemodialysis, several studies investigated the accuracy of prognostic models in identifying patients who did not benefit, i.e., demise despite receiving such treatments.

4.2.3 Applications of APACHE II: Parenteral Nutrition in the ICU

Two studies investigated the accuracy of APACHE II in identifying ICU patients who would not benefit from total parenteral nutrition (TPN). Hopefl et al. [180] prospectively recorded the APACHE II scores of 62 patients on their ICU admission day and TPN initiation day. The sensitivity (predicting mortality) and the specificity (predicting survival) of *admission-APACHE II* were 34.5% and 87.5%, respectively. For APACHE II determined before TPN initiation, the sensitivity was 27.5%, and specificity was 96.9%. These results show that the APACHE II had limited utility when used in isolation. In contrast, Chang et al. [181] demonstrated that a sequential composite score derived from the daily APACHE II score and a series of organ failure coefficients could effectively identify patients who would not benefit from TPN. In a group of 50 ICU patients placed on parenteral nutrition, they demonstrated that such a score had sensitivity and specificity of 72.2% and 100%, respectively.

4.2.5 Applications of APACHE II: Dialysis in the ICU

The hospital mortality rate of ICU patients on dialysis can be as high as 76% [182]. Therefore, it may be beneficial to predict the risk of mortality and limit dialysis in critically ill patients who have a low survival probability. The predictive accuracy of APACHE II is summarised in Table 17. While most studies evaluated APACHE II calculated at ICU admission, van Bommel et al. [183] evaluated both admission and pre-dialysis scores.

Among patients on chronic dialysis and requiring dialysis in the ICU, admission APACHE II had good discrimination and calibration accuracy for hospital mortality (ROC 0.78; HL: 10.71, p-value: 0.22) [184]. Admission APACHE II was also demonstrated to support the decision to withhold dialysis [185]. However, this was possible in the context of high mortality rates (61%) among dialysis patients in the ICU. That is, in patients with greater than 70% predicted mortality, Dobkin and Cutler [185] showed that APACHE II had 100% positive predictive value for hospital mortality despite the low sensitivity (26%) of admission APACHE II.

For ICU patients with normal renal function before admission but requiring dialysis in the ICU, admission APACHE II had poor to moderate discriminative value (ROC: 0.52 – 0.64) for hospital and ICU mortality [184-186]. Interestingly, van Bommel et al. [183] showed that the ratio between admission APACHE II and pre-dialysis APACHE II had excellent discrimination (ROC: 0.92), and a ratio ≥ 1.10 had an observed mortality of 94%.

Table 19: Accuracy of prognostic models in predicting mortality outcome of dialysis in the ICU

Author and study design	No. of patients, patient type, & mortality rate	Mean	Sensitivity & Specificity	ROC	Calibration	Other statistical analysis
Heterogeneous patient who had dialysis						
Dobkin and Cutler [185] Retro	• n = 146 • All types of ICU patients who received IHD or CHD • Hosp mortality: 61.0%	**APACHE II:** NA	**Ref: 70% predicted hosp mortality risk:** **At admission** • Sensitivity: 0.26 (95% CI: 0.17-0.35) • PPV: 1.00, NPV • Specificity: 1.00 (95% CI: 0.95-1.00) • NPV: 0.46 **Prior to HD** • Sensitivity: 0.39 (95% CI: 0.29-0.49) • Specificity: 1.00 (95% CI: 0.95-1.00) PPV: 1.00, NPV: 0.51	NA	NA	NA
Akbaş et al. [184] Retro	• n = 222 • Medical ICU patients who had IHD, CHD or PD • ICU mortality: 58.1% • CD ICU mortality: 50.5% • AKI ICU mortality: 67.8%	**Adm-APACHE II:** • Survived ICU: 24.9 (7.1) • Demised: 29.6 (8.7) • p-value: 0.001	NA	**Ref: ICU mortality** **Adm-APACHE II in patients who did not have pre-morbid renal disease:** • 0.52 (95% CI: 0.39-0.66), p-value: 0.690 **Adm-APACHE II in patients who had pre-morbid renal disease:** • 0.78 (95% CI: 0.55-0.89), p-value: 0.004	**Ref: ICU mortality** **HL-C for adm-APACHE II in patients who had pre-morbid renal disease:** • 10.71, p-value: 0.218	**Adj-OR for ICU mortality with every 1.0 increase in adm-APACHE II in Patients who had pre-morbid renal disease:** 1.13 (95% CI: 1.02-1.26), p-value: 0.024

Table 17: Accuracy of prognostic models in predicting mortality outcome of dialysis in the ICU (cont.)

Author and study design	No. of patients, patient type & mortality rate)	Mean	Sensitivity & Specificity	ROC	Calibration	Other statistical analysis
Patients who did not have pre-morbid renal disease and had dialysis						
Douma et al. [182] Retro	• n =238 • ICU patients who had IHD, CHD or CPD • Hosp mortality: 76%	NA	NA	**Ref: Hosp mortality** **Adm-APACHE II** • 0.62	NA	
Lin et al. [186] Prosp	• n =101 • ICU patients who had IHD or CHD • Hosp mortality: 56.4%	**Adm-APACHE II:** • Survived hosp: 16.8 (1.1) • Demised: 20.1 (0.9) • p-value: 0.003	**Hosp mortality for adm-APACHE II score ≥ 15:** • Sensitivity: 0.67 • Specificity: 0.55 • Youden index: 0.22	**Ref: Hosp mortality** **Adm-APACHE II:** • 0.64 (95% CI: 0.52-0.77), p-value: 0.024	**Ref: Hosp mortality** **HL for adm-APACHE II:** • 8.80, p-value: 0.359	

Table 17: Accuracy of prognostic models in predicting mortality outcome of dialysis in the ICU (cont.)

Author and study design	No. of patients, patient type & mortality rate)	Mean	Sensitivity & Specificity	ROC	Calibration	Other statistical analysis
van Bommel et al. [183] Retro	• n =104 • Surgical ICU patients who had CHD • ICU mortality: 51.0% Hosp mortality: 54.8%	**Adm-APACHE II** • Survived ICU: 24.2 (4.2) • Demised: 23.0 (3.3) • p-value: 0.260 **APACHE II before dialysis** • Survived ICU: 27.0 (4.4) • Demised: 22.4 (3.5) • p-value: < 0.001 **Ratio of adm-APACHE II and APACHE II before dialysis:** • Survived ICU: 1.12 (0.1) • Demised: 0.97 (0.1) • p-value: < 0.001	NA	**Ref: ICU mortality** **Adm-APACHE II** • 0.56 **APACHE II before dialysis** • 0.78 **Ratio of adm-APACHE II and APACHE II before dialysis** • 0.92	NA	**Adj-OR for ICU mortality with every 0.1 increase in the ratio of adm-APACHE II and APACHE II before dialysis:** 13.8 (95% CI: 4.7-40.2), p-value: < 0.001 **Observed ICU mortality rate at ratio of:** • ≤ 1.00: 4% • 1.01-1.09: 45% • ≥ 1.10: 94%

Values are mean (standard deviation) unless otherwise stated. **Adm:** Admission; **Ajd-OR:** Adjusted odds ratio; **APACHE II:** Acute physiology and chronic health evaluation II, **CHD:** Continuous haemodialysis; **CPD:** Continuous peritoneal dialysis; **CI:** Confidence interval; **HL:** Hosmer-Lemeshow Goodness-of-fit; **Hosp:** Hospital, **ICU**: Intensive care unit; **IHD:** Intermittent haemodialysis; **NA:** Not available; **NPV:** Negative predictive value; **PD:** Peritoneal dialysis; **PPV:** Positive predictive value; **Prosp:** Prospective study; **Ref:** Reference; **Retro:** Retrospective study; **ROC:** Receiver operating characteristic

Providing prognosis to patients and surrogate decision makers

Critical illness causes patients and their surrogate decision-makers to experience a tremendous amount of psychological stress [187]. The prognostic information provided by the physician can have a substantial impact on their choice of treatment or care. Medical social workers can provide emotional support for patients and their decision-makers by working through personal values and beliefs. This may alleviate but not eliminate the pressure faced in making decisions. However, prognostic information can provide direction on plausible treatment options and vindicate decisions on end-of-life care [188]. Such information was also demonstrated to help surrogate decision makers better cope with the situation [189, 190]. Therefore, ICU physicians have the responsibility to provide accurate estimates of disease severity and mortality risk.

Disease severity and mortality risk can be estimated objectively via prognostic models or subjectively via the experience of ICU physicians. Sinuff et al. [191] compared the mortality prediction accuracy of ICU physicians versus prognostic models via a systematic review. Twelve observational studies were identified, and the mortality prediction accuracies of APACHE II, Simplified Acute Physiology Score II, and the Mortality Probability Model were compared with the prediction provided by ICU physicians. It was concluded that ICU physicians could more accurately discriminate survivors and non-survivors than the prognostic models.

Several issues are not addressed by the systematic review conducted by Sinuff et al. [191]. Firstly, several studies demonstrated that the prediction accuracies of ICU physicians depend on their level of experience. Poses et al. [192] demonstrated that ICU physicians with more experience underestimate mortality risk, while the opposite was observed in less experienced physicians. Conversely, Barrera et al. [193] and Vicente et al. [194] demonstrated that the experience of ICU physicians was shown to be positively correlated with the accuracy of outcome prediction. Given the varying levels of experience, discordant prognosis among colleagues would increase stress among physicians and also cause undue stress to patients and family members [188]. Secondly, besides discrimination, the systematic review did not quantify the calibration accuracy of

physicians in predicting mortality risk. Knaus et al. [195] and McClish and Powell [196] demonstrated that the calibration accuracy of physicians is inferior to prognostic models. Consequently, ICU physicians may not be able to accurately quantify the risk of mortality to facilitate patients or surrogate decision-makers who require such information to determine treatment options and extent of care. Although most may argue that prognostic models should not be used to predict risk at the individual level [197-199], ICU physicians can use objective predictions provided by prognostic models as "the drunken man uses the lamppost for support rather than illumination" [200] in providing prognostic information to patients and surrogate decision makers. In other words, prognostic models are not meant to replace qualitative reasoning; instead, they are intended to provide objective and impartial prognostic information for healthcare providers, patients, and caregivers to supplement their reasoning and decision making [47].

In summary, the APACHE II is used to objectively quantify disease severity and predict mortality risk in the ICU. Hospital administrators use APACHE II and other prognostic models to assess the quality of care and set benchmarks to improve cost-effectiveness. For research studies conducted in the critical care setting, APACHE II is used to check the efficacy of randomisation and/or to adjust for differences in disease severity during statistical analysis. Outside of its conventional use, clinicians may use the objective predictions provided by APACHE II to support their clinical judgement when determining the type and extent of treatment. This may be especially useful for junior clinicians since the accuracy of their predictions depend on their amount of experience. In totality, applications of APACHE II rely on its mortality prognostic accuracy. Since this has never been empirically assessed in Singapore, the next section aims to determine the mortality prognostic validity of the APACHE II in NTFGH via a prospective cohort study.

4.2.4 Performance of APACHE II reported in the literature

A literature review was carried out in PubMed to determine the performance of APACHE II over the past ten years. Studies that recruited heterogeneous ICU patients and reported hospital mortality were included in the review. Fifteen studies were identified, and their sample sizes ranged from 76 [201] to 44,112 patients [202], while hospital mortality

ranged from 8.2% [203] to 54.9% [204] (Table 18). Discrimination ranged from good (0.729 [40]) to excellent (0.915 [205]). In contrast, only 4 out of 12 studies demonstrated good calibration [201, 206-208]. All studies reported SMRs (ranged from 0.46 [208] to 1.34 [209]) except for Parajuli et al. [201] and Quach et al. [210]. SMRs evidently deteriorate with time, and this is likely due to the declining mortality rate over the years [207, 211, 212]. Indeed, due to advances in medical care since 1985, large multicentre studies reported that the mortality rate of severe sepsis decreased by 16.7% between 2012 and 2000 [213], and the overall hospital mortality of critically ill patients reduced by 5.5% between 2009 and 2000 [173]. This decline in mortality rate resulted in the gradual deterioration of the discrimination and calibration accuracy of APACHE II [207]. While recalibration of APACHE II was demonstrated to improve SMRs, discrimination, and calibration accuracy [205, 212], this was not consistently observed [202]. Taken together, APACHE II appears to have variable discrimination and calibration accuracies in the past ten years.

All ICUs of the public hospitals in Singapore use APACHE II for quality audits, in which hospital mortality rates among the critically ill are compared within or between hospitals. Despite the pervasive use of APACHE II, its prognostic accuracy in Singapore remains questionable since it has never been validated locally with established statistical methods (e.g., ROC and Hosmer-Lemeshow C). Therefore, a study was conducted primarily to determine the performance of APACHE II in the prediction of hospital mortality in a mixed ICU. The secondary aim was to customise APACHE II and to evaluate its performance in NTFGH.

The ensuing sections (4.3 to 4.7) are published in the Proceedings of Singapore Healthcare. Since the manuscript is based on the above literature review, some repetition from previous sections might be encountered, especially in Section 4.3.

Table 20: Performance of APACHE II over the past 10 years

Authors, Study design, Data collection period, & Country	Number of patients & sites	Hospital mortality rate & SMR	Mean (SD)† Median (Interquartile range)‡	Discrimination measured by ROC	Calibration measured by HL-C
Ho et al. [214] Prosp. 2008-2013 Australia	• n = 9549 • 1 site	• Observed mortality: 13.3% • Predicted mortality: 16.2% **All patients** • SMR: 0.82 (95% CI: NA)	**Worst 24h score** • **Total:** 17.0 (7.7) • **Surv:** 16 {12.0, 21.0} • **Non-surv:** 27.0 {22.0, 32.0} • p-value: 0.001	• **All patients:** 0.845 (95% CI: 0.834-0.856) • **Elec surg:** 0.805 (95% CI: 0.751-0.859) • **Emerg surg:** 0.830 (95% CI: 0.817-0.843)	• **All patients:** 185 (p-value: 0.001) • **Elec surg:** 19 (p-value: 0.016) • **Emerg surg:** 109 (p-value: 0.001)
Serpa Neto et al. [208] Retro. 2011-2012 Brazil	• n = 1920 • 1 site	• Observed mortality: 14.2% • Predicted mortality: 30.7% **All patients** • SMR: 0.46 (95% CI: NA)	**Worst 24h score** • **Total:** 18.2 (7.1) • **Surv:** NA • **Non-surv:** NA • p-value: NA	• **All patients:** 0.802 (95% CI: 0.770-0.834) • **Med adm:** 0.817 (95% CI: 0.780-0.854) • **Elec surg;** 0.788 (95% CI: 0.709-0.867) • **Emerg surg:** 0.799 (95% CI: 0.693-0.905)	• **All patients:** 14.30 (p-value: 0.074) • **Med adm:** 17.92 (p-value: 0.022) • **Elec surg;** 6.52 (p-value: 0.481) • **Emerg surg:** 4.37 (p-value: 0.822)
Parajuli et al. [201] Prosp. Period: NA Nepal	• n = 76 • 1 site	• Observed mortality: 32.9% • Predicted mortality: NA **All patients** • SMR: NA (95% CI: NA)	**Worst 24h score** • **Total:** 18.3 (7.4) • **Surv:** 21.0 (5.4) • **Non-surv:** 23.7 (6.5) • p-value: 0.085	• **All patients:** 0.73 (95% CI: NA)	• **All patients:** 7.9 (p-value: 0.34)
Ilker et al. [204] Retro. 2008-2010 Turkey	• n = 466 • 1 site	• Observed mortality: 54.9% • Predicted mortality: 60.6% **All patients** • SMR: 0.89 (95% CI: NA)	**Worst 24h score** • **Total:** NA • **Surv:** NA • **Non-surv:** NA • p-value: NA	• **All patients:** 0.734 (95% CI: NA)	NA

Table 18: Performance of APACHE II over the past 10 years (cont.)

Authors, Study design, Data collection period, & Country	Number of patients & sites	Hospital mortality rate & SMR	Mean (SD)† Median (Interquartile range)‡	Discrimination measured by ROC	Calibration measured by HL-C
Harrison et al. [211] Prosp 2007-2009 United Kingdom	• n = 23626 • 24 sites	**Observed mortality** • 2007: 31.0% • 2008: 29.3% • 2009: 28.8% **Predicted mortality** • 2007: 33.3% • 2008: 32.9% • 2009: 32.8% **All patients** • SMR in 2007: 0.93 • SMR in 2008: 0.89 • SMR in 2009: 0.88	**Worst 24h score** • **Total:** 19.1 (8.1) • **Surv:** NA • **Non-surv:** NA • p-value: NA	**All patients:** • **2007:** 0.793 (95% CI: 0.800-0.812) • **2008**: 0.808 (95% CI: 0.800-0.812) • **2009:** 0.817 (95% CI: 0.800-0.812)	**All patients:** • **2007:** 44.9 (p-value: < 0.001) • **2008:** 85.1 (p-value: < 0.001) • **2009:** 120 (p-value: < 0.001)
Kim et al. [40] Prosp 2009 South Korea	• n = 826 • 9 sites	• Observed mortality: 19.5% • Predicted mortality: NA **All patients** • SMR: 0.76 (95% CI: 0.62-0.85) **Med** • SMR: 0.85 (95% CI: 0.69-0.97) **Surg** • SMR: 0.40 (95% CI: 0.2-0.59)	**Worst 24h score** • **Total:** 17 {11, 23} • **Surv:** 15 {10, 21} • **Non-surv:** 23.5 {20, 28} • p-value: < 0.001	• **All patients:** 0.729 (95% CI: NA) • **Med:** 0.651 (95% CI: 0.69-0.97) • **Surg:** 0.704 (95% CI: erroneously reported)	• **All patients:** 55.99 (p-value: < 0.001) • **Med:** 73.83 (p-value: < 0.001) • **Surg:** 33.34 (p-value: < 0.001)
Bilgili et al. [209] Prosp 2004 Turkey	• n = 200 • 1 site	• Observed mortality: 51% • Predicted mortality: 38% **All patients** • SMR: 1.34 (95% CI: NA)	**Worst 24h score** • **Total:** 21.0 (7.7) • **Surv:** 16.7 (6.3) • **Non-surv:** 25.1 (6.6) • p-value: < 0.001	• **All patients:** 0.80 (95% CI: NA)	NA

Table 18: Performance of APACHE II over the past 10 years (cont.)

Authors, Study design, Data collection period & Country	Number of patients & sites	Hospital mortality rate, & SMR	Mean (SD)† Median (Interquartile range)‡	Discrimination measured by the ROC	Calibration measured by the HL-C
Litton et al. [215] Prosp. 2004-2006 Australia	• n = 2634 • 1 site	• Observed mortality: 14.6% • Predicted mortality: 13.4% **All patients** • SMR: 1.10 (95%CI: NA)	**Worst 24h score** • **Total:** 16 {11, 21} • **Surv:** NA • **Non-surv:** NA • p-value: NA	• **All patients:** 0.80 (95% CI: 0.78-0.82)	• **All patients:** 42.0 (p-value: <0.01)
Mann et al. [212] Prosp 1997-2005 was used for recalibration 2006-2008 was used for validation New Zealand	• n = 7703 for recalibration • n = 2080 for validation • 1 site	**Recalibration cohort** • Observed mortality: 15.8% • Predicted mortality: 19.0% **All patients** • SMR: 0.83 (95%CI: NA) **Validation cohort** • Observed mortality: 14.7% • Predicted mortality using the conventional APACHE II: 20.8% • Predicted mortality using the recalibrated APACHE II: 15.3% **All patients** • SMR: 0.96 (95%CI: NA)	**Worst 24h score** • **Total:** NA • **Surv:** NA • **Non-surv:** NA p-value: NA	**Recalibration cohort** • **All patients:** 0.763 (95% CI: 0.734-0.792) **Validation cohort** • **All patients:** 0.732 (95% CI: 0.701-0.763)	**Recalibration cohort** • **All patients:** 211 (p-value: <0.001) **Validation cohort** • **All patients:** 381 (p-value: <0.001)
Christensen et al. [206] Prosp 2007 Denmark	• n = 469 • 1 site	• Observed mortality: 17.7% • Predicted mortality: NA **All patients** • SMR: 1.10 (95%CI: NA)	**Worst 24h score** • **Total:** 36 {26, 47} • **Surv:** NA • **Non-surv:** NA • p-value: NA	• **All patients:** 0.73 (95% CI: 0.67-0.78)	• **All patients:** 13.66 (p-value: 0.19)

Table 18: Performance of APACHE II over the past 10 years (cont.)

Authors, Study design, Data collection period & Country	Number of patients & sites	Hospital mortality rate, & SMR	Mean (SD)† Median (Interquartile range)‡	Discrimination measured by the ROC	Calibration measured by the HL-C
Brinkman et al. [202] Prosp 2006-2009 Netherlands	• n = 44112 • 59 sites	• Observed mortality: NA • Predicted mortality: NA **SMR of the recalibrated APACHE II** • **All patients** 1.00 (95%CI: 0.98-1.02) • **Med**: 1.04 (95%CI: 1.02-1.06) • **Emerg surg**: 0.97 (95%CI: 0.95-0.98) • **Elect surg**: 0.87 (95%CI: 0.85-0.90)	**Worst 24h score** • **Total:** 15 {10, 21} • **Surv:** NA • **Non-surv:** NA • p-value: NA	**Recalibrated APACHE II** • **All patients:** 0.84 (95% CI: 0.83-0.84) • **Med:** 0.81 (95% CI: 0.80-0.82) • **Emerg surg:** 0.78 (95% CI: 0.77-0.80) • **Elect surg:** 0.80 (95% CI: 0.78-0.82)	**Recalibrated APACHE II** • **All patients:** 91.21 (p-value: NA) • **Med:** 86.88 (p-value: NA) • **Emerg surg:** 30.78 (p-value: NA) • **Elect surg:** 66.71 (p-value: NA)
Mann et al. [207] Retro 1997-2005 New Zealand	• n = 7703 • 1 site	• Observed mortality: 17.7% • Predicted mortality: NA **All patients** • SMR in 1997: 0.94 (95%CI: 0.82-1.06) • SMR in 2005: 0.66 (95%CI: 0.55-0.76)	**Worst 24h score** • 1997**:** 14 {9, 21} • 2005: 13 {9, 21} • p-value: 0.0001	**All patients** • **1997:** 0.858 • **1998:** 0.884 • **1999:** 0.871 • **2000:** 0.874 • **2001:** 0.858 • **2002:** 0.819 • **2003:** 0.853 • **2004:** 0.846 • **2005:** 0.812	**All patients:** • **1997-2002:** 3.31-11.14 (p-value: 0.084-0.769) • **2003:** 25.31 (p-value: 0.0003) • **2004:** 21.49 (p-value: 0.001) • **2005:** 19.41 (p-value: 0.004)
Quach et al. [210] Prosp 2002-2004 Canada	• n = 3778 • 1 site	• Observed mortality: 27.2% • Predicted mortality: NA **All patients** • SMR: NA (95%CI: NA)	**Worst 24h score** • **Total:** 19.6 (8.6) • **Surv:** NA • **Non-surv:** NA p-value: NA	• **All patients:** 0.808 (95% CI: NA)	NA

Table 18: Performance of APACHE II over the past 10 years (cont.)

Authors, Study design, Data collection period & Country	Number of patients & sites	Hospital mortality rate, & SMR	Mean (SD)† Median (Interquartile range)‡	Discrimination measured by the ROC	Calibration measured by the HL-C
Mbongo et al. [203] Retro 2006 Spain	• n = 864 • 1 site	• Observed mortality: 8.2% • Predicted mortality: 11.1% **All patients** • SMR**:** 0.73 (95%CI: 0.58-0.92)	**Worst 24h score** • **Total:** 9.0 (7.1) • **Surv:** 8.4 (6.3) • **Non-surv:** 20.0 (11.3) p-value: <0.001	• **All patients:** 0.893 (95% CI: 0.850-0.937)	• **All patients:** 18.9 (p-value: 0.015)
Khwannimit and Bhurayanontachai [205] Prosp 2004-2008 Thailand	• n = 2040 • 1 site	• Observed mortality in the training sample: 27.5% • Observed mortality in the validation sample: 26.8% • Predicted mortality using the conventional APACHE II: 22.7% • Predicted mortality using the recalibrated APACHE II: 22.7% **All patients** • SMR in the training sample**:** 0.76 (95%CI: 0.67-0.86) • SMR in the validation sample**:** 0.97 (95%CI: 0.86-1.09)	**Worst 24h score** • **Total in the training sample:** 12 {7, 20} • **Surv:** NA • **Non-surv:** NA • p-value: NA • **Total in the validation sample:** 17 {11, 25} • **Surv:** NA • **Non-surv:** NA • p-value: NA	• **All patients in the training sample:** 0.915 (95% CI: 0.895-0.935) • **All patients in the validation sample:** 0.925 (95% CI: 0.906-0.944)	• **All patients in the training sample:** 74.54 (p-value: NA) • **All patients in the validation sample:** 7.65 (p-value: NA)

Values are mean (standard deviation) or median {interquartile range} unless otherwise stated. **APACHE II**: Acute physiology and chronic health evaluation II; CI: Confidence interval; **Emerg**: Emergency; **Elect**: Elective; **HL-C**: Hosmer Lemeshow-C statistics; **Hosp**: hospital; **h:** hours; **Med**: Medical; **n**: Number; **Prosp**: Prospective; **Retro**: Retrospective; **ROC**: Receiver operating characteristic; **SMR**: Standardised mortality ratio; **Surg**: Surgery; **Surv**: Survivor

The following section contains material from:

Lew CCH, Wong GJY, Tan CK, Miller M. Performance of the Acute Physiology and Chronic Health Evaluation II (APACHE II) in the prediction of hospital mortality in a mixed ICU in Singapore. Proceedings of Singapore Healthcare 2018.

Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 75%
- Writing and editing: 95%

I made a major contribution to the conception of the manuscript, design of the research, and acquisition, analysis, and interpretation of the data. I drafted the manuscript and revised it according to the recommendations provided by my co-authors and the peer reviewers.

4.3 Introduction

The Acute Physiology and Chronic Health Evaluation II (APACHE II) was developed in 1985 to objectively quantify disease severity and predict hospital mortality risk [39]. Despite newer versions such as APACHE III [160] and IV [161], APACHE II continues to be widely used in research and clinical practice. This is due in part to the ease of calculation and the possibility of comparative consistency by reason of its long history of use.

Hospital mortality rates of critically ill patients are used to assess the performance of ICUs because it reflects important characteristics associated with good clinical practices (e.g., accurate diagnosis and timely therapies) [170]. Since some hospitals will inherently admit patients with higher disease severity and thus have higher mortality rates than others, APACHE II plays an essential role in the adjustment of mortality risk. That is, the predicted mortality rate derived from APACHE II can be compared to the observed mortality rate, a procedure termed the "standardised mortality ratio" (SMR) [170]. The accuracy of the SMR in assessing ICU performance is underpinned by the accuracy of the predicted hospital mortality risk since

under- or overestimation of such risk will, respectively, inflate or understate the actual performance of the ICU.

All ICUs of the public hospitals in Singapore use APACHE II for quality audits. Despite the pervasive use of APACHE II, its prognostic accuracy in Singapore remains questionable since it has never been validated locally with established statistical methods. Therefore, this study primarily aims to determine the performance of APACHE II in the prediction of hospital mortality in a mixed ICU. The secondary aim is to customise APACHE II and evaluate the performance of this new model.

4.4 Methods

Patient and Setting

This prospective cohort study was conducted in a 35-bed mixed ICU at Ng Teng Fong General Hospital. The ICU functions as a closed unit in which board-certified intensivists and residents provide care for both medical and surgical patients. Between August 2015 and October 2016, all adult ICU patients ≥ 21 years old who had ≥ 24 hours length-of-stay were enrolled. For patients readmitted to the ICU during the same hospitalisation, only the data on the first admission was included. The Domain Specific Review Board approved this study (NHG DSRB Ref: 2014/00878), and informed consent was not required as this study was deemed a clinical audit.

Data collection

All data required to calculate APACHE II score and predicted mortality risk (demography, physiological parameters, admission diagnoses and comorbidities) were prospectively recorded in the electronic medical records. Calculation of APACHE II was carried out by methods described by Knaus et al. [39]. However, several established modifications were carried out. *Glasgow Coma Score (GCS):* In most cases, the lowest GCS during the first 24 hours of ICU admission were used to calculate APACHE II. However, in patients who were anaesthetised before ICU admission, the GCS recorded before anaesthesia

was used [216]. *Acute Kidney Injury (AKI):* The diagnosis of AKI was in accordance with the latest definition i.e., increase in serum creatinine by ≥ 26.5 mmol/L within 48 hours or by ≥ 1.5 times of baseline, or urine volume < 0.5 ml/kg/hour for 6 hours [217]. *Missing data:* Parameters not measured in the first 24 hours of ICU admission were considered normal [160].

The predicted hospital mortality was calculated using a formula that comprised a constant, the APACHE II score multiplied by a coefficient, exposure status for emergency surgery multiplied by a coefficient, and the admission diagnosis coefficient outlined in Knaus et al. [39], e.g. Ln(R/I-R) = -3.517 + (APACHE II score X 0.146) + admission diagnostic coefficient + 0.603 if exposed to emergency surgery, where Ln = natural logarithm and R = risk of hospital mortality [39]. The coefficient corresponding to the principal diagnosis resulting to ICU admission was chosen. In cases of multiple diagnoses, the condition with the worst prognosis (e.g., haemorrhagic shock rather than sepsis) will be taken [170]. For observed hospital mortality, patients were followed until hospital discharge or death for up to one year after ICU admission.

Statistical Analysis

Performance of APACHE II

Performance was assessed by its discriminative ability and calibration accuracy. Discrimination refers to the ability of APACHE II in distinguishing discrete outcomes (e.g., died/survived). This was measured by the area under the Receiver Operating Characteristic curve (ROC), in which "perfect," "excellent," "very good," "good," "moderate," and "poor" discrimination are defined as ROC of 1.00, 0.90 – 0.99, 0.80 – 0.89, 0.70 – 0.79, 0.60 – 0.69, and < 0.60, respectively [171]. In contrast to discrimination, calibration accuracy refers to the ability of APACHE II in quantifying risk across the continuum of mortality risk. Calibration was measured using two methods. Firstly, the Hosmer-Lemeshow C test, in which accurate calibration is defined as p-value > 0.05, indicating no significant difference between the observed and predicted mortality [172], and secondly by plotting a calibration curve, with the observed and predicted mortality across all risk ranges presented in a graphical plot.

The SMR, or the ratio of observed versus predicted hospital mortality estimated by APACHE II and its 95% confidence interval (CI), was also calculated for the purpose of future comparisons. The 95% CI was derived by dividing the 95% CI of the observed mortality by the predicted mortality [218]. An SMR with 1.0 within the 95% CI indicates overall good ICU performance.

Customisation and validation of customised APACHE II

The study population was randomly split into equal training and validation groups. The training group was used to customise APACHE II, in which new coefficients for the APACHE II score and exposure to emergency surgery as well as a new constant were computed from logistic regression with hospital mortality as the dependent variable. Thereafter, in the validation group, the discriminative ability and calibration accuracy of the customised model were determined by methods described above.

Patient characteristics of the training and validation groups were reported as mean and standard deviation, medians, and inter-quartile range or counts and percentages, and the Student's t-test, Mann-Whitney U-test, or Chi-square test were used as appropriate to compare patient characteristics. All statistical analyses were performed using STATA 14.2 (Stata Corp, College Station, TX, USA), with significance assumed at $p < 0.05$.

4.5 Results

There were 844 admissions, of which 503 were enrolled (Figure 9). A majority of patients were from the emergency department and admitted to the ICU for medical reasons. Other characteristics of the enrolled patients in the overall, training, and validation groups are summarised in Table 19. Hospital mortality was 31% in the overall group, and no patients were lost to follow-up since the longest hospital length-of-stay was 255 days.

Overall Sample

Discrimination was good as evidenced by the ROC, but calibration accuracy measured by the Hosmer-Lemeshow C test was poor (Table 20). This was supported by the calibration curve, which showed an overestimation of predicted hospital mortality risk in nearly all deciles (Figure 10).

Customisation

The new customised equation used to quantify predicted hospital mortality risk was Logit = -4.587 + (APACHE II score X 0.143) + existing diagnostic weight, as outlined in Knaus et al. [39]. Exposure to emergency surgery was not significantly associated with hospital mortality (p-value: 0.324) and hence was omitted in this new model.

Discrimination was good in the validation group and very good in the training group (Table 20 and Figure 11). Although customisation of APACHE II considerably improved the accuracy of the predicted hospital mortality risk in all deciles (Figure 10: overall versus validation group), significant inaccuracies remained in which predicted hospital mortality risks were under-estimated in patients with ≤ 40% observed hospital mortality risk and overestimated in patients with > 40% observed hospital mortality risk. Calibration accuracy was good for medical patients in both the training and validation group but poor in surgical patients in the validation group. Similarly, the SMR in medical patients, as opposed to surgical patients, appears to be more reliable, as evidenced by the tighter confidence interval.

Table 21: Patient characteristics

Characteristics	All patients (n=503)	Training group (252)	Validation group (251)	p-value
Age (years)	61.2 (15.8)	60.9 (16.2)	61.5 (15.4)	0.674
Male	302 [60.0]	153 [60.7]	149 [59.4]	0.757
Location before admission				0.886
Emergency department	219 [43.5]	111 [44.0]	109 [43.4]	
High dependency	82 [16.3]	38 [15.1]	44 [17.5]	
Operation theatre	114 [22.7]	57 [22.6]	56 [22.3]	
Wards	88 [17.5]	46 [18.3]	42 [16.7]	
Type of admission				0.445
Medical	333 [66.2]	164 65.1]	169 [67.3]	
Elective surgery	18 [3.6]	7 [2.8]	11 [4.4]	
Emergency surgery	152 [30.2]	81 [32.1]	71 [28.3]	
APACHE II	24.5 (8.2)	24.7 (8.6)	24.3 (7.7)	0.561
Lead time (days)	1.0 {0.0, 1.0}	1.0 {0.0, 1.0}	1.0 {0.0, 2.0}	0.447
Admission reasons				0.373
Cardiovascular	102 [20.7]	56 [22.2]	48 [19.1]	
Respiratory	88 [17.5]	47 [18.7]	41 [16.3]	
Sepsis	113 [22.5]	50 [19.8]	63 [25.1]	
Trauma	13 [2.6]	8 [3.2]	5 [2.0]	
Metabolic/Renal	11 [2.2]	5 [2.0]	6 [2.4]	
Gastrointestinal	48 [9.5]	20 [7.9]	28 [11.2]	
Post operation	17 [3.4]	10 [4.0]	7 [2.8]	
Orthopaedics	7 [1.4]	6 [2.4]	1 [0.4]	
Neurological	102 [20.3]	50 [19.8]	52 [20.7]	
ICU LOS (days)	2.0 {2.0, 5.0}	2.0 {1.0, 5.0}	2.0 {2.0, 4.0}	0.841
Hospital LOS (days)	13.0 {6.0, 24.0}	13.0 {6.0, 24.0}	13.0 {6.0, 25.0}	0.985
ICU mortality	93 [18.5]	46 [18.3]	47 [18.7]	0.892
Hospital mortality	156 [31.0]	83 [32.9]	73 [29.1]	0.350

Values are mean (SD), median {q1, q3}, or count [percentage]. **APACHE II:** Acute physiology and chronic health evaluation II; **LOS**: Length-of-stay; **ICU:** Intensive care unit.

Table 22: Discriminative ability and calibration accuracy of APACHE II in all patients – training and validation groups

Patients groups	ROC (95% CI)	HL-C (p-value)	SMR (95% CI)
All patients	0.756 (0.715 - 0.792)	146.54 (< 0.001)	0.609 (0.532 - 0.692)
Medical (n = 333)	0.762 (0.713 - 0.807)	86.97 (< 0.001)	0.648 (0.557 - 0.745)
Surgical (n = 170)	0.728 (0.656 - 0.795)	75.30 (< 0.001)	0.513 (0.383 - 0.672)
Training group	0.804 (0.744 - 0.865)	9.95 (0.445)	1.015 (0.830 - 1.223)
Medical (n = 169)	0.794 (0.720 - 0.867)	9.24 (0.510)	1.024 (0.818 - 1.252)
Surgical (n = 82)	0.806 (0.691 - 0.921)	5.87 (0.826)	0.986 (0.616 - 1.504)
Validation group	0.722 (0.654 - 0.790)	31.47 (0.001)	1.131 (0.940 - 1.339)
Medical (n = 164)	0.734 (0.654 - 0.815)	11.58 (0.314)	1.061 (0.858 - 1.281)
Surgical (n = 88)	0.681 (0.553 - 0.809)	29.51 (0.001)	1.382 (0.936 – 1.950)

CI: Confidence interval; **HL-C:** Hosmer-Lemeshow C test; **ROC:** Receiver operating characteristic; **SMR:** Standardised mortality ratio

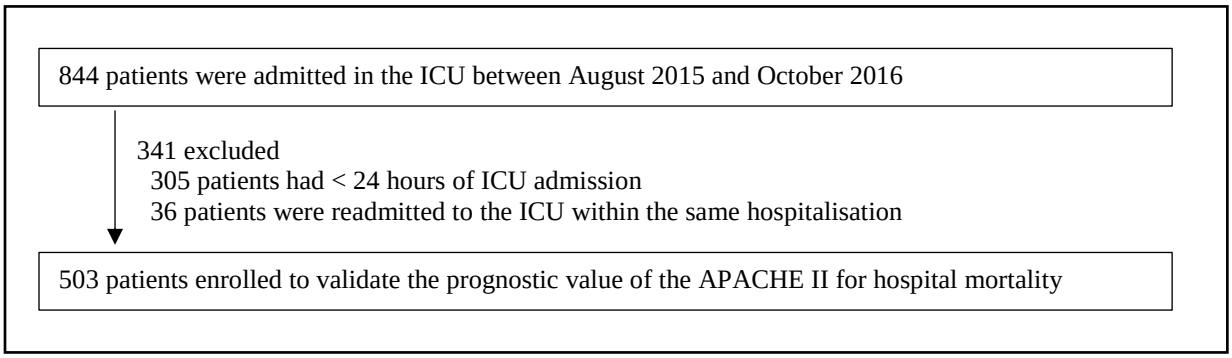


Figure 9: Enrollment of patients

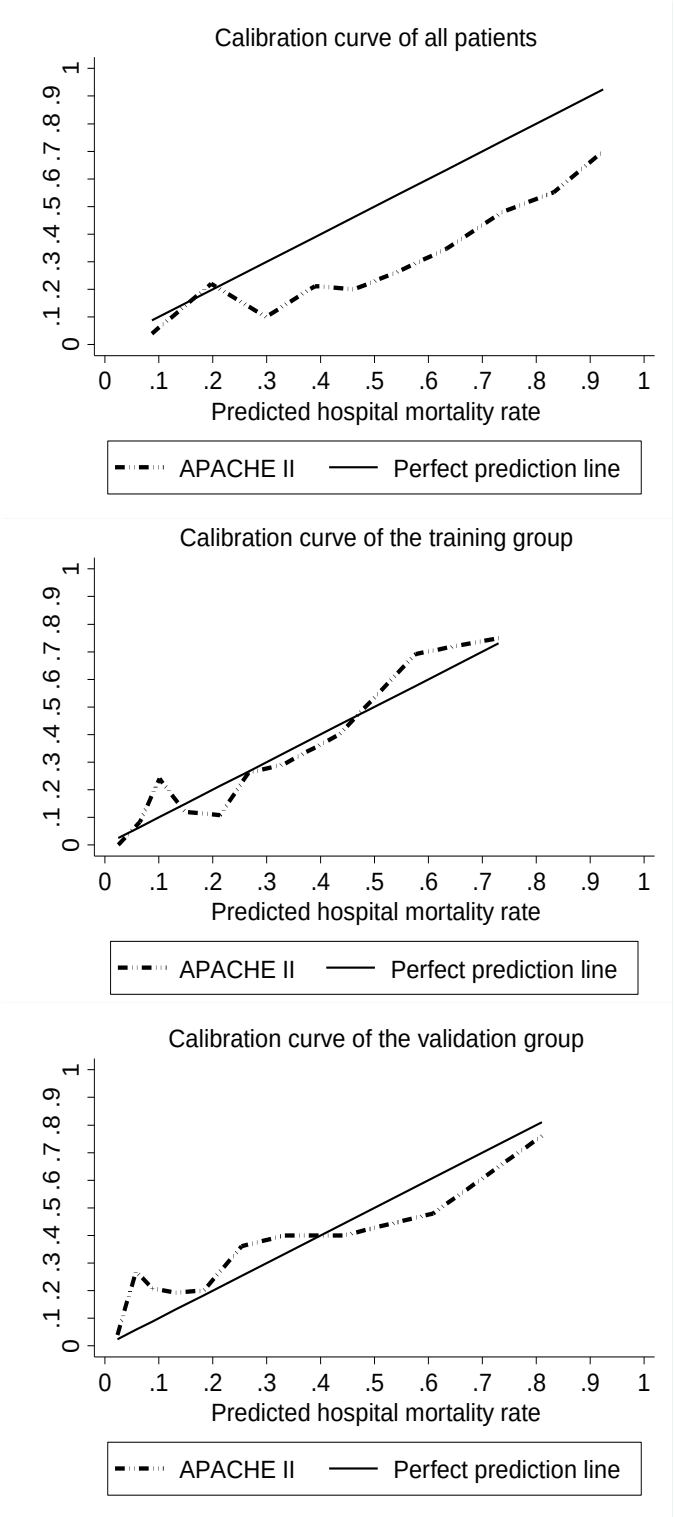


Figure 10: Calibration curves for all patients, training group, and validation group

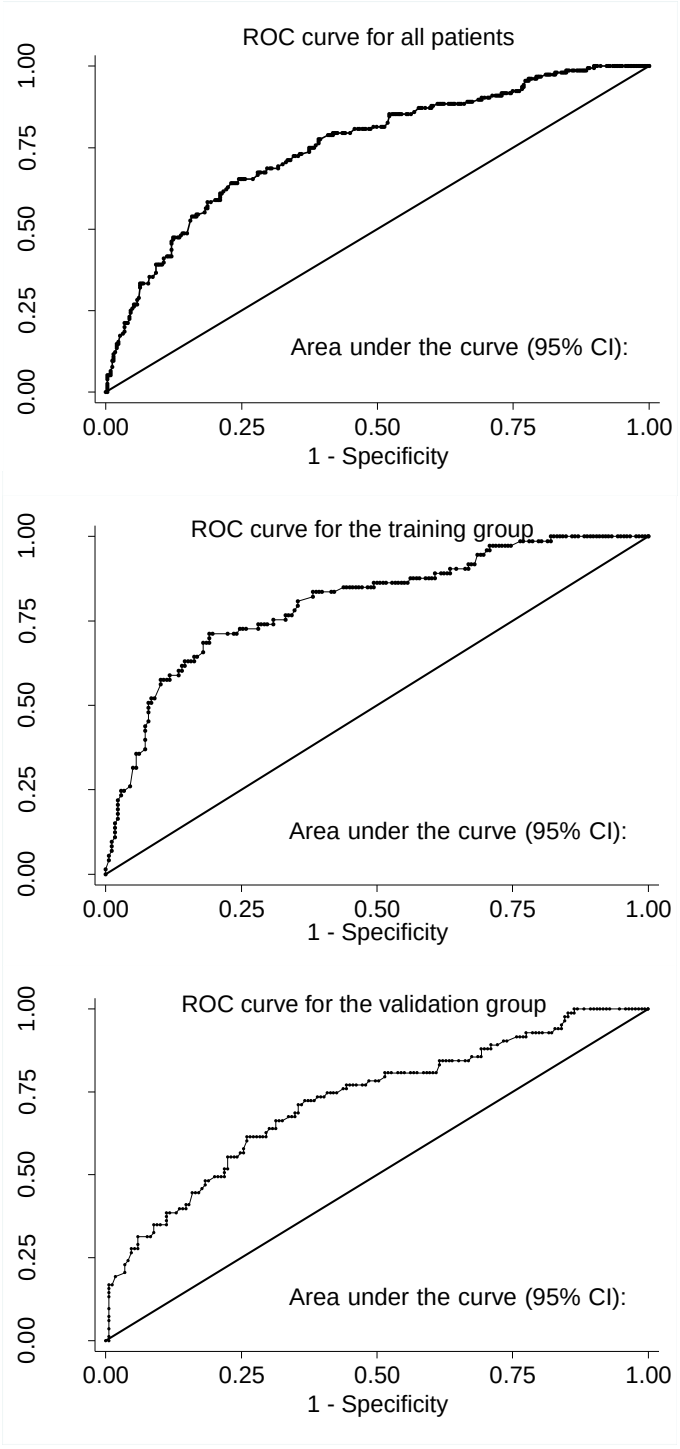


Figure 11: Receiver operating characteristic curves for all patients, training group, and validation group

4.6 Discussion

This is the largest study conducted in Singapore to evaluate the validity of APACHE II in predicting hospital mortality. While APACHE II has demonstrated good discrimination, poor calibration accuracy for hospital mortality and customisation of APACHE II did not significantly improve its calibration accuracy in the local setting.

In 1985, Knaus et al. [39] used data (12 physiological parameters, comorbidities, emergency surgery, age and admission diagnosis) from a reference population of 5,815 patients from 13 hospitals in the United States to develop APACHE II so as to quantify the predicted hospital mortality risk of critically ill patients via an equation. Therefore, all subsequent evaluations of ICU performance using APACHE II are in effect weighted against the reference population. Given advances in ICU treatment modalities since 1985, it is crucial to validate APACHE II before using it in the local setting.

This is the fifth validation study performed in Singapore, yet results of the present study cannot be compared with those of three previous studies as they did not report the discrimination and calibration accuracy of APACHE II [219-221]. Nevertheless, we were able to estimate the SMR and calibration accuracy from the crude results reported by Lee et al. [219]. These authors prospectively calculated the APACHE II scores of 131 patients in the medical ICU, and the SMR was estimated to be 0.89, with good correlation (r=0.95, p-value: 0.001) between observed and predicted mortality, suggesting good calibration. Similar results were demonstrated in the surgical ICU, in which there were very good discrimination and likely good calibration (correlation between observed and predicted mortality: 0.97; p-value unreported) [222]. The good prognostic performance of APACHE II in these studies [219, 222] was likely due to the close proximity between APACHE II development (i.e., 1985) and the validation period (1991), in which treatment modalities were likely similar. Evidently, reduction in observed hospital mortality over time due to advances in treatment modalities gradually reduces the discrimination and calibration accuracy of APACHE II [211, 212]. This may be attributed to discordance in results between the present study and those of Lee et al. [219] and Chen et al. [222].

Compared to recent studies conducted in other countries, patients in the present study had higher disease severity, as evidenced by the higher observed hospital mortality and mean APACHE II score (24.5 versus 17 to 21 [40, 201, 204, 208, 209, 211, 214]). Similar to recent studies, APACHE II in the present study also had good discriminative validity (i.e. 0.756 versus 0.729 to 0.805 [40, 201, 204, 208, 209, 211, 214]) and poor calibration accuracy [40, 204, 209, 211, 214]. It has been shown that the latter will have a negative impact on statistical risk adjustment in research studies and the SMR used in clinical audits [170]. Therefore, customisation of APACHE II is often carried out in the literature in an effort to improve calibration accuracy.

There are two levels of customisation. First-level customisation refers to computing a new constant and new coefficients for the APACHE II score and exposure to emergency surgery, while second-level customisation involves computing new coefficients for the admission diagnoses in addition to the first-level steps above [205]. In the present study, second-level customisation was not performed because it may result in overfitting when conducted in a small sample of patients [223]. Although first-level customisation considerably improved calibration, it remained insufficient to improve calibration accuracy significantly. This is similar to Brinkman et al. [202] and Mann et al. [212], in which customisation also did not improve calibration accuracy.

This study has a number of strengths. Selection, attrition, and treatment biases were minimised by the use of consecutive recruitment, complete follow-up, and blinding of the treatment team to the objectives of the study, respectively. However, there are some limitations. Since the study was conducted in a single centre, the results lack generalizability. Moreover, although the study was the largest to have been conducted in the local setting, the sample size did not allow for robust subgroup analyses.

Future directions

Poor calibration after customisation is indicative of the need to either conduct a local multicentre study to perform robust second-level customisation or to develop a new prognostic model with the addition of strong predictors such as exposure to cardiopulmonary resuscitation

before ICU admission and nutritional status [2, 5]. This will allow for comparisons of ICU performance among local hospitals as well as internal quality assessment and benchmarking based on historical baseline performance data (e.g., baseline SMR). The SMR of APACHE II is reported in the present study for future comparison. Since the customised APACHE II did not demonstrate good calibration, the SMR was not further stratified by risk levels. For future studies, best practice would be to stratify the SMR by low-, medium-, and high-risk patients to better understand the performance of APACHE II in different risk groups. This is because the proportion of high-risk patients within a cohort will disproportionately affect the aggregated SMR since most high-risk patient will die [170].

4.7 Conclusion

APACHE II demonstrated good discrimination but poor calibration accuracy in the prediction of hospital mortality in a mixed ICU in Singapore. First-level customisation was attempted to improve calibration accuracy, but this proved futile. Therefore, there is an urgent need for future studies to recruit a larger sample of patients from multiple hospitals to perform second-level customisation or develop a new prognostic model that will better predict hospital mortality. *Alternatively, new predictors could be added to the existing APACHE II model to improve the overall prognostic accuracy. An example of this is the mNUTRIC score, in which APACHE II is combined with four other predictors to quantify the 28-day mortality risk of critically ill patients. The validity of this score will be examined in the next two chapters.*

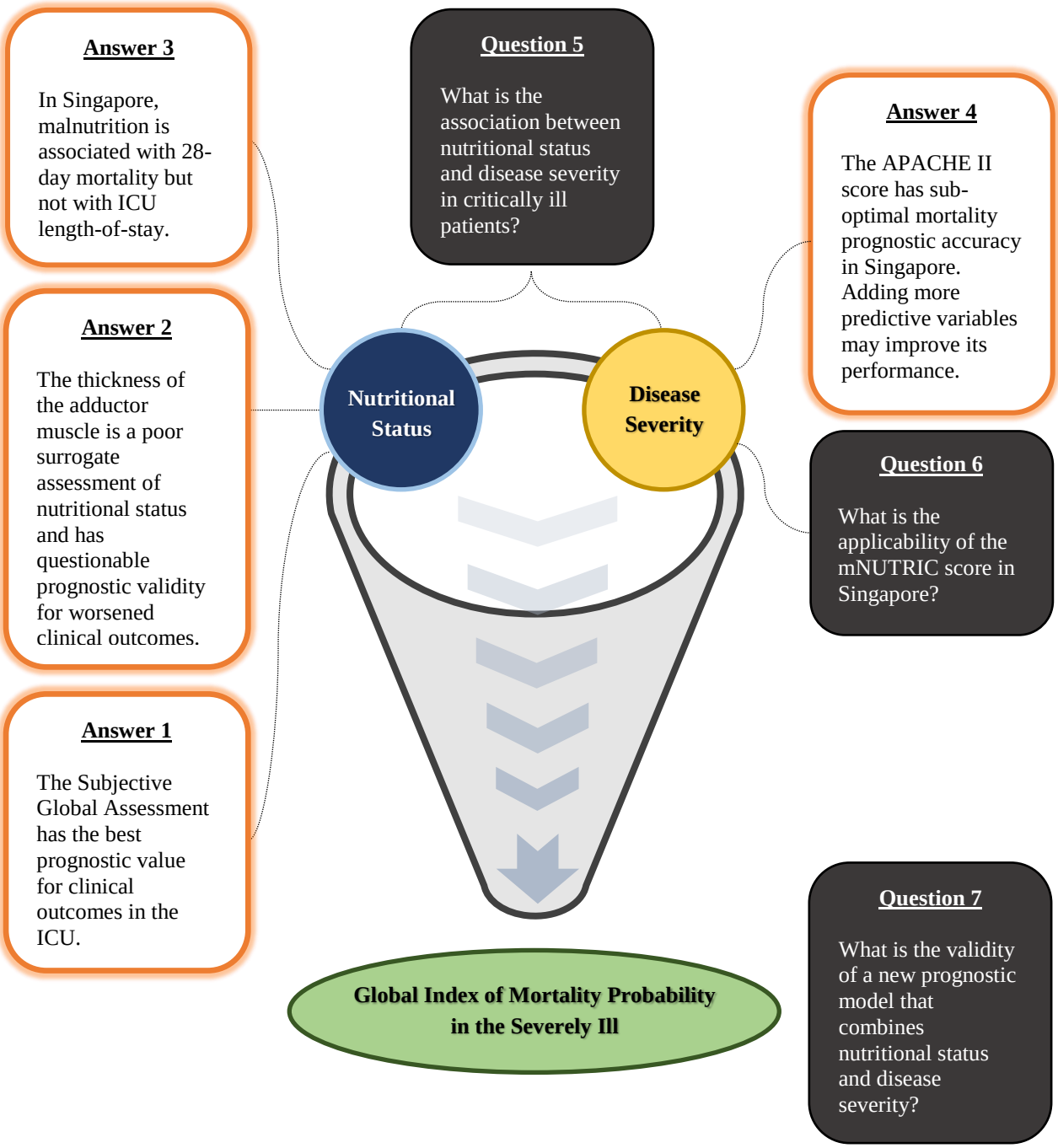


Figure 12: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 4

Chapter 5: What is the association between nutritional status and disease severity in critically ill patients?

5.1 Contribution to the overall research objective

Heyland et al. [38] developed the NUTRIC Score in 2011 to quantify the 28-day mortality risk of critically ill patients and identify those that would derive the most benefit from nutrition support in the ICU (see Table 21 for a summary of the prognostic performance of the NUTRIC score). The original NUTRIC score comprised six components (age, APACHE II, SOFA, number of comorbidities, days in hospital before admission to ICU, and interleukin-6), but it was subsequently modified to exclude interleukin-6 concentrations (mNUTRIC) as this parameter is rarely measured outside of research settings [41].

To date, 10 studies (8 prospective and 2 retrospective cohort studies) have validated the external prognostic performance of mNUTRIC (Table 21). These studies included 190 to 2,853 patients with age, APACHE II, mNUTRIC, and 28-day mortality ranging from 52 to 79 years, scores of 20 to 26, 3.7 to 6.4, and 20.7% to 54.6%, respectively. Patients were mostly admitted to the ICU for respiratory, sepsis, cardiovascular, post-operation, or neurological issues. However, half of the studies [224-228] suffered from selection bias as patients with missing data (mortality outcome, mNUTRIC score) were excluded.

Prognostic performance of mNUTRIC

The discriminative accuracy of mNUTRIC ranged from poor to good (C-index ranging from 0.58 [229] to 0.77 [226]). Sensitivity of mNUTRIC was generally higher than its specificity (sensitivity: 72% to 88%; specificity: 49% to 63%) except for the study conducted by Kalaiselvan et al. [229], in which specificity was higher than sensitivity. Each increment in score was associated with 1.34 to 1.68 higher odds of 28-day mortality.

There were signals of poor calibration accuracy since there was discordance between mean mNUTRIC scores and 28-day mortality across the studies. For example, the mean

mNUTRIC score and the corresponding 28-day mortality rate in the study conducted by Bi et al. [224] were 5.8 and 20.7%, respectively, whereas these values were 3.7 and 54.6% for Moretti et al. [228]. These observations were in line with Rahman et al. [41] since the Hosmer Lemeshow goodness-of-fit test demonstrated poor calibration (p-value: 0.013). Furthermore, the range of max-rescaled R-square (0.057 to 0.158) suggested poor model fit.

The cut-off point used to define low- and high-mNUTRIC score was inconsistent. While most studies used ≥ 5 to defined high-mNUTRIC, Rahman et al. [41] and Lee et al. [230] defined high-mNUTRIC as ≥ 6. This cut-off point was validated in a recent study conducted by Jeong et al. [227] with the use of the Youden index.

Comparison of mNUTRIC and SGA

At face value, the mNUTRIC score appears to be a disease severity score rather than a nutrition assessment tool since three of the six variables used in calculating it are indices of disease severity (i.e., APACHE II and SOFA scores). In contrast, all components of the SGA (weight history, dietary changes, gastrointestinal symptoms, functional capacity, degree of metabolic stress, loss of muscle mass and subcutaneous fat, and fluid accumulation) are used to defined nutritional status. Nevertheless, it is unclear whether the mNUTRIC score and the SGA are associated. In the event that they are not (because one measures disease severity while the other measures nutritional status), it is unclear whether a combination of both tools could better predict the clinical outcomes of critically ill patients. Therefore, an original study was carried out to determine the association between mNUTRIC and the SGA in the ICU. The manuscript was submitted in February 2017 and accepted in July 2017. To keep this chapter up-to-date and preserve the integrity of the published manuscript as much as possible, pertinent new information was added and footnotes are used to indicate sections added to the published manuscript.

Table 23: Summary of studies that measured the prognostic performance of NUTRIC and mNUTRIC scores

Author Study design Country	Selection criteria	Subject characteristics	Admission Dx (%)	Disease severity	Discrimination Calibration	Odd ratio for 28-day mortality	Others
Heyland et al. [38] Prospective observational study at 3 ICUs Canada & United States	• > 18 y and > 24 hrs ICU-LOS • Excluded cases of drug overdose and elective surgery	**n:** 597 **M/S:** 63/37 **Age:** 64 {52, 73} **BMI:** 26.5 {23.2, 31.3}	Cardio 8.5 Resp: 27.8 Sepsis: 6.7 Neuro: 5.9 Trauma: 7.9 Metab: 6.7 Gastro: 16.6 Post-op: 12.5 Renal: 4.3 Ortho: 3.0	**APACHE II:** 21.0 {16.0, 27.0} **SOFA:** 7.0 {5.0,9.0} **NUTRIC:** 4.7(2.2)* **28-day mortality:** 23.1%	**For 28-day mortality** **C-index:** 0.78 (95% CI: NA) **HL:** 0.28 **Sensitivity (%):** NA **Specificity (%):** NA	**Each increment in NUTRIC score:** 1.74 (95% CI: 1.55, 1.97), p-value: < 0.001*	**Max-rescaled R-square:** 0.256
Moretti et al. [228] Prospective observational study at 1 ICU Argentina	• > 18 y and > 24 hrs ICU-LOS and on MV • Excluded cases where mNUTRIC score could not be calculated	**n:** 368 **M/S:** 74/26 **Age:** 52 (NA) **BMI:** NA	Cardio 11.7 Resp: 28.5 Sepsis: 7.1 Neuro: 12.0 Trauma: 11.1 Metab: NA Gastro: NA Post-op: 15.2 Renal: NA Ortho: NA	**APACHE II:** 20.7 (7.8) **SOFA:** 7.7 (3.5) **mNUTRIC:** 3.7(1.9) **28-day mortality:** 54.6%	**For ICU mortality** **C-index:** 0.67 (95% CI: NA) **HL:** NA **Sensitivity (%):** NA **Specificity (%):** NA	NA	**Best cut-off mNUTRIC score:** 3.26 **Sensitivity (%):** 63.3 **Specificity (%):** 58.1 **mNUTRIC score for present and absence of** • **VAP:** 3.2 (1.6) vs 3.8 (2.0), p-value: 0.034 **Prolonged MV**: 3.7 (1.4) vs 3.7 (2.0), p-value: 0.825
Rahman et al. [41] Post-hoc analysis of RCT conducted in 40 ICUs Europe and North America	• Cases of MOF with expected ICU-LOS of > 5 days and placed on MV	**n:** 1199 **M/S:** 79/21 **Age:** 63 (NA) **BMI:** 29.8 (NA)	Cardio: 19.5 Resp: 30.8 Sepsis: 31.0 Neuro: 1.1 Trauma: 2.5 Metab: 2.3 Gastro: 7.8 Post-op: NA Renal: 0.6 Ortho: 0.5	**APACHE II:** 26.3 (NA) **SOFA:** 8.4 (NA) **mNUTRIC:** 5.5 (1.6) **28-day mortality:** 29.0%	**For 28-day mortality** **C-index:** 0.65 (95% CI: NA) **HL:** 0.013 **Sensitivity (%):** NA **Specificity (%):** NA	**Each increment in mNUTRIC score:** 1.4 (95% CI: 1.3, 1.5), p-value: NA	**Max-rescaled R-square:** 0.0573 (corrected value as published value is likely erroneous) mNUTRIC scores were positively associated with higher 6-month mortality (p-value < 0.0001)

Table 21: Summary of studies that measured the prognostic performance of NUTRIC and mNUTRIC scores (cont.)

Author Study design Country	Selection criteria	Subject characteristics	Admission Dx (%)	Disease severity	Discrimination Calibration	Odd ratio for 28-day mortality	Others
Bi et al. [224] Retrospective examination of prospectively collected data at 1 ICU China	• > 18 y and > 5 days ICU-LOS • Excluded cases with missing baseline data or lost to follow-up	**n:** 261 **M/S:** NA **Age:** 59 (19) **BMI:** NA	Cardio: 7.3 Resp: 10.0 Sepsis: 5.0 Neuro: 30.3 Trauma: 4.6 Metab: NA Gastro: 6.1 Post-op: 21.5 Renal: NA Ortho: NA	**APACHE II:** 25.1 (6.9) **SOFA:** 3.5 {7.5, 11.0} **mNUTRIC:** 5.8 (1.7) **28-day mortality:** 20.7%	**<u>For 28-day mortality</u>** **C-index:** NA **HL:** NA **Sensitivity (%):** NA **Specificity (%):** NA	**Each increment in mNUTRIC score:** 1.34 (95% CI: 1.10, 1.63), p-value: 0.003	**Odd ratio of 90-day mortality for each increment in mNUTRIC score:** 1.45 (1.23, 1.71), p-value: < 0.001
Mukhopadhyay et al. [153] Prospective observational study at 1 ICU Singapore	• > 18 y and > 24 hrs ICU-LOS • Excluded cases which are readmitted	**n:** 401 **M/S:** NA **Age:** 60 (16) **BMI:** 23.9 (6.2)	Cardio: 4.7 Resp: 8.2 Sepsis: 39.9 Neuro: 12.0 Trauma: NA Metab: 3.7 Gastro: 8.0 Post-op: NA Renal: 3.7 Ortho: NA	**APACHE II:** 25.3 (NA) † **SOFA:** 8.7 (NA) † **mNUTRIC:** 5.0† **28-day mortality:** 21.7%	**<u>For 28-day mortality</u>** **C-index:** 0.71 (95% CI: NA) **HL:** NA **Sensitivity (%):** 72 **Specificity (%):** 63	**Each increment in mNUTRIC score:** 1.48 (95% CI: 1.25, 1.74), p-value: < 0.001	NA
Compher et al. [225] Prospective observational study at 202 ICUs International	• ≥ 16 y and > 72 hrs of ICU-LOS • MV within 48 hrs and ICU-LOS ≥ 4 days • Excluded incomplete data for 60-day mortality	**n:** 2853 (> 4 days ICU-LOS) **n:** 1605 (> 12 days ICU-LOS) **M/S:** 65/35 **Age:** 61.2 (17.3) **BMI:** 27.0 (7.5)	Cardio: NA Resp: NA Sepsis: NA Neuro: NA Trauma: NA Metab: NA Gastro: NA Post-op: NA Renal: NA Ortho: NA	**APACHE II:** 22.5 (8.5) **SOFA:** 8.9 (3.7) **mNUTRIC:** 4.8 (2.0) **60-day mortality:** 30.8%	**<u>For 60-day mortality</u>** **C-index:** 0.65 (95% CI: NA) **HL:** NA **Sensitivity (%):** NA **Specificity (%):** NA	NA	**Max-rescaled R-square:** 0.085

Table 21: Summary of studies that measured the prognostic performance of NUTRIC and mNUTRIC scores (cont.)

Author Study design Country	Selection criteria	Subject characteristics	Admission Dx (%)	Disease severity	Discrimination Calibration	Odd ratio for 28-day mortality	Others
Mendes et al. [231] Prospective observational study at 15 ICUs Portugal	• > 18 y and > 72 hrs of ICU-LOS • Excluded cases of readmission, transfers from other ICU, or brain dead at admission	**n:** 1143 **M/S:** NA **Age:** 64 {51, 75} **BMI:** 26.2 {23.4, 29.7}	Cardio: 10.3 Resp: 23.0 Sepsis: 20.2 Neuro: 9.5 Trauma: 14.6 Metab: 3.2 Gastro: 4.3 Post-op: 13.9 Renal: 1.1 Ortho: NA	**APACHE II:** 20 {14, 26} **SOFA:** 7 {5, 10} **mNUTRIC:** 4.0 {3.0, 6.0} **28-day mortality:** 21.7%	**<u>For 28-day mortality</u>** **C-index:** 0.72 (95% CI: 0.69, 0.75) **HL:** NA **Sensitivity (%):** 73.0 **Specificity (%):** 58.0	**High vs Low mNUTRIC score (≥ 5 vs. ≤ 4):** 3.84 (95% CI: 2.80, 5.26), p-value: < 0.001	**High vs Low mNUTRIC score (≥ 5 vs ≤ 4) for:** **ICU-LOS (days)** • 10 {5, 16.5} vs 8 {5, 14}, p-value: < 0.001 **MV-free days** • 2 {1, 4} vs 3 {1, 4}, p-value: < 0.001 **Max-rescaled R-square:** 0.158
Kalaiselvan et al. [229] Prospective observational study at 1 ICU India	• Adults, and > 48 hrs of MV • Excluded cases of readmission, transfers from other ICU	**n:** 678 **M/S:** 77/23 **Age:** 55.7 (17.5) **BMI:** 24.3 (3.9)	Cardio: NA Resp: NA Sepsis: NA Neuro: NA Trauma: NA Metab: NA Gastro: NA Post-op: NA Renal: NA Ortho: NA	**APACHE II:** 22.2 (7.3) **SOFA:** 6.7 (3.0) **mNUTRIC:** 4.0 (2.0) **ICU mortality:** 31.7%	**<u>For ICU-mortality</u>** **C-index:** 0.58 (95% CI: 0.54, 0.63) **HL:** NA **Sensitivity (%):** 41.5 **Specificity (%):** 73.8	NA	**High vs Low mNUTRIC score (≥ 5 vs ≤ 4) for:** **ICU-LOS (days)** • 9.0 (4.2) vs 7.8 (2.8), p-value: < 0.01 **MV-free days** • 2.0 (2.8) vs 1.7 (1.9), p-value: 0.10

Table 21: Summary of studies that measured the prognostic performance of NUTRIC and mNUTRIC scores (cont.)

Author Study design Country	Selection criteria	Subject characteristics	Admission Dx (%)	Disease severity	Discrimination Calibration	Odd ratio for 28-day mortality	Others
de Vries et al. [226] Retrospective observational study at 1 ICU Netherlands	• ≥ 18 y and > 24 hrs of ICU-LOS • MV within 24 hrs • Exclude patients with no mNUTRIC data and cases of readmissions	**n:** 475 **M/S:** 64/36 **Age:** 69.8 {NA} † **BMI:** 26.3 {NA} †	Cardio: 27.6 Resp: 29.9 Sepsis: 12.2 Neuro: 2.5 Trauma: 0.6 Metab: 2.1 Gastro: 19.6 Post-op: 2.9 Renal: 1.9 Ortho: 0.6	**APACHE II:** 20.0 {NA} † **SOFA:** 7.5 {NA} † **mNUTRIC:** 5.3 {NA} † **28-day mortality:** 25.5%	**<u>For 28-day mortality</u>** **C-index:** 0.77 (95% CI: 0.72, 0.81) **HL:** NA **Sensitivity (%):** 88.4 **Specificity (%):** 48.9	NA	**C-index for prolonged ventilation:** 0.67 (95% CI: 0.62, 0.72)
Hsu et al. [232] Prospective observational study at 1 ICU Taiwan	• ≥ 65 y, APACHE II ≥ 15, > 48 hrs MV and on NGT feeding • Excluded patients on TPN, > 5 days of fasting, brain dead, terminally ill from cancer	**n:** 190 **M/S:** 100/0 **Age:** 79.1 (7.2) **BMI:** 22.4 (4.7)	Cardio: NA Resp: NA Sepsis: NA Neuro: NA Trauma: NA Metab: NA Gastro: NA Post-op: NA Renal: NA Ortho: NA	**APACHE II:** NA **SOFA:** NA **mNUTRIC:** 6.4 (1.4) **Hosp mortality:** 27.4	**<u>For Hosp mortality</u>** **C-index:** NA **HL:** NA **Sensitivity (%):** NA **Specificity (%):** NA	**Each increment in mNUTRIC score:** 1.64 (95%CI: 1.24, 2.15)	**High vs Low mNUTRIC score (≥ 5 vs ≤ 4) for:** **Hosp-LOS (days)** • 26.9 (15.3) vs 21.5 (8.7), p-value: 0.03 **MV (days)** • 13.5 (10.2) vs 9.8 (5.7), p-value: 0.03

Table 21: Summary of studies that measured the prognostic performance of NUTRIC and mNUTRIC scores (cont.)

Author Study design Country	Selection criteria	Subject characteristics	Admission Dx (%)	Disease severity	Discrimination Calibration	Odd ratio for 28-day mortality	Others
Jeong et al. [227] Retrospective observational study at 1 ICU South Korea	• ≥ 18 y and > 24 hrs of ICU-LOS and had sepsis • Excluded patients lost-to-follow-up, lacked IL-6 levels,	**n:** 482 **M/S:** NA **Age:** 66 {56, 74} **BMI:** 23 {20, 25}	Cardio: NA Resp: NA Sepsis: 100 Neuro: NA Trauma: NA Metab: NA Gastro: NA Post-op: NA Renal: NA Ortho: NA	**APACHE II:** 21.0 {16, 28} **SOFA:** 10 {7, 14} **mNUTRIC:** NA **28-day mortality:** 37.8%	**For 28-day mortality** **NUTRIC** **C-index:** 0.76 (95% CI: NA) **HL:** NA **Sensitivity (%):** 79.7 **Specificity (%):** 60.2 **mNUTRIC ≥ 5** **C-index:** 0.76 **HL:** NA **Sensitivity (%):** 87.3 **Specificity (%):** 45.1	**Each increment in mNUTRIC score:** 1.68 (95% CI: 1.42, 1.98)	**Best cut-off for mNUTRIC by Youden index: ≥ 6** **For mNUTRIC ≥ 6** **C-index:** 0.76 (95% CI: 0.72, 0.81) **HL:** NA **Sensitivity (%):** 75.3 **Specificity (%):** 64.8

Values are mean (standard deviation), median {Interquartile range}, counts, or percentages unless specified. * Reported in [41]; † Estimated; **Age:** Rounded to the nearest year; **APACHE II:** Acute physiology and chronic health evaluation II; **BMI:** Body mass index in kg/m^2; **Cardio:** cardiovascular; **CI:** Confidence interval; **Dx:** Diagnosis; **Gastro:** Gastroenterology; **HL:** Hosmer-Lemeshow goodness-of-fit; p-value > 0.05 indicates good calibration; **hrs:** Hours; **ICU-LOS:** Intensive care unit length-of-stay; **Metab:** Metabolic; **mNUTRIC:** Modified nutrition risk in the critically ill score; **MOF:** Multi-organ failure; **MV:** Mechanical ventilation; **M/S:** Percentage of medical versus surgical patients; **n:** Numbers; **NA:** Not available; **Neuro:** Neurology; **NUTRIC:** Nutrition risk in the critically ill score; **Ortho:** Orthopedics; **Post-op:** Post-operation; **Resp:** Respiratory; **SOFA:** Sequential organ failure assessment; **TPN:** Total parenteral nutrition; **VAP:** Ventilator-associated pneumonia; **vs:** Versus; **y:** Years

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Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 75%
- Writing and editing: 90%

I made a major contribution to the conception of the manuscript, design of the research, and acquisition, analysis, and interpretation of the data. I drafted the manuscript and revised it according to the recommendations provided by my co-authors and the peer reviewers.

5.2 Introduction[†]

The SGA [58] is an established nutrition assessment tool designed to diagnose malnutrition and comprising eight components (weight history, dietary changes, gastrointestinal symptoms, functional capacity, degree of metabolic stress, loss of muscle mass, loss of subcutaneous fat, and fluid accumulation). A recent systematic review showed that the SGA has good predictive validity for hospital mortality in critically ill patients and hence is a useful nutrition assessment tool in the critical care settings [1].

An alternative assessment tool is NUTRIC, a composite score of six components (age, APACHE II, SOFA, number of comorbidities, days in hospital before admission to ICU, and interleukin-6 concentration) identifying patients who would most benefit from aggressive nutrition support [38]. The mNUTRIC, where interleukin-6 concentration is omitted from the

[†] The content of Sections 5.2 to 5.6 is similar to an original published article. To keep this thesis up-to-date, new information in the form of italicised texts was added to the published article.

score (as it is not commonly measured outside of research environments) has also been shown in several observational studies to have fair predictive ability for 28-day mortality [153, 225, 231]. In clinical practice, either the SGA or mNUTRIC are used to guide nutritional interventions in critically ill patients but seldom in combination.

A combined mNUTRIC and SGA assessment has been proposed in previous studies [71, 233]. However, such recommendation may lack validity since the prognostic ability of the combination was not adequately assessed. Therefore, this study aims to: 1) determine agreement between SGA and mNUTRIC scores; and 2) quantify their utility in discriminating and quantifying hospital mortality risk both independently and in combination.

5.3 Methods

This was a prospective observational study conducted in a 35-bed mixed ICU in Ng Teng Fong General Hospital, Singapore. Between August 2015 and October 2016, all patients ≥ 18 years old who had ≥ 24 hours length-of-stay in the ICU were enrolled. For patients readmitted to the ICU during the same hospitalisation, only data from the first admission were included. Intensivists and nurses were unaware of the study's objectives. The Domain Specific Review Board approved this quality assessment project (NHG DSRB Ref: 2014/00878), and informed consent was not required.

Nutrition assessment and data collection

As part of routine care, all patients received a nutrition assessment (SGA) from a dietitian within 48 hours of admission to the ICU. Information was gathered either from the patients or their main caregivers, and nutritional status was dichotomized into well-nourished (SGA-A) and malnourished (SGA-B/C). The mNUTRIC was not part of routine care. All data required to calculate the mNUTRIC were automatically and prospectively recorded in the electronic medical records and retrospectively calculated at the end of the study. Patients with values of 0-4 were classified as low-mNUTRIC and 5-9 as high-mNUTRIC [41]. The primary outcome was hospital mortality, and all patients were followed until discharge or death for up

to one year after admission to the ICU. Other parameters known to be covariates of hospital mortality were also collected (Table 22).

Statistical analysis

Continuous data are reported as mean and standard deviation (parametric) or median and inter-quartile range (non-parametric), and groups were compared by Student's t-test, Mann-Whitney U-test, ANOVA, and Kruskal-Wallis H test, as appropriate. Categorical variables were described as counts and percentages and compared by Chi-square test. Agreement and mortality discriminative value (i.e., discrimination) of the two-category classification of mNUTRIC (Low- and high-mNUTRIC) and SGA (SGA-A and SGA-B/C) were assessed by Kappa statistics and C-index, respectively. The C-index of both tools was further compared with the DeLong test [234]. To quantify the association between high-mNUTRIC, malnutrition, and their combination (mNUTRIC ≥ 5 and SGA-B/C) with hospital mortality, a multivariable logistic regression was used to generate their respective adjusted odds ratios. Fourteen candidate predictors ($p < 0.05$) (Table 22) were identified, and collinearity (indicated by high variance inflation factors and low tolerances) was excessively high for APACHE II, predicted mortality, SOFA, and mNUTRIC. Hence, these were omitted in the statistical adjustment. Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and C-indexes were generated using STATA 11.1 (Stata Corp, College Station, TX, USA). For all comparisons, a p-value < 0.05 was considered significant.

Table 24: Comparison of characteristics between survivors and non-survivors in the hospital

Patient characteristics	All (n = 439)	Survivor (n = 309)	Non-survivor (n = 130)	p-value
Age (years)	61.4 (15.8)	59.4 (16.0)	66.0 (14.2)	< 0.001
Male	259 [59.0]	185 [59.9]	74 [56.9]	0.641
Ethnicity				
Chinese	272 [62.0]	187 [60.5]	85 [65.4]	0.163
Malay	113 [25.7]	77 [24.9]	36 [27.7]	
Indian	28 [6.4]	24 [7.8]	4 [3.1]	
Others	26 [5.9]	21 [6.8]	5 [3.8]	
BMI (kg/m^2)	24.8 (6.6)	24.8 (6.6)	24.7 (6.4)	0.864
LOS before ICU adm (days)	0.0 {0.0, 1.0}	0.0 {0.0, 1.0}	1.0 {0.0, 3.0}	0.001
Number of comorbidities	2.0 {1.0, 4.0}	2 {1.0, 4.0}	2 {1.0, 4.0}	0.316
APACHE II	24.5 (8.1)	22.6 (7.4)	29.2 (7.8)	< 0.001
Predicted Mortality Risk (%)	48.4 (26.1)	43.7 (24.0)	67.7 (23.2)	< 0.001
SOFA	8.6 (3.8)	7.8 (3.4)	10.7 (3.9)	< 0.001
mNUTRIC	5.3 (2.1)	4.8 (2.1)	6.5 (1.6)	< 0.001
Length of MV (days)	2.0 {1.0, 5.0}	2.0 {1.0, 3.0}	3.0 {2.0, 7.0}	< 0.001
ICU LOS (days)	2.0 {2.0, 5.0}	2.0 {1.0, 4.0}	3.0 {2.0, 7.0}	< 0.001
Hospital LOS (days)	14.0 {7.0, 24.0}	14.0 {9.0, 27.0}	11.0 {4.0, 19.0}	< 0.001
Vasoactive drugs before ICU adm	192 [43.7]	123 [39.8]	69 [53.1]	0.014
CPR before ICU adm	52 [11.8]	17 [5.5]	35 [26.9]	< 0.001
Nutritional status				
Well-nourished	316 [72.0]	241 [76.3]	75 [23.7]	< 0.001
Malnourished	123 [28.0]	68 [55.3]	55 [44.7]	
mNUTRIC categories				< 0.001
Low (score 1-4)	141 [32.1]	128 [90.8]	13 [9.2]	
High (score 5-9)	298 [67.9]	181 [60.7]	117 [39.3]	

Values are mean (standard deviation), median {interquartile range}, or counts [%]. **Adm:** admission; **APACHE II**: Acute physiologic and chronic health evaluation II; **BMI:** Body mass index; **CPR:** Cardiopulmonary resuscitation; **ICU:** Intensive care unit; **LOS:** Length-of-stay; **MV:** Mechanical ventilation; **mNUTRIC:** Modified nutrition risk in critically ill; **SOFA:** Sequential organ failure assessment

5.4 Results

A total of 503 eligible patients were enrolled. Of these, 64 lacked SGA data and were excluded from further analysis. Excluded patients had slightly fewer comorbidities (1 vs. 2, p-value: 0.007) and a shorter length of hospital admission (8.0 days vs. 14.0 days, p-value < 0.001) but were otherwise similar to the studied patients.

The final study group thus comprised 439 patients (medical: 294, surgical: 145). The hospital mortality rate was 29.6%. No patients were lost to follow-up as the longest hospitalization period was 255 days. Of the studied group, 123 (28.0%) were classified as

malnourished (SGA-B/C), 298 (67.9%) had high-mNUTRIC, and 100 (22.8%) were both malnourished and had high-mNUTRIC (Table 23). Independent of the nutritional status, patients with high-mNUTRIC were significantly older and had higher disease severity and mortality risk as compared to patients with low-mNUTRIC. The body mass index of malnourished patients (SGA-B/C) regardless of mNUTRIC score were significantly lower than those that were well-nourished (SGA-A).

There was poor concordance between the mNUTRIC and SGA (kappa statistics: 0.13, p-value < 0.001). However, their individual discriminative value for hospital mortality were similar, with C-indexes for High-mNUTRIC and malnutrition being 0.66 (95% CI: 0.62, 0.70) and 0.60 (95% CI: 0.55, 0.65), respectively, p-value: 0.12. The combination of mNUTRIC and SGA had a significantly better discriminative ability [0.70 (95% CI: 0.66, 0.75)] than either of these tools alone (p-value: 0.002 and < 0.001, respectively) (Figure 13).

Multivariable logistic regression indicated that the odds ratio for hospital mortality in patients with high-mNUTRIC was higher than for those who were malnourished (Table 23). However, the risk of hospital mortality was highest in patients who were both malnourished and had high-mNUTRIC [14.43 (95% CI: 5.38, 38.78); p-value < 0.001].

Table 25: Comparison of characteristics and mortality risk among patients with and without malnutrition and high mNUTRIC score

Patient characteristics	Well-nourished and low-mNUTRIC (SGA-A and mNUTRIC ≤ 4)	Malnourished (SGA-B/C)	High-mNUTRIC (mNUTRIC ≥ 5)	Malnourished and high-mNUTRIC (SGA-B or C and mNUTRIC ≥ 5)
n (%)	118 [26.9]	23 (5.2)	198 [45.1]	100 [22.8]
Age (years)	50.8 (15.8)	54.6 (17.0)	65.1 (12.9)†	68.1 (13.8)†
BMI (kg/m^2)	25.7 (7.6)	22.0 (5.7)‡	26.0 (5.4)	22.3 (6.6)§
APACHE II score	16.8 (4.9)	17.8 (4.6)	27.7 (6.6)†	28.9 (7.0)†
PMR (%)	24.9 (15.1)	31.1 (16.8)	60.8 (21.2)†	66.1 (21.7)†
SOFA score	5.7 (2.6)	5.3 (3.3)	9.9 (3.1)†	10.4 (3.8)†
mNUTRIC score	2.8 (1.2)	3.1 (1.2)	6.4 (1.1)†	6.7 (1.2)†
Length of MV (days)	2.0 {1.0, 4.3}	2.0 {1.0, 3.0}	2.0 {1.0, 5.0}	2.0 {1.0, 5.0}
ICU LOS (days)	2.0 {1.8, 5.3}	2.0 {1.0, 4.0}	3.0 {1.8, 5.0}	3.0 {2.0, 5.0}
Hospital LOS (days)	12.0 {6.0, 24.0}	14.0 {6.0, 27.0}	14.0 {7.0, 24.0}	16.0 {9.0, 26.8}
Hospital mortality	9 [7.6]	4 [17.4]	66 [33.3]	51 [51.0]
Adjusted Odds ratio¶	Reference	4.27 (95% CI 1.03, 17.71) p-value: 0.046	5.32 (95% CI 2.15, 13.17) p-value: < 0.001	14.43 (95% CI 5.38, 38.76) p-value: < 0.001

Values are mean (standard deviation), median {interquartile range}, counts [%], or adjusted odds ratio (95% confidence interval).
APACHE II: Acute physiology and chronic health evaluation II; **BMI:** Body mass index; **ICU:** Intensive care unit; **LOS:** Length-of-stay; **MV:** Mechanical ventilation; **mNUTRIC:** Modified nutrition risk in the critically ill; **PMR:** Predicted mortality risk; **SGA:** Subjective global assessment; **SOFA:** Sequential organ failure assessment.

† p-value < 0.01 compared to Well-nourished and low-mNUTRIC and Malnourished

‡ p-value < 0.05 compared to High-mNUTRIC

§ p-value < 0.01 compared to Well-nourished and low-mNUTRIC and High-mNUTRIC

¶ Adjusted for age; length-of-stay, and use of vasoactives and cardiopulmonary resuscitation before ICU admission; length of mechanical ventilation; hospital and ICU length-of-stay

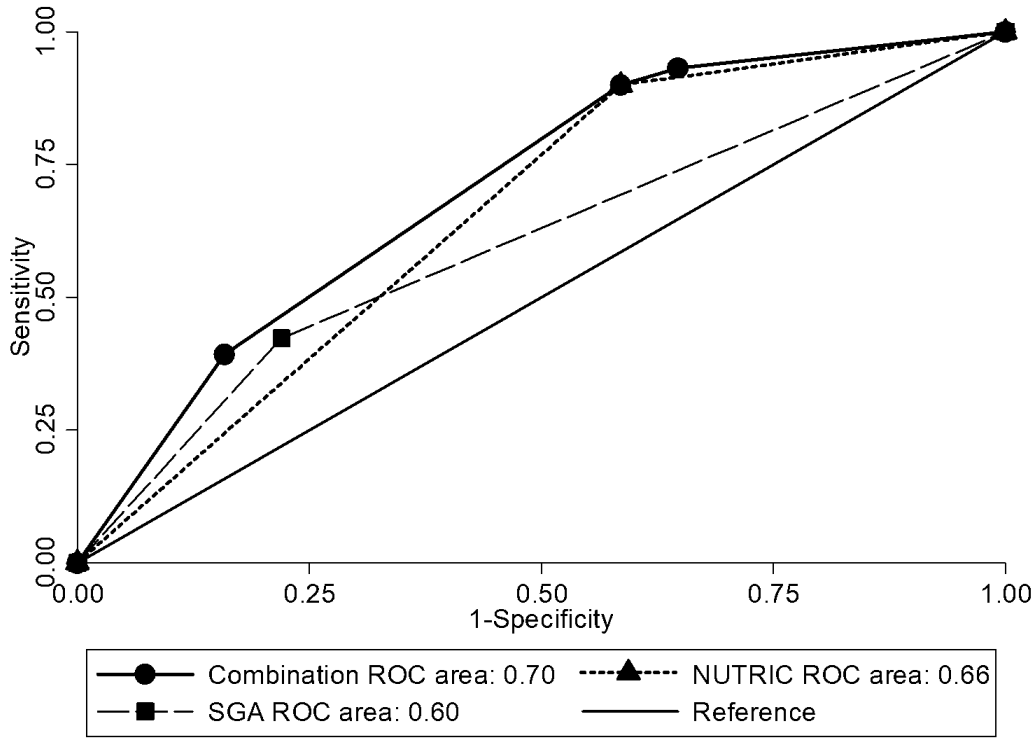


Figure 13: Receiver operating characteristic curve (ROC) for modified Nutrition Risk in Critically ill Score (mNUTRIC), Subjective Global Assessment (SGA) and their combination for predicting hospital mortality

5.5 Discussion

This is the first study to use established statistical approaches to evaluate agreement between the mNUTRIC and SGA and compare their ability in discriminating and quantifying mortality risk independently and in combination. While the two tools had poor inter-test agreement, their combination could better discriminate and quantify the hospital mortality risk of critically ill patients.

The low concordance between mNUTRIC and SGA appeared to be independent of the prevalence of high-mNUTRIC and malnutrition. In a cohort of 294 patients in which 80% were malnourished and 26% had high-mNUTRIC, Coltman et al. [71] demonstrated that the agreement between both tools was 14.4% (kappa statistic unavailable). Although the prevalence of malnutrition and high-mNUTRIC was notably different in the present study, the

concordance between both tools was similarly very poor. This poor agreement could be explained by the different compositions of the two tools. The mNUTRIC is arguably not a true nutrition assessment tool since it does not contain the key parameters needed to diagnose malnutrition [49]. In contrast, the SGA uses a composite of nutritional parameters to diagnose malnutrition. Despite the differences, adequate nutrition support has been suggested to attenuate the mortality risk in patients with high-mNUTRIC or malnutrition risk [35, 38, 41, 153, 225].

Interestingly, the mNUTRIC and SGA individually had similar discriminative value for hospital mortality despite poor agreement between them. However, the combination of both of these tools had significantly better discriminative value. *For example, the body mass index was negatively associated with mortality in previous studies [108, 153, 235], and patients who failed both assessments (SGA: B/C and high-mNUTRIC) had significantly lower body mass index than those who had only high-mNUTRIC. However, this did not explain increased hospital deaths in patients who failed both assessments since as in Heyland et al. [38], the body mass index was not a significant prognostic parameter in the multivariable model in the present study. This highlights the importance of combining a comprehensive nutrition assessment such as the SGA with mNUTRIC.* This is consistent with the view that factors such as malnutrition, disease severity, and metabolic stress are all important co-factors associated with hospital mortality (Figure 13). The results of the present study also reveal the unique properties and complementary role of each tool as disease severity (quantified by mNUTRIC) can augment the mortality risk of malnourished patient and vice versa (Table 23). This was also observed in other studies, even though the magnitude of the association was not quantified [71] and only the crude mortality rates were reported [233]. Taken together, these observations provide support for the use of both SGA and mNUTRIC. The SGA identifies malnourished patients who require urgent nutrition support, whereas mNUTRIC helps identify well-nourished patients with high disease severity where malnutrition could ensue if adequate nutrition support is not provided. *This is evidenced by a recent study that reported an association between mNUTRIC and macronutrient deficiencies in critically ill patients [236]. After adjusting for possible confounders, patients with high-mNUTRIC had significantly higher odds of energy deficit (≥ 6000 kcal; adjusted-OR: 2.73; 95% CI 1.66, 4.50) and protein deficit*

(≥ 300 g; adjusted-OR: 2.35; 95% CI 1.43, 3.85) over a span of ≤ 14 days of exclusive nutrition support [236].

There are a number of strengths to the data presented in this work. These include the prospective design, consecutive recruitment, complete follow-up, and inclusion of both medical and surgical patients, which helped minimize the potential for selection and information biases. In addition, separate execution of the SGA and mNUTRIC minimised the risk of diagnostic review bias. However, there are several limitations of this study to consider before generalisation of the findings to clinical practice. Firstly, since the work was undertaken as a single-centre observational study, the data require further validation from multicentre studies. Secondly, patients excluded from the study (due to lack of SGA data) had fewer comorbidities and a shorter hospital length-of-stay. However, this is unlikely to have a significant impact on the results since the number of comorbidities did not predict hospital mortality. In addition, the length of hospitalisation was adjusted in the multivariable models. Thirdly, despite efforts to include as many covariates as possible, residual confounding factors cannot be ruled out due to the observational nature of the study.

The results of this study provide further evidence for the prognostic value of the SGA and mNUTRIC for mortality. While this provides a rationale for aggressive nutrition support, it was beyond the scope of this study to evaluate patient outcomes from adequate nutrition support as *such data were still being collected at that point in time*. Nonetheless, the study highlights the need to better elucidate the role of nutrition support in the ICU. *This is especially crucial since the effects of adequate nutrition support in malnourished patients and those with high-mNUTRIC score have never been evaluated in RCTs.* Future studies are needed to compare the effects of aggressive nutrition support in patients identified as malnourished by the SGA, who have high-mNUTRIC, or both. The results of such a study may provide a possible explanation for the discrepancy in the outcomes of aggressive nutrition support in patients with high-mNUTRIC scores [41, 237]. This may reflect the lack of baseline nutrition assessment in both studies, which prevented stratification of the analysis by nutritional status.

5.6 Conclusion

Although the mNUTRIC and SGA have similar discriminative value for hospital mortality, they have poor agreement. This most likely reflects the different components each used to quantify mortality risk. However, their combination better identifies patients who are at higher risk of hospital death than either measure alone, suggesting that a combination of nutritional status and disease severity can better predict mortality outcomes in the critically ill. *This was a leap towards developing GLIMPSE, a prognostic model that combines nutritional status and disease severity to better: 1) prognosticate mortality, and 2) identify patients who would derive the most benefit from aggressive nutrition support in the critical care setting.*

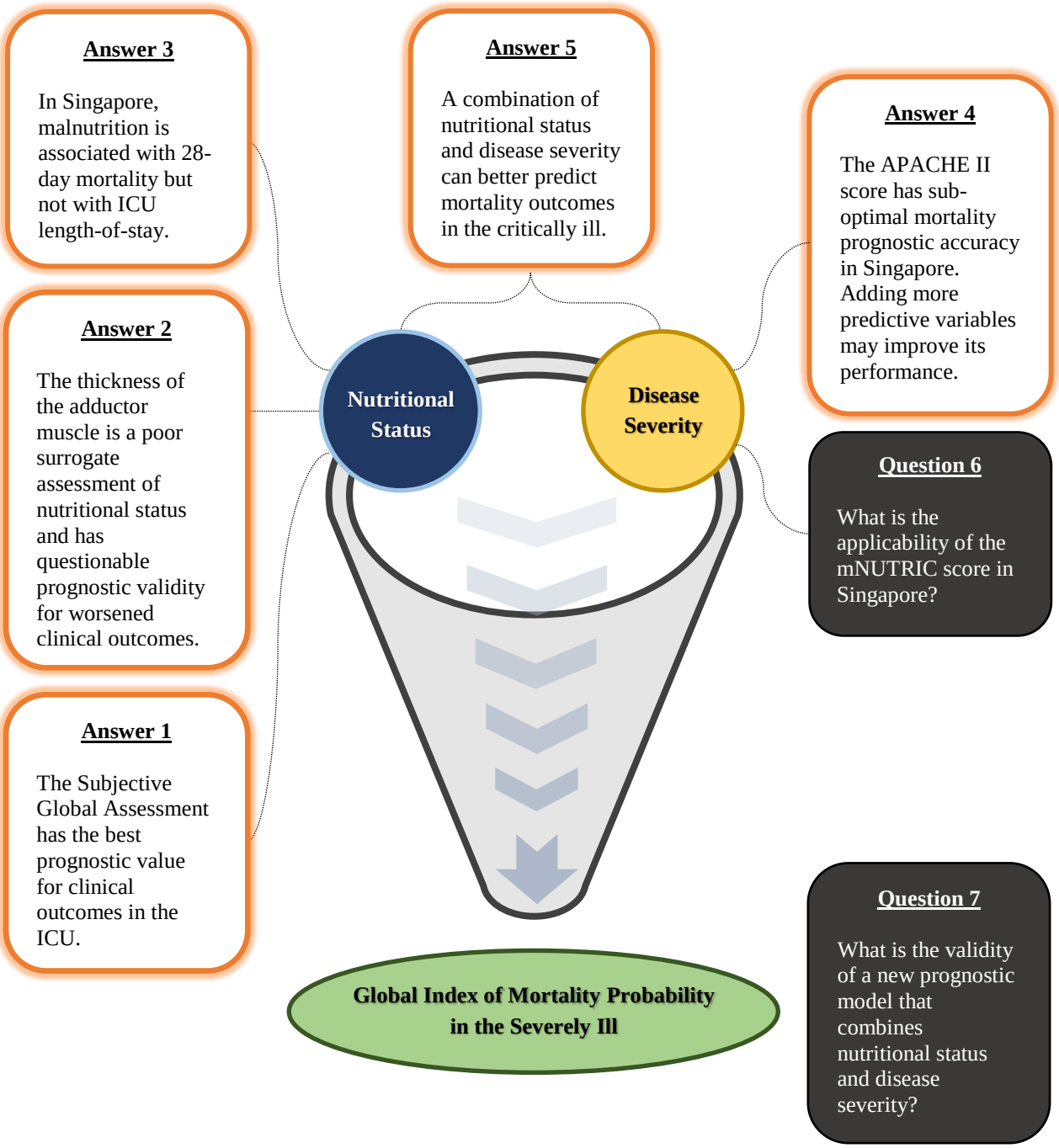


Figure 14: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 5

Chapter 6: What is the applicability of the modified Nutrition Risk in the Critically Ill (mNUTRIC) score in Singapore?

6.1 Contribution to the overall research objective

In this research project, it was hypothesized that baseline nutritional status and disease severity can individually and in combination prognose mortality outcomes in the critically ill. Therefore, the objective of this research project was to develop an ICU prognostic model that can better predict mortality outcomes and identify patients whose mortality outcome may be modified by aggressive nutrition support. To achieve this aim, the previous five chapters focused on identifying indices of nutritional status and disease severity associated with mortality outcomes. It was established that malnutrition diagnosed by the SGA as well as disease severity quantified by mNUTRIC score and APACHE II are prognostic of mortality outcomes.

In contrast to previous chapters, this chapter aimed to determine if aggressive nutrition support can modify mortality outcomes in critically ill patients. This aim could be achieved only at this stage because the data collection of energy and protein intakes required a considerable amount of time and was only completed in June 2017.

To date, 10 studies determined the external validity of the mNUTRIC score in identifying patients who benefit most from adequate nutrition support (Table 24). These studies enrolled 154 to 5,649 patients (mainly medical) with mean age, APACHE II, body mass index, and mNUTRIC score ranging from 51 to 79 years, and scores of 21.0 to 30.1, 22.4 to 29.8 kg/m^2, score 4.2 to 6.4 respectively. The duration of nutrition support ranged from ≥ 4 days to ≥ 12 days, and the achieved energy and protein goals ranged from 44.0% to 87.5% and 45.3% to 85.1%, respectively. The 28-day, 60-day, and 180-day mortality ranged from 21.3% to 29.0% [41, 153, 237-239], 30.8% to 44.8% [225, 230], and 30.3% to 68.3% [41, 237], respectively.

A review of the above studies revealed several interesting findings. Among the 10 studies, only seven demonstrated that patients with high-mNUTRIC (≥ 5 or ≥ 6 in [41])

benefited from higher energy [41, 153, 225, 232, 238-240] and protein [225, 240] intake. However, the reduction in predicted 28-day mortality can be as low as 2.6% [153] or as high as 15% [41] when energy intake was to be increased from 50% to 100% of goal (estimated from the figures provided in the primary papers). Of note, several of these studies may have selection bias whereby patients: of moribund status [153, 239], with missing data [225, 238, 241], or kept nil-by-mouth for any amount of time [239] were excluded.

In contrast to the above seven studies, Arabi et al. [237] demonstrated that higher energy intake in patients with high-mNUTRIC did not result in lower mortality. In fact, patients with high-mNUTRIC and exposed to ≤ 12 days of nutrition support had significantly higher 90-day mortality risk [242]. Harm associated with higher energy and protein intakes was also demonstrated in another recent study. In an observational cohort study, Lee et al. [230] demonstrated that patients with low-mNUTRIC score and receiving more than 66.7% of energy and protein goals had significantly higher 60-day mortality risk.

These disparate results may be explained by the differences in timing and dose of nutrition support (not reported in the primary studies). There is emerging evidence that the timing and dose of nutrition support can have an impact on mortality outcomes. This is evidenced by the INTACT group, which clearly showed that early aggressive nutrition support may significantly increase the mortality risk of critically ill patients with acute respiratory distress syndrome (ARDS) [243, 244]. Therefore, it is timely to conduct a prospective cohort study to determine if timing and dose of nutrition support in critically ill patients may modify the association between mNUTRIC categories (low and high) and 28-day mortality. Section 6.2 consists of a manuscript published in the Annals of Intensive Care.

Table 26: Summary of studies that measured the validity of NUTRIC and mNUTRIC scores in identifying patients who benefit most from nutrition support

Author Study design Country	Selection criteria	Subject	Disease severity	Nutritional adequacy (%)	Others
Heyland et al. [38] Prospective observational study at 3 ICUs Canada & United States	• > 18 y, > 3 days ICU-LOS and started MV within 48 hrs of admission • Excluded cases of DO & ES	**n:** 211 **M/S:** 78/22 **Age:** 65 {52, 74} **BMI:** 26.8 {22.9, 32.0}	**APACHE II:** 23.0 {19.0, 28.0} **SOFA:** 7.0 {5.0,10.0} **NUTRIC:** NA **28-day mortality:** NA	NA	• **Interaction between NUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 28-day mortality**: p-value: 0.01 • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** 7.5%*
Rahman et al. [41] Post-hoc analysis of RCT conducted in 40 ICUs Europe and North America	• All cases of MOF on MV with expected ICU-LOS of > 5 days • Excluded moribund patients	**n:** 1199 **M/S:** 79/21 **Age:** 63 (NA) **BMI:** 29.8 (NA)	**APACHE II:** 26.3 (NA) **SOFA:** 8.4 (NA)* **mNUTRIC:** 5.5 (1.6) **28-day mortality:** 29.0% **180-day mortality:** 68.3%	**Energy:** 50.2 (29.5) **Protein:** 45.3 (NA)* **Duration:** 7-8 days*	• **Interaction between mNUTRIC scores ≤ 5 vs ≥ 6 and energy adequacy for predicted 28-day mortality:** p-value: 0.029 • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** 15%* • **Interaction between mNUTRIC scores ≤ 5 vs ≥ 6 and energy adequacy for 6-mth mortality:** p-value: 0.038 • Among patients with mNUTRIC score ≥ 6, each 25% increase in energy prescription received was associated with an 18% (95%CI: 8%, 27%) hazard risk reduction in 6-month mortality. No effects was found for mNUTRIC score < 6
Mukhopadhyay et al. [153] Prospective observational study at 1 centre Singapore	• > 18 y, > 24 hr ICU-LOS, had > 48 hrs of MV and on enteral or parenteral nutrition support • Excluded all readmissions	**n:** 273 **M/S:** NA **Age:** 58 (NA)* **BMI:** 24.1 (NA)*	**APACHE II:** 27.3 (8.0) **SOFA:** 9.9 (NA)* **mNUTRIC:** 5.3 (NA)* **28-day mortality:** 25.3%	**Energy:** 44 {15, 70} **Duration:** unknown	• **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 28-day mortality**: p-value: < 0.001 • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** 2.6%* • Each additional 1000 kcal/day was associated with 2.2 days shorter LOS – univariate analysis • **mNUTRIC scores ≤ 4:** Each additional 1000 kcal/day was associated with 1.1 days shorter LOS – univariate analysis • **mNUTRIC scores ≥ 5:** Each additional 1000 kcal/day was associated with 2.9 days shorter LOS – univariate analysis

Table 24: Summary of studies that measured the validity of NUTRIC and mNUTRIC scores in identifying patients who benefit most from nutrition support (cont.)

Author Study design Country	Selection criteria	Subject	Disease severity	Nutritional adequacy (%)	Others
Arabi et al. [237] Arabi et al. [242] Post-hoc analysis of RCT conducted in 7 ICUs Saudi Arabia and Canada	• 18-80 y, start enteral feeding within 48 hrs of ICU adm, expected to remain for > 72hrs • Excluded moribund patients	**n:** 894 **M/S:** 97/3 **Age:** 51 (NA)* **BMI:** 29.3 (NA)*	**APACHE II:** 21.0 (8.0)* **SOFA:** 9.9 (NA)* **mNUTRIC:** 4.2 (NA)* **28-day mortality:** 21.3% **90-day mortality:** 27.7 **180-day mortality:** 30.3%	**Energy:** 58.5 (NA)* **Duration:** 9 days	Arabi et al. [237]: • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 90-day mortality**: p-value 0.53 • 378 patients (42.3%) had mNUTRIC ≥ 5 and full-feeding (achieving 70.7% of energy requirements, n=189) did not result in lower 90-day mortality (adj-OR: 0.84; 95% CI: 0.56, 1.27; p-value: 0.40) Arabi et al. [242] • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 90-day mortality**: p-value: 0.02 • Among patient with mNUTRIC ≥ 5 and received ≤ 12 days of nutrition support, full-feeding is associated with increased risk of 90-day mortality (adj-OR: 1.79; 95% CI: 1.05, 3.03; p-value: 0.03) • Among patient with mNUTRIC ≥ 5 and received ≥12 days of nutrition support, full-feeding is not associated to lower risk of 90-day mortality (adj-OR: 0.65; 95% CI: 0.33, 1.25; p-value: 0.19)
Lee et al. [230] Prospective observational study conducted in 1 ICU Malaysia	• ≥ 18 y and > 72 hrs of ICU-LOS and MV within 48 hrs • Excluded moribund, readmissions, or transferred from other ICU	**n:** 154 **M/S:** 77/23 **Age:** 51 (16) **BMI:** 26.5 (6.7)	**APACHE II:** 26.7 (7.4) **SOFA:** 12.4 (3.7) **mNUTRIC:** 5.7 (1.9) **60-day mortality:** 44.8%	**Energy:** 64.5 (21.5) **Protein:** 56.5 (20.6) **Duration:** 10 days	• **In patients with mNUTRIC ≤ 5:** receiving ≥ 66.7% of energy and protein requirements was associated with an increased risk of 60-day mortality (adj-OR: 6.30; 95% CI: 1.17, 33.8; p-value: 0.032) • **In patients with mNUTRIC ≥ 6:** receiving ≥ 66.7% of energy and protein requirements was not associated with a reduction in the risk of 60-day mortality (adj-OR: 1.21; 95% CI: 0.39, 3.76; p-value: 0.741)

Table 24: Summary of studies that measured the validity of NUTRIC and mNUTRIC scores in identifying patients who benefit most from nutrition support (cont.)

Author Study design Country	Selection criteria	Subject	Disease severity	Nutritional adequacy (%)	Others
Compher et al. [225] Prospective observational study at 202 ICUs International	• ≥ 16 y, MV within 48 hrs and ICU-LOS ≥ 4 days • Excluded patient with missing data	**n:** 2853 (> 4-days ICU-LOS) **n:** 1605 (≥ 12-days of nutrition support) **M/S:** 65/35 **Age:** 61 (17) **BMI:** 27.0 (7.5)	**APACHE II:** 22.5 (8.5) **SOFA:** 8.9 (3.7) **mNUTRIC:** 4.8 (2.0) **60-day mortality:** 30.8%	**Energy:** 62.4 (25.8) **Protein:** 58.9 (25.9) **Duration:** • Unknown for the 4-day cohort • ≥12 days for the 12-day cohort	**For each 10% achievement of energy and protein goals among patients with ICU-LOS ≥ 4 day and mNUTRIC ≥ 5** **Adjusted odds of 60-day mortality:** • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy and protein adequacy for predicted 60-day mortality**: p-value 0.56 and 0.34, respectively • Reduced by 8.6% (95% CI: 4.7%-12.5%) and 7.9% (95% CI: 3.5%-12.0%), respectively • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** 9%* • **Predicted mortality difference between meetings 100% and 50% of protein requirements:** 9%* **Adjusted hazard ratio for time to discharge alive:** • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy and protein adequacy for predicted 60-day mortality**: p-value: 0.84 and 0.16, respectively • Reduced by 1.6% (95% CI: -2.2, 5.5%) and 2% (95% CI: -1.9%, 6.0%), respectively

Table 24: Summary of studies that measured the validity of NUTRIC and mNUTRIC scores in identifying patients who benefit most from nutrition support (cont.)

Author Study design Country	Selection criteria	Subject	Disease severity	Nutritional adequacy (%)	Others
					For each 10% achievement of energy and protein goals among patients with ICU-LOS ≥ 12 dat and mNUTRIC ≥ 5 **Adjusted odds of 60-day mortality:** • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy and protein adequacies for predicted 60-day mortality**: p-value 0.01 and 0.02, respectively • Reduced by 11.6% (95% CI: 5.9%,17.1%) and 10.1% (95% CI: 3.7%-16.0%) respectively • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** 11%* • **Predicted mortality difference between meetings 100% and 50% of protein requirements:** 10%* **Adjusted hazard ratio for time to discharge alive:** • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy and protein adequacies for predicted 60-day mortality**: p-value 0.01 and 0.04, respectively • Reduced by 9.9% (95% CI: 3.8%, 16.4%) and 9.8% (95% CI: 3.8%, 16.1%), respectively
Compher et al. [241] Prospective observational study at 74 ICUs International	• ≥ 16 y and > 72 hrs of ICU-LOS • MV within 48 hrs and ICU-LOS ≥ 4 days • Excluded patients with missing BMI	**n:** 5649 **M/S:** 64/36 **Age:** 60 (18) **BMI:** 26.8 (7.4)	**APACHE II:** 22.2 (8.2) **SOFA:** 7.6 (3.8) **mNUTRIC:** 4.5 (2.1) **60-day mortality:** NA	**Energy:** 60.8 (26.6) **Protein:** 57.5 (27.1) **Duration:** 4-12 days	**For each 10% achievement of energy and protein goals among patients with BMI < 20 and mNUTRIC ≥ 5** **Adjusted odds of 60-day mortality:** • **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy and protein adequacies for predicted 60-day mortality**: NA • Reduced by with 5.5% (95% CI: 2.0%-8.9%) and 5.7% (95% CI: 2.1%-9.2%), respectively

Table 24: Summary of studies that measured the validity of NUTRIC and mNUTRIC scores in identifying patients who benefit most from nutrition support (cont.)

Author Study design Country	Selection criteria	Subject	Disease severity	Nutritional adequacy (%)	Others
Hsu et al. [232] Prospective observational study at 1 ICU Taiwan	• ≥ 65 y • APACHE II ≥ 15 • > 48 hrs MV and on nasogastric feeding • Exclude patients on total parenteral nutrition, > 5 days of fasting, brain dead, terminally Ill from cancer	**n:** 190 **M/S:** 100/0 **Age:** 79 (7) **BMI:** 22.4 (4.7)	**APACHE II:** NA **SOFA:** NA **mNUTRIC:** 6.4 (1.4) **Hosp mortality:** 27.4	**Energy:** 87.5 **Protein:** 85.1 **Duration:** Unknown	• **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 28-day mortality:** NA, but available figures suggest nil interactions • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** NA, figures were presenting in kcal/day and protein/day • **Comparison of hospital mortality in patients with mNUTRIC ≥ 5, and < 80% vs ≥ 80% of energy goal :** 40.3% vs 23.4 %, p-value: 0.02 • **Comparison of hospital mortality in patients with mNUTRIC ≥ 5, and < 80% vs ≥ 80% of protein goal :** 40.3% vs 23.4 %, p-value: 0.02 **Note:** • Although the rate of 28-day mortality was not presented in the study, figures depicted the association between energy and protein intakes and predicted 28-day mortality • The figure for total energy intake (enteral and parenteral) showed an inverse association between energy intake and 28-day mortality • The figure for total protein intake (enteral and parenteral) showed nil association between protein intake and 28-day mortality

Table 24: Summary of studies that measured the validity of NUTRIC and mNUTRIC scores in identifying patients who benefit most from nutrition support (cont.)

Author Study design Country	Selection criteria	Subject	Disease severity	Nutritional adequacy (%)	Others
Jung et al. [238] Retrospective observational study at 1 ICU South Korea	• Adult, had gastrointestinal surgery for complicated intra-abdominal infection, and > 24 hrs MV. • Excluded patients with missing data	**n:** 165 **M/S:** 0/100 **Age:** 71 (NA) **BMI:** 22.5 (NA)	**APACHE II:** 30.1 (NA) **SOFA:** 7.4 (NA) **mNUTRIC:** 6.0 (NA) **Hosp mortality:** 37.0 **30-day mortality**: 26.7	**Energy:** 58.5 **Protein:** NA **Duration:** Up to 5 days	• **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 28-day mortality:** NA • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** NA • **Comparison of 30-day mortality in patients with mNUTRIC ≥ 5, and 44% vs 88% of energy goal :** 34.2% vs 11.1 %, p-value: 0.002
Wang et al. [239] Retrospective observational study at 1 ICU Taiwan	• > 20 y, had MV, and LOS > 48 hrs. • Excluded patients with upper gastrointestinal bleeding or had any period of NBM	**n:** 742 **M/S:** 100/0 **Age:** 68 (16) **BMI:** 23.6 (4.8)	**APACHE II:** 27.0 (6.8) **SOFA:** NA **mNUTRIC:** 5.6 (1.8) **Hosp mortality:** 31.9 **28-day mortality:** 22.0	**Energy:** NA **Protein:** NA **Duration:** Up to 7 days	• **Interaction between mNUTRIC scores ≤ 4 vs ≥ 5 and energy adequacy for predicted 28-day mortality:** NA • **Predicted mortality difference between meetings 100% and 50% of energy requirements:** NA • **Odds of hospital mortality in patients with mNUTRIC ≥ 5, and ≤ 800 vs > 800 kcal/day: 1.71 (1.14, 2.58),** p-value: 0.01 • **Odds of 28-day mortality in patients with mNUTRIC ≥ 5, and ≤ 800 vs > 800 kcal/day: 1.85 (1.15, 2.99),** p-value: 0.012

Values are mean (standard deviation), median {Interquartile range}, or percentages unless specified. * Estimated; **adj-OR:** Adjusted odds ratio; **Age:** Rounded to the nearest year; **APACHE II:** Acute physiology and chronic health evaluation II; **BMI:** Body mass index in kg/m^2; **DO:** Drug overdose; ES: Elective surgery; **hrs:** hours; **ICU-LOS:** Intensive care unit length-of-stay; **mNUTRIC:** Modified nutrition risk in the critically ill score; **MOF:** Multi-organ failure; **MV:** Mechanical ventilation; **M/S:** Percentage of medical versus surgical patients; **n:** Numbers; **NBM:** Nil by mouth; **NUTRIC:** Nutrition risk in the critically ill score; **SOFA:** Sequential organ failure assessment; **vs:** versus; **y:** Years

The following section contains material from:

Lew CCH, Wong GJY, Cheung KP, Fraser RJ, Chua AP, Chong MFF, et al. When timing and dose of nutrition support were examined, the modified Nutrition Risk in Critically Ill (mNUTRIC) score did not differentiate high-risk patients who would derive the most benefit from nutrition support: a prospective cohort study. Ann Intensive Care. 2018;8(1):98.

Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 80%
- Writing and editing: 90%

I made a major contribution to the conception of the manuscript, design of the research, and acquisition, analysis, and interpretation of the data. I drafted the manuscript and revised it according to the recommendations provided by my co-authors and the peer reviewers.

6.2 Introduction

No-volitional nutrition support is frequently required in the intensive care unit (ICU). This seemingly straightforward therapy has garnered increased attention in the literature, reflecting conflicting evidence surrounding the optimal timing, dose, rate of advancement, and composition of nutrition support [245]. While several studies demonstrated delayed [14, 246] or permissive underfeeding [11, 33, 247] to be either benign or beneficial, these modes of feedings have been reported to be detrimental in other studies [19, 34, 41]. A possible explanation for the disparate findings is that a one-size-fits-all approach to nutrition support is not applicable to the needs of a heterogeneous group of critically ill patients [245].

To address this issue, Heyland et al. [38] developed a score (NUTRIC) to better determine patients in a heterogeneous ICU population that would be more likely to benefit from adequate nutrition support. While the original score comprised six components, it was subsequently revised to exclude interleukin-6 concentrations as this is rarely measured outside of research settings [41]. Consequently, the modified NUTRIC (mNUTRIC) has five components (age, APACHE II, SOFA, number of comorbidities, and days in hospital before admission to ICU) with scores 0 to 4 and 5 to 9 classified as low-mNUTRIC and high-mNUTRIC, respectively [153, 225]. There are now four published validation studies [41, 153, 225, 237], with three showing acceptable external validity for the mNUTRIC score as high-mNUTRIC patients who received higher average energy [41, 153, 225] and protein [225] intake were observed to have lower mortality. These results suggest that energy and protein goals should be achieved as soon as possible via early aggressive (i.e., high-dose) nutrition support, including: 1) starting enteral feeding at goal rate [31], 2) using prokinetic agents prophylactically to enhance enteral feeding tolerance[248], and/or 3) using supplemental or total parenteral nutrition support when enteral nutrition cannot meet requirements within the first few days of ICU admission [17, 19]. These feeding strategies are however not in line with the latest ESPEN guidelines [249] which recommend gradual provision of nutrition support to reduce the risk of harm associated with aggressive feeding.

Recent evidence conflicts with the above aggressive feeding practices. In patients with ARDS, Braunschweig et al. [243] and Peterson et al. [244] reported that early aggressive nutrition support with a higher energy intake at the most acute phase of critical illness (around day-1 to day-7 of ICU admission) was associated with increased mortality. A close examination on patient characteristics in Braunschweig et al. [243] revealed that most would be classified as high- mNUTRIC (score = 5 since mean age, SOFA, APACHE II, and length of hospitalisation before ICU admission were 59 years old, 8.3, 22.5, and 3 days, respectively). In addition, Doig et al. [250] showed that early aggressive feeding at the initial stage of ICU admission was associated with higher mortality in patients with refeeding syndrome (even with adequate phosphate replacement). These studies suggest that early aggressive nutrition support may not benefit all critically ill patients.

To date, although the mNUTRIC recommendations appear to support early aggressive nutrition treatment for high-mNUTRIC patients, the concerns of potential harm associated with early aggressive nutrition call into question the generalisability of the mNUTRIC score to all patients. It is therefore timely to re-evaluate if early aggressive nutrition support is of benefit to all high-mNUTRIC patients in a heterogeneous ICU. Since the effects of timing and dose of nutrition support have not been investigated in previous mNUTRIC studies, we therefore aimed to determine whether timing and dose of nutrition support in critically ill patients may modify the association between mNUTRIC categories (low-mNUTRIC and high-mNUTRIC) and 28-day mortality in a single-centre cohort study.

6.3 Methods

Patient and Setting

A prospective observational cohort study was conducted in a 35-bed ICU in Ng Teng Fong General Hospital (Singapore) between August 2015 and October 2016. The ICU functions as a closed unit, where board-certified intensivists and residents provide care for both medical and surgical patients. Treatment bias was minimised by blinding the intensivists and nurses to the objectives of the study.

To determine whether the association between mNUTRIC categories and 28-day mortality was modified by not only the dose of nutrition support (as in the original study) but also its timing, all patients ≥ 21 years old and who had > 48 hours of mechanical ventilation and enteral or parenteral feeding planned were included in the study. In addition, these patients were not declared moribund by an intensivist and had nutritional status determined by a dietitian (using the SGA [58]) within 48 hours of ICU admission. Nutritional status was an inclusion criterion because it has been previously associated with mortality in ICU patients [1, 2, 5].

As per usual clinical practice in the ICU, all patients received a nutrition assessment and were prescribed an appropriate enteral or parenteral feeding regime within 48 hours of ICU admission. As mNUTRIC was not part of the routine nutrition assessment, it was calculated at

the end of the study to minimise treatment bias. For the calculation of energy and protein goals, actual body weight taken at ICU admission using weighing bed was used. In obese patients (body mass index > 30 kg/m^2), adjusted body weight [(actual body weight – ideal body weight) × 0.25 + ideal body weight] [251] was used. The dose of enteral and/or parenteral formulas received was recorded in the electronic medical records and verified by the attending nurse at the end of each shift.

Data collection

All data (demographics, disease severity scores such as APACHE II, comorbidities, baseline nutritional status, admission diagnoses, medications, intravenous fluids, energy and protein provided by enteral and/or parenteral nutrition, and clinical outcomes) were prospectively measured and recorded in the electronic medical records. The daily energy and protein intakes of patients were calculated while receiving exclusive nutrition support (ENS), either enterally and/or parenterally, from ICU admission to a maximum of 14 days, unless death occurred earlier. Energy and protein intakes were calculated from enteral formulas, protein modular, and ready-to-use or compounded parenteral formulas. In addition, energy provided by propofol and dextrose-containing intravenous fluids were included in the calculation of total energy intake.

The dose of nutrition support was calculated by dividing the total energy and protein received by the number of days on ENS and expressed as a percentage of the goals established at baseline [21]. Nutrition support received on the day of death was excluded in the calculation of total energy and protein intakes since patients would not have received the entire prescription [38]. Ethics approval was granted by the Domain Specific Review Board (NHG DSRB Ref: 2014/00878).

Statistical Analysis

The association between energy and protein intakes and 28-day mortality was examined in two sets of multivariable Cox proportional hazard regressions. In the first set, we examined the association between each 10% increase in goal energy and protein intakes and 28-day

mortality for the entire cohort. In the second set, the effects of timing and dose of nutrition support on 28-day mortality were examined. Braunschweig et al. [243] and Peterson et al. [244] observed that the dose of energy intake in the early phase of critical illness (ICU day-1 to day-7) was positively associated with mortality, and a crossover effect was observed at the later phase in patients who required longer-term nutrition support (ICU day-8 onward). Therefore, we determined whether this phenomenon was also present in our cohort by calculating average percentage of goal energy and protein intake from day-2 (mean of day-1 and day-2) to day-14 (mean of day-1 to day-14) in survivors and non-survivors, and plotting their relationships stratified by mNUTRIC categories (low- and high-mNUTRIC). Thereafter, we defined "short-term ENS" and "longer-term ENS" intervals by observing crossover associations between the percentage of goal energy and protein intake in survivors and non-survivors.

The associations between energy and protein intake and 28-day mortality were determined by multivariable Cox proportional hazard regression. Covariates to be adjusted were identified by comparing the patients' baseline characteristics using Student's t-test, Chi-square test, or Mann-Whitney U-test, as appropriate. Characteristics that were significantly different (p-value < 0.05) between survivors and non-survivors at the univariate level were included as covariates in the multivariable Cox proportional hazard regressions to generate the adjusted hazard ratio (adj-HR). Variance inflation factors and tolerances were used to check for multicollinearity. The above steps were repeated in multivariable logistic regressions to generate figures that depicted the associations between goal energy and protein intakes and 28-day-day mortality (Supplementary Table 1 and Figure 1). Statistical analyses were performed using STATA 14.2 (StataCorp, College Station, TX, USA). For all comparisons associations and interactions, p-value < 0.05 was considered significant.

6.4 Results

There were 252 patients enrolled (Figure 15), and no patients were lost to follow-up. Mortality at day-28 following ICU admission was 33.3%, and the characteristics of survivors and non-survivors are summarised in Table 25. Non-surviving patients had a significantly higher mNUTRIC score, were more likely to be malnourished, admitted for medical reasons,

transferred from the general ward, or resuscitated before ICU admission. Excluded patients had similar characteristics to those enrolled, apart from a lower SOFA score (median 8 versus 9, p-value < 0.001) and a higher number of comorbidities (median 3 versus 2, p < 0.001).

The cut-off intervals that defined short-term ENS and longer-term ENS were set at ≤ 6-days (n=106) and ≥ 7-days (n=146) of ENS, respectively, as clear separation was observed between the percentage of goal energy and protein intakes in survivors and non-survivors at the univariate level (Figure 16). In patients with short-term ENS and classified as high-mNUTRIC (n=64), a large proportion perished in the first six days of ENS (Figure 17), and enteral and/or parenteral feeding was ceased due to quick progression to oral feeding or early death. In addition, a higher proportion were admitted for medical reasons compared to patients with longer-term ENS. However, median mNUTRIC scores and the proportion of high-mNUTRIC patients between both groups were not significantly different (Table 25).

Mean (SD) percentage of goal energy and protein intakes were 65.3% (24.7) *[16.6 (7.0) kcal/kg]* and 61.2% (27.4) *[0.71 (0.34) g/kg]*, respectively. To ensure valid comparison for associations between energy and protein intakes and 28-day mortality in patients with short- and longer-term ENS, only the first six days of ENS in both groups were assessed. Patients with short-term ENS had significantly lower energy [48.0% versus 68.7% , p-value < 0.001 *(12.0 kcal/kg versus 17.5 kcal/kg*] and protein intake [41.6% versus 64.8% versus , p-value < 0.001 *(0.47 g/kg versus 0.77 g/kg*], and higher incidence of feeding intolerance when compared to those with longer-term ENS (p = 0.001) (Table 26). In addition, patients who required longer-term ENS had a significantly higher percentage of energy provided in the form of protein compared to patients with short-term ENS (17.6% versus 14.8%, p-value <0.001).

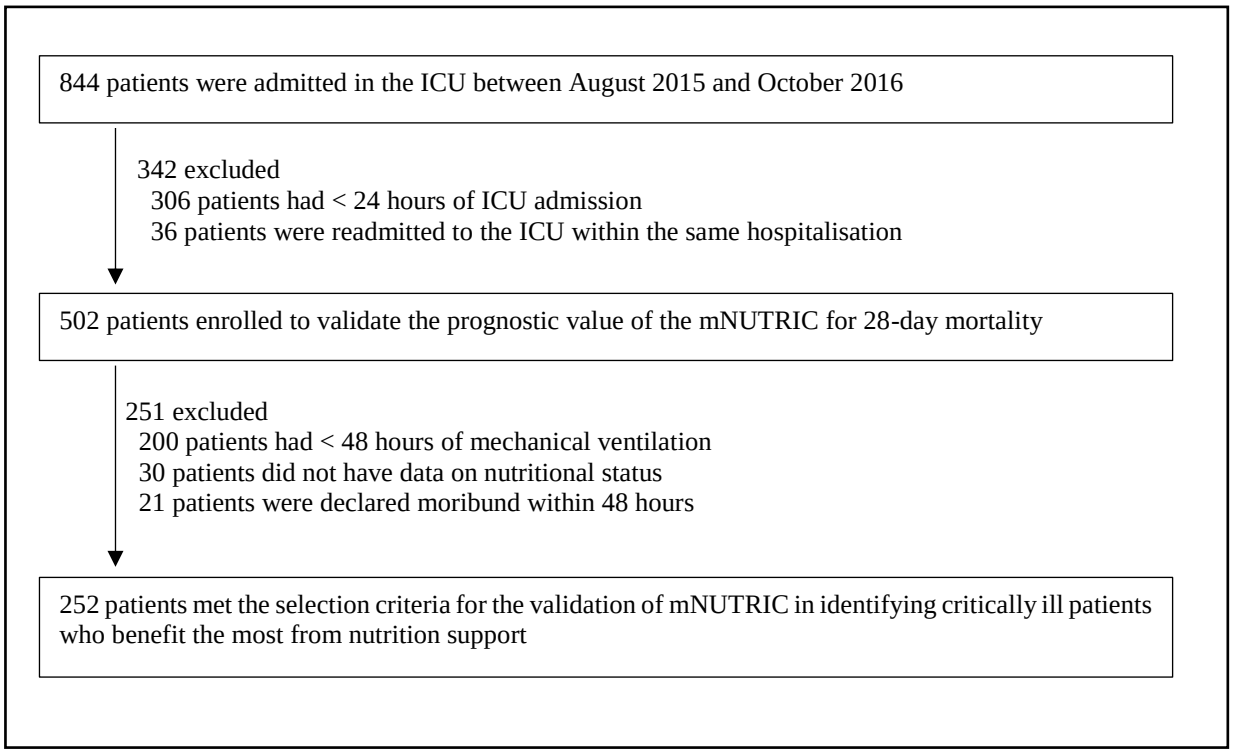


Figure 15: Enrollment of patients

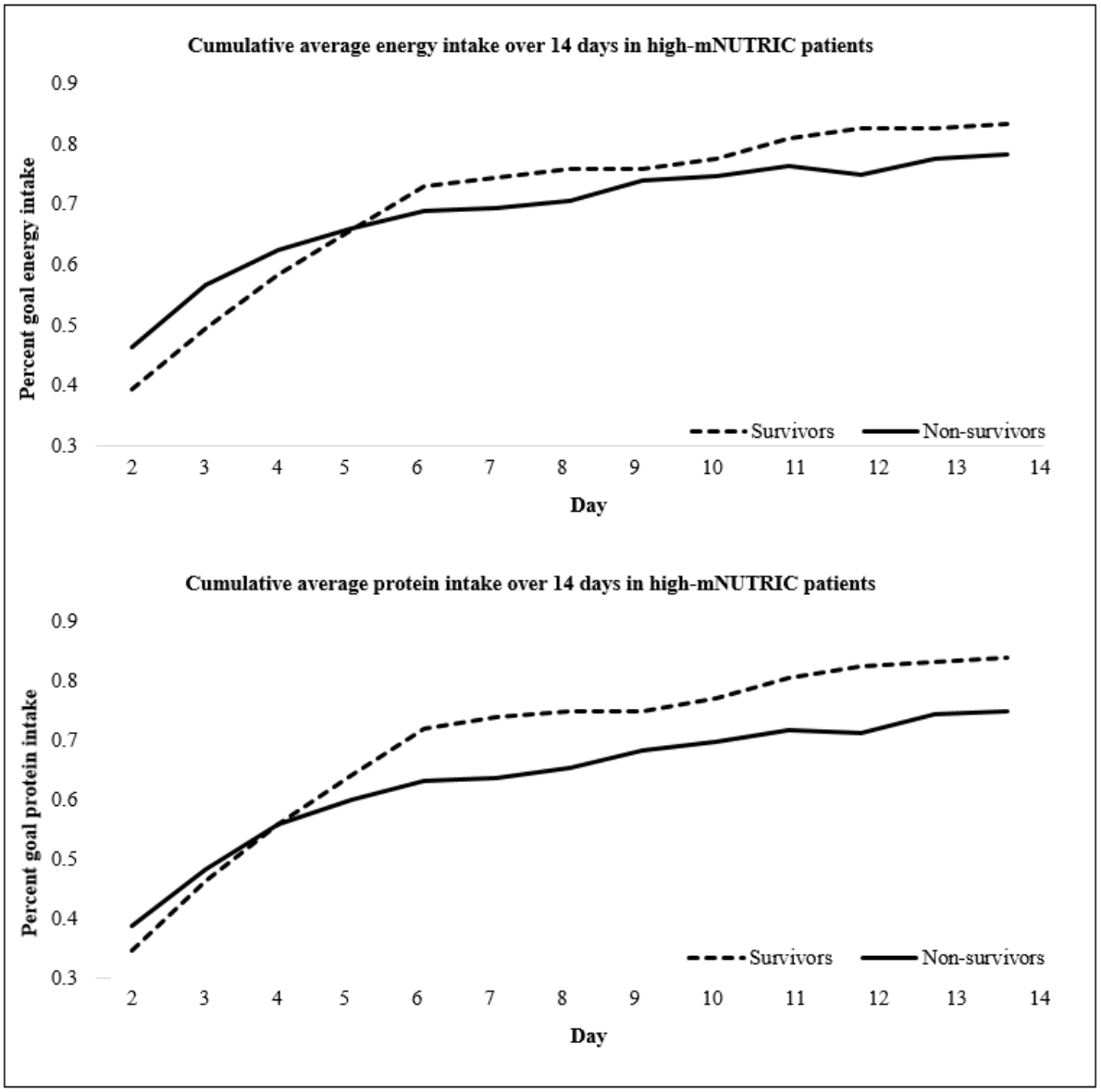
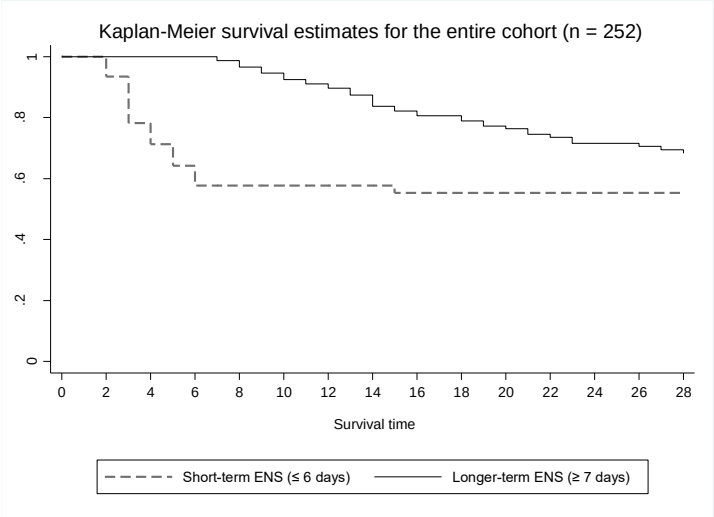
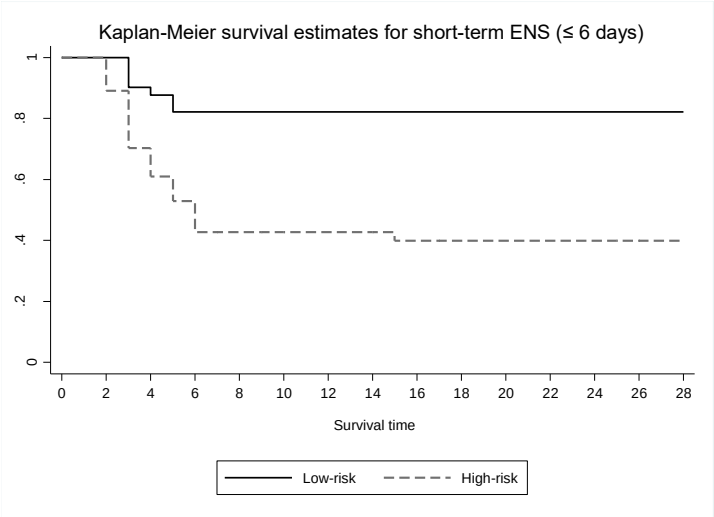


Figure 16: Cumulative average percentage of goal energy and protein intakes in 28-day survivors and non-survivors with high-mNUTRIC as defined by the modified Nutrition Risk in Critically ill (mNUTRIC) score





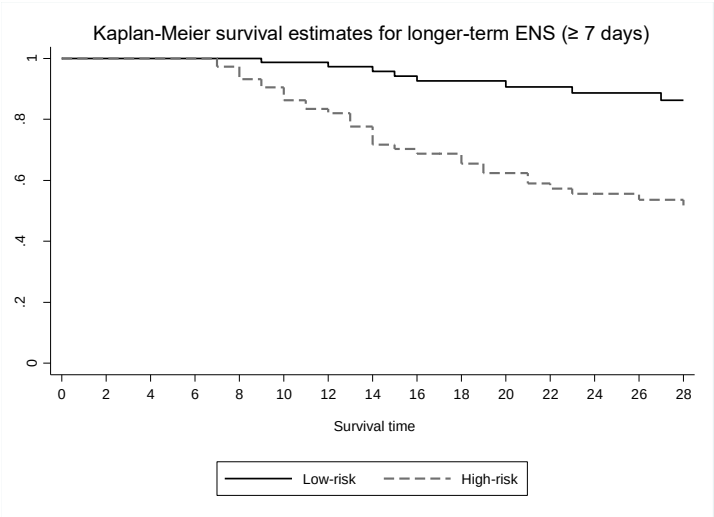


Figure 17: Kaplan-Meier survival estimates stratified by short- and longer-term exclusive nutrition support as well as low- and high-mNUTRIC patients

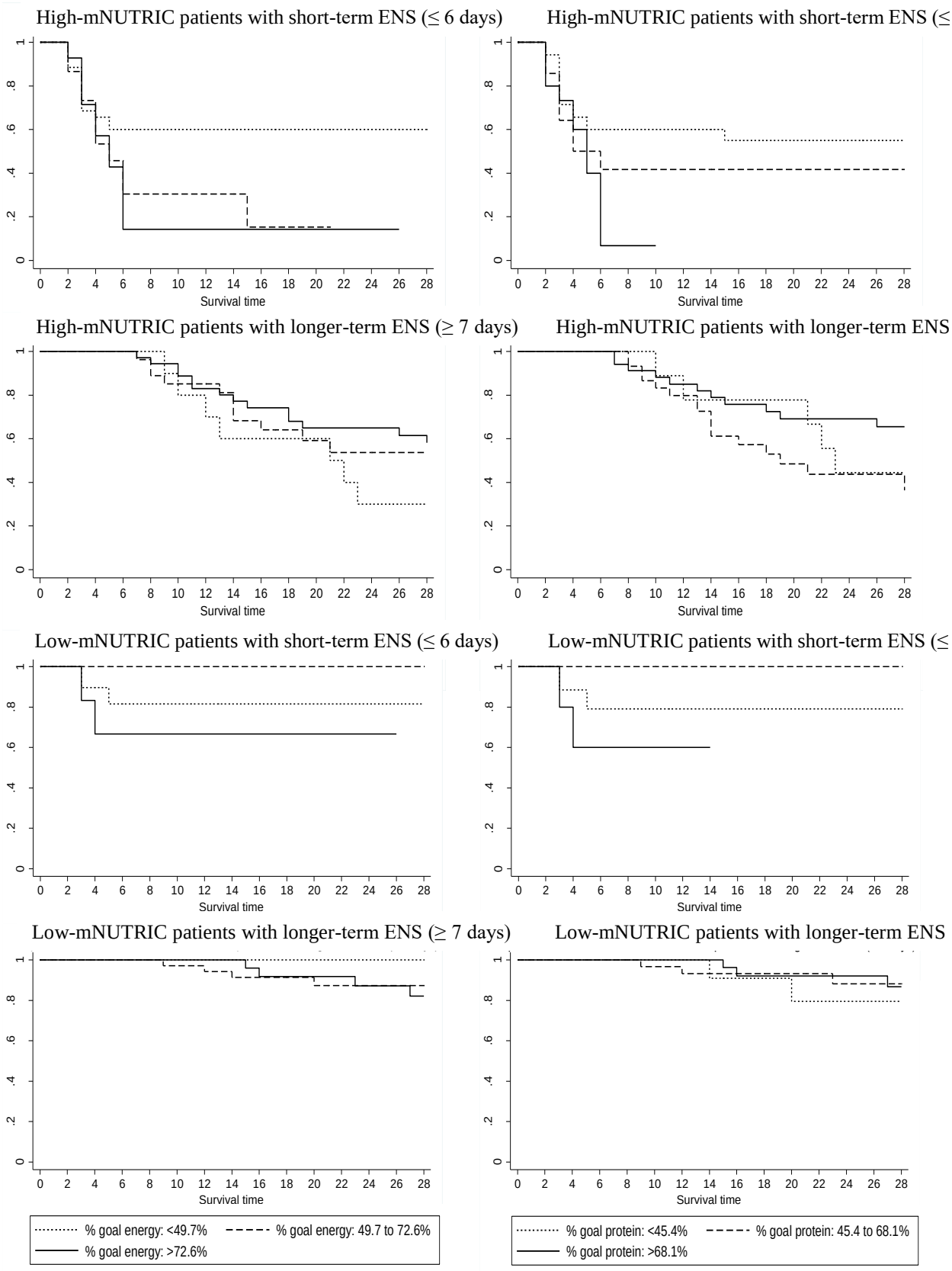


Figure 18: Kaplan-Meier survival estimates of associations between percentage of goal energy and protein intakes stratified by tertiles and 28-day mortality in low- and high-mNUTRIC patients with short- and longer-term exclusive nutrition support

Table 27: Comparison of characteristics between survivors and non-survivors of 28-day mortality in all patients and patients in validation group

Patient Characteristics	All patients			Validation group*		
	Survivor (n=355)	Non-survivor (n=148)	p-value	Short-term ENS (≤ 6 days) (n=106)	Longer-term ENS (≥ 7 days) (n=146)	p-value†
Age (years)	56.6 (15.6)	66.5 (15.1)	< 0.001	60.4 (16.9)	59.5 (15.5)	0.655
Male	108 [64.3]	47 [56.0]	0.200	63 [59.4]	92 [63.0]	0.564
BMI (kg/m^2)	24.5 {21.6, 28.5}	24.7 {22.1, 29.0}	0.673	24.5 {21.2, 29.5}	24.6 {21.8, 28.4}	0.726
Location before adm			0.002			0.976
ED/HD/OT	148 [88.1]	61 [72.6]		88 [83.0]	121 [82.9]	
Wards	20 [11.9]	23 [27.4]		18 [17.0]	25 [17.1]	
Type of adm			0.001			0.001
Medical	94 [56.0]	65 [77.4]		80 [75.5]	79 [54.1]	
Surgery	74 [44.0]	19 [22.6]		26 [24.5]	67 [45.9]	
No of comorbidities	2.0 {1.0, 3.0}	3.0 {2.0, 4.0}	0.007	3.0 {1.0, 4.0}	2.0 {1.0, 3.0}	0.002
LOS before ICU adm (days)	0.0 {0.0, 1.0}	1.0 {0.0. 2.0}	0.068	0.0 {0.0, 1.3}	0.0 {0.0, 1.3}	0.730
APACHE II	23 {18, 28}	29 {23, 33}	< 0.001	26 {19, 31}	23 {20, 30}	0.557
SOFA	8 {6, 10}	11 {8, 11}	< 0.001	9 {7, 12}	9 {6, 12}	0.630
mNUTRIC	5 {3, 6}	7 {6, 8}	< 0.001	6 {4, 7}	6 {4, 7}	0.266
High mNUTRIC (≥ 6)	68 [40.5]	69 [82.1]	< 0.001	64 [60.4]	73 [50.0]	0.103
Malnutrition‡	38 [22.6]	28 [33.3]	0.048	31 [29.2]	35 [24.0]	0.347

Table 25: Comparison of characteristics between survivors and non-survivors of 28-day mortality in all patients and patients in the validation (cont.)

Patient Characteristics	All patients			Validation group*		
	Survivor (n=355)	Non-survivor (n=148)	p-value	Short-term ENS (≤ 6 days) (n=106)	Longer-term ENS (≥ 7 days) (n=146)	p-value†
Admission reasons			< 0.001			0.020
Cardiovascular	11 [6.5]	26 [31.0]		19 [17.9]	18 [12.3]	
Respiratory	31 [18.5]	14 [16.7]		24 [22.6]	21 [14.4]	
Sepsis	48 [28.6]	27 [32.1]		36 [34.0]	39 [26.7]	
Trauma	8 [4.8]	0 [0.0]		4 [3.3]	4 [2.7]	
Metabolic/Renal	4 [2.4]	0 [0.0]		2 [1.9]	2 [1.4]	
Gastrointestinal	8 [4.8]	3 [3.6]		3 [2.8]	8 [5.5]	
Post-operation	7 [4.2]	0 [0.0]		4 [3.8]	3 [2.1]	
Orthopaedics	3 [1.8]	0 [0.0]		1 [0.9]	2 [1.4]	
Neurological	48 [28.6]	14 [16.7]		13 [12.3]	49 [33.6]	
CPR before ICU adm	11 [6.5]	25 [29.8]	< 0.001	18 [17.0]	18 [12.3]	0.297
Length of MV (days)	4.0 {2.0, 8.0}	5.0 {3.0, 9.0}	0.111	3.0 {2.0, 4.0}	7.0 {4.0, 13.0}	< 0.001
ICU LOS (days)	4.0 {2.0, 8.0}	4.0 {3.0, 8.0}	0.327	3.0 {2.0, 4.0}	7.0 {4.0, 12.0}	< 0.001
Hospital LOS (days)	24.0 {13.5, 43.5}	10.0 {4.0, 16.0}	< 0.001	8.0 {4.0, 15.3}	24.0 {16.0, 45.0}	< 0.001

Values are mean (standard deviation), median {interquartile range}, or count [percentage]. **adm:** admission; **APACHE II:** Acute physiology and chronic health evaluation II; **BMI:** Body mass index; **CPR:** Cardiopulmonary resuscitation; **ED:** Emergency department; **ENS:** Exclusive nutrition support; **HD:** High dependency; **ICU:** Intensive care unit; **LOS:** Length-of-stay; **MV:** Mechanical ventilation; **mNUTRIC:** Modified nutrition risk in critically ill; **OT:** Operation theatre; **SOFA:** Sequential organ failure assessment; * Excluded patients who were moribund, without nutritional status data, and with < 2 days of mechanical ventilation; † Short-term versus longer-term exclusive nutrition support; ‡ Based on 440 patients with data on nutritional status

Table 28: Comparison of mode of feeding, source, goal, and achieved energy and protein intakes between 28-day survivors and non- survivors stratified by days of exclusive nutrition support

Nutrition parameters	Short-term exclusive nutrition support (≤ 6 days)			Longer-term exclusive nutrition support (≥ 7 days)		
	Survivor (n=62)	Non-survivor (n=44)	p-value	Survivor (n=106)	Non-survivor (n=40)	p-value
Mode of feeding						
Enteral	60 [96.8]	42 [95.5]	0.725	92 [86.8]	31 [77.5]	0.169
Parenteral	1 [1.6]	0 [0.0]	0.397	8 [7.5]	4 [10.0]	0.630
Combination	1 [1.6]	2 [4.5]	0.370	6 [5.7]	5 [12.5]	0.163
Energy						
Goal (kcal/kg)	25.5 (5.5)	25.9 (6.3)	0.680	25.9 (4.4)	24.8 (4.3)	0.166
Actual Intake (kcal/kg)	10.0 (6.0)	15.0 (6.4)	< 0.001	17.7 (5.2)	16.9 (5.7)	0.389
Actual intake (% goal/kg)	40.0 (22.4)	59.2 (24.1)	< 0.001	68.8 (17.8)	68.2 (19.5)	0.857
Energy sources (%)						
Enteral	82.2 (24.9)	80.8 (28.7)	0.785	82.6 (29.5)	86.0 (23.3)	0.506
IV dextrose	6.7 (17.5)	11.4 (21.3)	0.215	1.4 (2.9)	1.5 (3.3)	0.769
Propofol	10.1 (14.7)	4.1 (6.2)	0.005	5.2 (6.5)	5.3 (9.4)	0.944
Parenteral	1.0 (7.8)	3.7 (17.2)	0.333	10.8 (29.4)	7.1 (21.8)	0.468
Protein						
Goal (g/kg)	1.14 (0.20)	1.15 (0.26)	0.779	1.20 (0.21)	1.15 (0.26)	0.281
Actual Intake (g/kg)	0.39 (0.26)	0.57 (0.30)	0.001	0.79 (0.24)	0.71 (0.28)	0.125
Actual intake (% goal/kg)	34.7 (21.6)	51.4 (26.4)	0.001	66.1 (18.9)	61.6 (19.4)	0.206
Protein sources (%)						
Enteral	98.8 (9.6)	95.5 (20.8)	0.338	88.5 (31.2)	92.3 (23.7)	0.486
Parenteral	1.2 (9.6)	4.5 (20.8)	0.338	11.5 (31.2)	7.7 (23.7)	0.486
Percentage of protein energy*	14.6 (5.1)	15.1 (5.9)	0.600	17.9 (3.5)	16.8 (3.8)	0.100
Fed ≤ 48 hours of ICU adm	59 [95.2]	43 [97.7]	0.495	101 [95.3]	37 [92.5]	0.510
Days on ENS	3.0 {3.0, 4.0}	3.0 {3.0, 5.0}	0.735	14.0 {12.0, 14.0}	14.0 {9.3, 14.0}	0.126
Blood glucose (mmol/L)†	8.7 (2.9)	8.8 (2.3)	0.846	8.7 (2.3)	9.1 (2.3)	0.345
GRV > 200 ml‡	0.0 {0.0, 0.3}	0.3 {0.0, 0.7}	0.001	0.2 {0.0, 0.5}	0.0 {0.0, 0.3}	0.140
Hypoglycaemia ‡ §	0.0 {0.0, 0.0}	0.0 {0.0, 0.3}	0.420	0.2 {0.0, 0.5}	0.0 {0.0, 0.3}	0.440

Values are mean (standard deviation), median {interquartile range}, or count [percentage]. **adm:** Admission, **ENS:** Exclusive nutrition support. **GRV:** Gastric residual volume; **ICU:** Intensive care unit; **IV:** Intravenous; **mNUTRIC:** Modified nutrition risk in critically ill; *****Percentage of energy provided by protein relative to the total energy intake; † Average of daily measurements at 8 am on exclusive nutrition support; ‡ Episodes per day on exclusive nutrition support; § Blood glucose < 4.0 mmol/L

Predictive value of mNUTRIC for 28-day mortality

The C-statistic for mNUTRIC was 0.724 (95% CI: 0.678, 0.769), and the Youden Index (J) showed that an optimal cut-off score of 6 (J were 28.97, 35.63 and 28.43 for scores of 5, 6, and 7, respectively). The sensitivity and specificity at cut-off score of 6 were 77% and 59%, respectively. In addition, each increment in the mNUTRIC score was significantly associated with increased odds for 28-day mortality [odds ratio (OR): 1.58, (95%CI: 1.40, 1.78), p-value < 0.001].

Association between energy intake and 28-day mortality during the first six days of ENS

Given the crossover associations between percentage of goal energy and protein intakes and 28-day mortality at the univariate level, these associations were adjusted for covariates in multivariable Cox proportional hazard regressions (Table 27). Covariables in the Cox models include days-on-ENS because energy and protein intakes increase with time [21, 252] and adjustment for this immortal time bias is recommended and widely practised [21, 41, 225].

In the first analysis set (n = 252), where timing and dose of nutrition support were not examined, there was no significant association between each 10% increase in goal energy intake and 28-day mortality in high-mNUTRIC patients [adj-HR 1.22 (95% CI 0.98, 1.53), p-value: 0.081, interaction between mNUTRIC categories: 0.985].

In the second analysis set, which examined the effects of timing and dose of nutrition support, both univariate and multivariable analyses were performed to determine the associations between percentage of goal energy intake and 28-day mortality in low- and high-mNUTRIC patients with short- and longer-term ENS. *Univariate analyses* – Percentage of goal energy intake was divided into tertiles, and associations with 28-day mortality in low- and high-mNUTRIC patient with short- and longer-term ENS are illustrated in Figure 18. In low- and high-mNUTRIC patients with short-term ENS, goal energy intake in the highest tertiles was associated with the highest 28-day mortality risk. In contrast, goal energy intake in the highest tertile was associated with the lowest mortality risk in high-mNUTRIC patients with longer-term ENS. *Multivariable analyses* – In patients with short-term ENS, there was no significant

interaction in the group (p-value: 0.280) (Table 27). However, high-mNUTRIC patients had a 37% higher hazard (p-value < 0.001) of 28-day mortality with each 10% increase in goal energy intake, while low-mNUTRIC patients lost significance. Similarly, there was no significant interaction (p-value: 0.127) in patients with longer-term ENS. While there was an inverse association between percentage of goal energy intake and 28-day mortality in high-mNUTRIC patients, this was not statistically significant (p-value: 0.135).

Association between energy intake and 28-day mortality in patients with up to 14 days of ENS

There were significant interactions between mNUTRIC categories (p-value: 0.034), but the association between percentage of goal energy intake and 28-day mortality in both mNUTRIC categories was non-significant. Every 10% increase in goal energy intake was associated with a non-significant increased hazard of 28-day mortality in low-mNUTRIC patients [adj-HR 1.18 (95% CI: 0.83, 4.82), p-value: 0.122], whereas this was reversed in high-mNUTRIC patients [adj-HR 0.88 (95%CI: 0.70,1.09), p-value: 0.234].

Association between protein intake and 28-day mortality during the first six days of ENS

There was no significant association between protein intake and 28-day mortality in high-mNUTRIC patients when timing and dose of nutrition support were not examined [adj-HR for each 10% increase in goal protein intake for the entire cohort (n = 252): 1.14 (95% CI: 0.93, 1.39), p-value: 0.231, interaction between mNUTRIC categories: 0.881].

In the second analysis set, where the effects of timing and dose of nutrition support were examined, both univariate and multivariable analyses were performed to determine whether associations between percentage of goal protein intake and 28-day mortality in patients with low- and high-mNUTRIC were stratified by short- and longer-term ENS. *Univariate analyses* – Percentage of goal protein intake was divided into tertiles, and associations with 28-day mortality in low- and high-mNUTRIC patient with short- and longer-term ENS are illustrated in Figure 18. In low- and high-mNUTRIC patients with short-term ENS, goal protein intake in the highest tertile was associated with the highest 28-day mortality risk. In contrast,

goal protein intake in the highest tertile was associated with the lowest mortality risk in high-mNUTRIC patients with longer-term ENS. *Multivariable analyses* – In patients with short-term ENS, there was no significant interaction in the group (Table 27). However, high-mNUTRIC patients had a 31% higher hazard of 28-day mortality with each 10% increase in goal protein intake (p-value: 0.002). In patients with longer-term ENS, the association between percentage of goal protein intake and 28-day mortality varied by mNUTRIC categories along with a trend in interactions (p-value: 0.088): high-mNUTRIC patients had a 22% lower hazard of 28-day mortality with each 10% increase in goal protein intake (p-value: 0.006).

Association between protein intake and 28-day mortality in patients with up to 14 days of ENS

The association between percentage of goal protein intake and 28-day mortality varied by mNUTRIC categories (interaction p-value: 0.029), such that high-mNUTRIC patients had a 19% lower hazard of 28-day mortality with each 10% increase in goal protein intake [adj-HR 0.81 (95% CI: 0.67, 0.99), p-value: 0.036]. However, this association was not present in low-mNUTRIC patients [adj-HR 1.23 (95% CI: 0.78, 1.97), p-value: 0.375].

Table 29: Association between energy and protein intakes and 28-day mortality in patients with low and high mNUTRIC stratified by days on exclusive nutrition support – expressed by hazard ratio

Energy/Protein intake	Short-term exclusive nutrition support (≤ 6 days)			Longer-term exclusive nutrition support (≥ 7 days)		
	Low mNUTRIC* (n=42)	High mNUTRIC* (n=64)	Interaction (p-value)	Low mNUTRIC* (n=73)	High mNUTRIC* (n=73)	Interaction (p-value)
Energy intake (each 10% of goal)	0.93 (0.67, 1.28) p-value = 0.657	1.37 (1.17, 1.61) p-value < 0.001	0.280	1.18 (0.75, 1.84) p-value = 0.474	0.87 (0.73, 1.04) p-value = 0.135	0.127
Protein intake (each 10% of goal)	0.97 (0.70, 1.33) p-value = 0.846	1.31 (1.10, 1.56) p-value = 0.002	0.405	1.02 (0.69, 1.51) p-value = 0.913	0.78 (0.66, 0.93) p-value = 0.006	0.088

Values are hazard ratio (95% confidence interval) adjusted for exposure to cardiopulmonary resuscitation before admission to the intensive care unit, nutritional status, and days on exclusive nutrition support

* Low- and high-mNUTRIC is defined as scores of 0-5 and 6-9 of the modified Nutrition Risk in Critically ill (mNUTRIC) score, respectively [41]

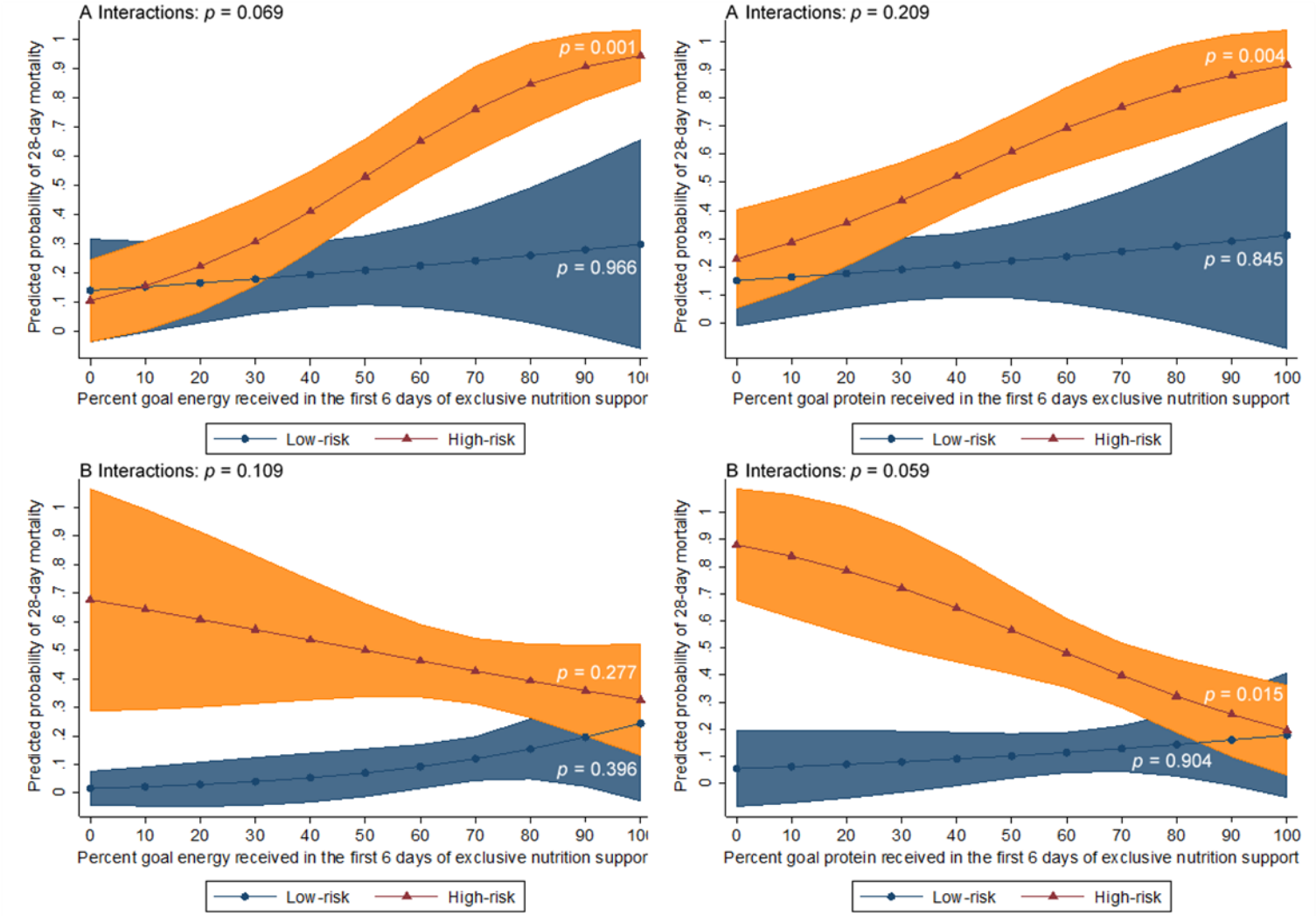
Supplementary Table 1: Association between energy and protein intakes and 28-day mortality in patients with low and high mNUTRIC stratified by days on exclusive nutrition support – expressed by odds ratio

Energy/Protein Intake	Short-term exclusive nutrition support (≤ 6 days)			Longer-term exclusive nutrition support (≥ 7 days)		
	Low-mNUTRIC* (n=42)	High-mNUTRIC* (n=64)	Interaction (p-value)	Low-mNUTRIC* (n=73)	High-mNUTRIC* (n=73)	Interaction (p-value)
Energy intake (each 10% of goal)	1.01 (0.67, 1.41) p-value = 0.966 HL-GOF = 0.384 R^2 = 0.356	1.91 (1.31, 2.80) p-value = 0.001 HL-GOF = 0.433 R^2 = 0.457	0.069	1.25 (0.75, 2.07) p-value = 0.396 HL-GOF = 0.815 R^2 = 0.128	0.85 (0.65, 1.11) p-value = 0.227 HL-GOF = 0.126 R^2 = 0.174	0.109
Protein intake (each 10% of goal)	1.04 (0.69, 1.56) p-value = 0.845 HL-GOF = 0.423 R^2 = 0.357	1.54 (1.15, 2.05) p-value = 0.004 HL-GOF = 0.387 R^2 = 0.357	0.209	1.03 (0.66, 1.59) p-value = 0.904 HL-GOF = 0.561 R^2 = 0.108	0.68 (0.50, 0.93) p-value = 0.015 HL-GOF = 0.020 R^2 = 0.258	0.059

Values are adjusted odds ratio (95% confidence interval) adjusted for exposure to cardiopulmonary resuscitation before admission to the intensive care unit, nutritional status, and days on exclusive nutrition support

HL-GOF: Hosmer-Lemeshow goodness of fit; **R^2:** Max-rescaled R-square

* Low and high risk is defined as scores of 0-5 and 6-9 of the modified Nutrition Risk in Critically ill (mNUTRIC) score, respectively [41]



Supplementary Figure 1: Predicted probability of 28-day mortality (adjusted odds ratio with 95% confidence interval as shaded regions) and percentage of goal energy and protein received during the first 6 days of exclusive nutrition support in patients with low- and high-mNUTRIC score

A: Patients with short-term exclusive nutrition support (≤ 6 days)
B: Patients with longer-term exclusive nutrition support (≥ 7 days)

6.5 Discussion

To our knowledge, this is the first study to suggest that the association between mNUTRIC score and 28-day mortality can be modified by the timing and dose of nutrition support. In high-mNUTRIC patients with short-term ENS (≤ 6 days), energy and protein intakes were positively associated with 28-day mortality risk. In contrast, protein intake was inversely associated with 28-day mortality in high-mNUTRIC patients who required longer-term ENS (≥ 7 days).

Association between energy intake and 28-day mortality

The average energy intake achieved in our study was similar to the findings of three previous studies that determined the validity of the mNUTRIC score (58.5% to 64.5% of energy goal) [225, 230, 237] but we had different observations. When our cohort was analysed in its entirety (irrespective of timing and dose of nutrition support), energy intake was not associated with 28-day mortality. These findings are consistent with previous work by Arabi et al. [237] but differ from those of Rahman et al. [41]. The reasons for this lack of concordance are unclear, but the latter was conducted as a post-hoc analysis of a multicentre randomised controlled trial (RCT) originally undertaken to examine the effects of glutamine and antioxidant supplementation in critically ill patients [253]. In the post-hoc analysis, the investigators examined the external validity of the mNUTRIC score in identifying those patients who would benefit most from adequate energy intake. It demonstrated an inverse association between energy intake and 28-day mortality in high-mNUTRIC patients. However, the lack of statistical adjustment for the amount of glutamine intake may limit the interpretation of this finding as it is possible that adequate energy, when combined with glutamine, may result in lower mortality [254, 255]. This potential confounder was avoided in the post-hoc analysis conducted by Arabi et al. [237] since the original study [33] was specifically designed to examine the effects of energy intake on mortality. Hence, Arabi's findings of the lack of significant association between energy intake and 28-day mortality (OR 0.93 (95% CI 0.60, 1.44), p-value: 0.74) are more likely to be reliable [237], and our study concurs with this result. It is also possible that the analysis of the timing and dose of energy intake in that study may

show an inverse association between energy intake and risk of 28-day mortality in high-mNUTRIC patients receiving longer-term nutrition support.

When timing and dose of nutrition support were considered in our analysis, a trend was observed towards an inverse association between energy intake and mortality risk in high-mNUTRIC patients who had up to 14 days of ENS. We hypothesise that the lack of significance could reflect the small sample size. This trend towards inverse association is in agreement with the findings by Compher et al. [225]. In this large multinational prospective cohort study, energy intake was shown to be inversely associated with 60-day mortality in high-mNUTRIC patients who had up to 12 days of ENS. Consequently, the investigators recommended that all high-mNUTRIC patients should receive early aggressive nutrition support as they will benefit most from near-goal energy intake [225]. However, as the present study suggests a positive association between early high-energy intake and 28-day mortality in high-mNUTRIC patients with short-term ENS, this recommendation may need to be applied with caution at the early stage of nutrition support.

Furthermore, some studies suggested that early high-energy intake is associated with increased mortality in certain groups of patients. A recent RCT (n = 78) demonstrated that high energy intake in the first 7 days of ARDS diagnosis resulted in higher mortality [247], and an energy threshold of 18 kcal/kg was significantly associated with mortality in the post-hoc analysis [243]. These findings were supported by a larger cohort study (n = 298) that included ARDS patients with higher mNUTRIC characteristics [244]. In addition, Arabi et al. [242] also demonstrated that early (≤ 12 days of ENS) high energy intake in a heterogeneous ICU population was significantly associated with 90-day mortality. Collectively, these studies suggested that high energy intake in the early stage of nutrition support may not benefit all high-mNUTRIC patients. However, the mechanism behind harm associated with early high energy intake has been poorly studied. Some would attribute it to mitochondrial toxicity caused by an oversupply of glucose and lipid [256], while others have linked it to the suppression of autophagy [257, 258].

Association between protein intake and 28-day mortality

Although the average protein goal achieved in our study was similar to two previous studies that determined the validity of the mNUTRIC score (56.5% and 58.9% of protein goal) [225, 230], we observed different results. In patients with short-term ENS, early higher protein intake was associated with increased mortality risk. However, it is unclear whether this risk is solely attributable to protein or is a reflection of the harm associated with early higher-energy intake. A recent study suggested that early high-protein intake (> 0.8 g/kg) was associated with a higher hazard of 6-month mortality when compared to patients who had protein restrictions during the first three days of ENS and thereafter a higher protein intake [259]. The average proportion of energy provided by protein (protein-energy) in the enteral feeds used in the hospital under study is 15%. This level of protein-energy coincides with that received in patients with short-term ENS (Table 26), suggesting that protein modular was minimally used. Since it is impossible to statistically separate protein from energy in the analyses, it will be challenging to differentiate the associations between mortality and protein (and energy) intake.

In contrast, the protein energy intake in patients with longer-term ENS was significantly higher than for those with short-term ENS, suggesting that a protein-modular was used to increase the protein-energy ratio. This suggests that the inverse association between protein intake and mortality risk in patients with longer-term ENS is more likely, a result concordant with earlier studies [225].

Strength and Limitations

There are a number of strengths in the current study. The consecutive recruitment, complete follow-up, and blinding of the treatment team to the objectives of the study minimised selection, attrition, and treatment biases. In addition, the exclusion of moribund patients reduced artificial inflation of the association between 28-day mortality and inadequate nutrition support since these patients generally receive little nutrition due to poor tolerance or comfort feeding, and death is mainly due to disease severity.

However, a number of limitations must be considered before drawing conclusions with clinical implications. This was a single-centre observational study with a small sample of heterogeneous patients. The positive association between early high energy intake and 28-day mortality in high-mNUTRIC patients was not expected. By indication, severely ill patients (hence with short survival time) would usually receive less nutrition due to enteral feeding intolerance, and this may artificially inflate the inverse association between nutrition intake and mortality. However, our results were in the opposite direction despite our best efforts to adjust for known confounders. Therefore, the presence of residual confounders inherently limits our results to association rather than causation. In addition, it was beyond the scope of our study to investigate possible causes for this observation. Therefore, our study should be considered hypothesis-generating and thus requires further confirmation from larger or more comprehensive studies that consider extensive number of confounders.

Future Research and Implications for Practice

In our study, energy and protein intakes were positively associated with 28-day mortality in high-mNUTRIC patients with short-term ENS, while they were not associated with 28-day mortality in the group with longer-term ENS. These results are disconcerting because the mNUTRIC score did not discriminate these two groups of patients (median mNUTRIC scores for both groups were 6), and it may not be possible for clinicians to accurately predict the length of ENS at ICU admission. Some characteristics of patients with short- and longer-term ENS are shown in Table 25. A higher proportion of patients with short-term ENS were admitted for medical reasons, and more had cardiovascular or respiratory issues as compared to those with longer-term ENS. Conversely, patients who required longer-term ENS were those admitted with neurological issues. Therefore, there is a need to identify sub-groups of patients who would likely benefit from or be harmed by early aggressive nutrition support.

The present study supports the requirement for larger confirmatory studies to further investigate the modifying effect of timing and dose of nutrition support in high-mNUTRIC patients. Ideally, this could be achieved by identifying biomarkers that define the different phases (i.e. acute, sub-acute and chronic) of critical illness [156], and testing whether limiting and increasing energy and protein intakes at different phases would be beneficial. Until this is

achieved, we suggest a prudent approach to nutrition support. The energy and protein intakes associated with identical mortality risks in patients with short- and longer-term ENS were 50% of goal (Supplementary Figure 1). Therefore, to achieve equipoise, clinicians may feed high-mNUTRIC patients at 50% of the energy and protein goals in the early periods of ICU admission, and intensify the provision of nutrition if ENS is required for a more extended period.

6.6 Conclusion

A modifying effect of the timing and dose of nutrition support may be present in some high-mNUTRIC patients where higher energy intake at the early phase of nutrition support was associated with higher 28-day mortality. Given the lack of parameters that would determine high-mNUTRIC patients' response to early high-energy intake, the need for future studies cannot be overemphasised.

A parameter that may improve the mNUTRIC score in differentiating the response to early high-energy intake in patients with high-mNUTRIC is baseline nutritional status. As discussed in Chapter 5, the combination of mNUTRIC (a disease severity score) and SGA (a valid nutrition assessment) can better prognose mortality, that is, malnourished patients with high-mNUTRIC had the highest mortality risk compared to patients with high-mNUTRIC or malnutrition. Therefore the next chapter aimed to develop a novel prognostic tool that accounts for both baseline nutritional status and disease severity.

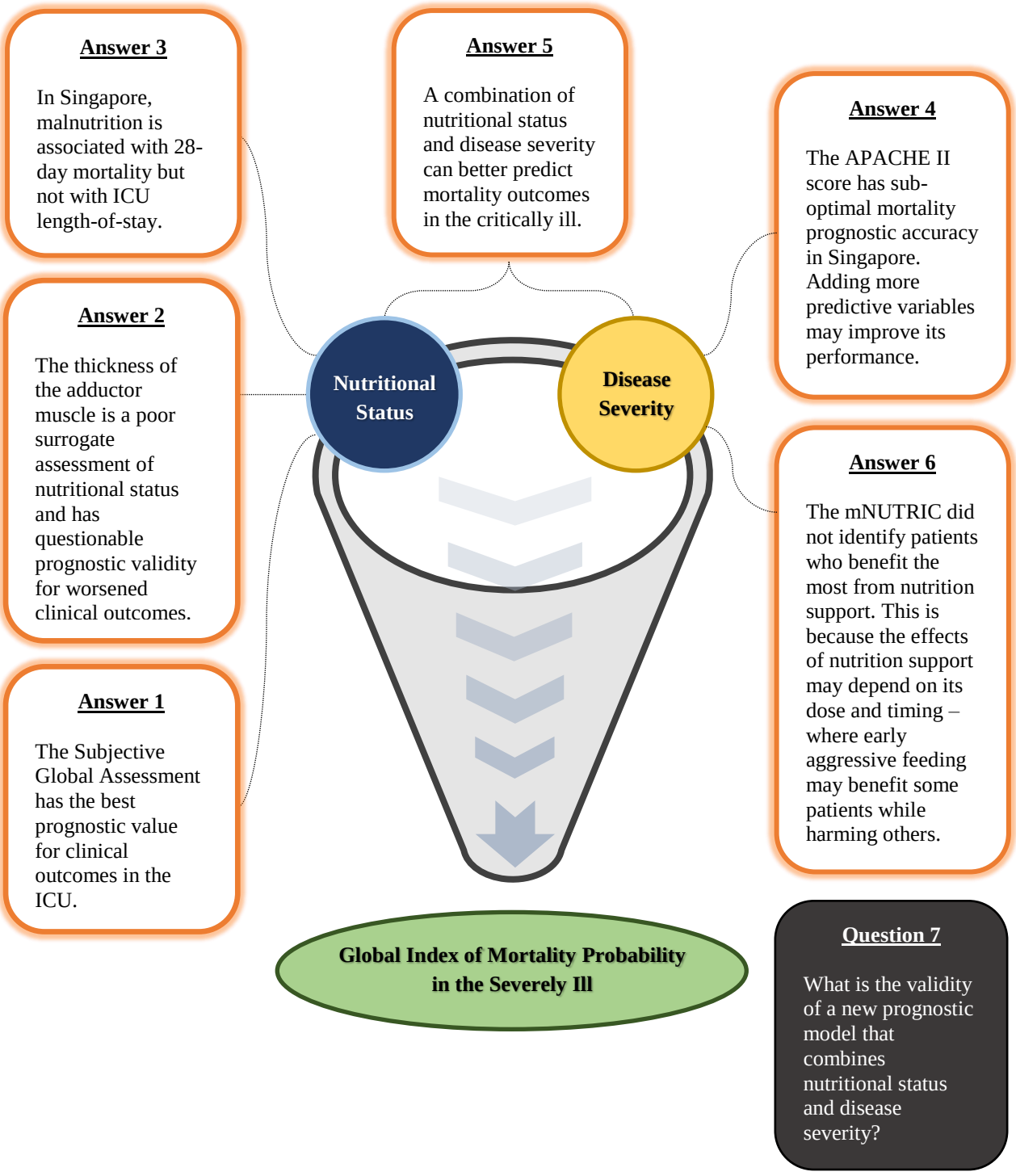


Figure 19: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 6

Chapter 7: What is the validity of a new prognostic model that combined nutritional status and disease severity?

7.1 Contribution to the overall research objective

The objective of this research programme was to develop a prognostic model (GLIMPSE) that incorporates baseline nutritional status and disease severity to predict 28-day mortality in critically ill patients. It was hypothesized that such a model would identify patients who would benefit from aggressive nutrition support.

In Chapters 1 to 5, it was demonstrated that nutritional status and disease severity established, respectively, by the SGA and the mNUTRIC both individually and in combination predict mortality outcomes in the critically ill. However, since association does not imply causality, the modifying effects of aggressive nutrition support were evaluated via an original study-Chapter 6 [260]. The data showed mNUTRIC to have good external validity in predicting 28-day mortality but failed to identify patients who benefited from aggressive nutrition support because not all patients with high-mNUTRIC benefited from early high energy and protein intakes. Specifically, early high energy and protein intakes were positively associated with 28-day mortality in patients with high-mNUTRIC and short-term ENS ($\leq$ 6 days) while the associations were inverse in high-mNUTRIC patients with longer-term ENS ($\geq$ 7 days).

The findings reported in Chapter 5 may explain the null association between mNUTRIC and nutrition support as the former was shown to reflect disease severity rather than function as a nutrition screening or assessment tool. Since patients with high-mNUTRIC score ($\geq$ 5) are not necessarily malnourished (kappa statistics for mNUTRIC and SGA: 0.13, p-value < 0.001), and malnourished patients are more likely to derive the greatest benefit from nutrition support [35], the absence of a nutrition parameter in mNUTRIC may confound the association between energy and protein intakes and 28-day mortality. Therefore, the study reported in this chapter aimed to develop a new prognostic model that takes both baseline nutritional status and disease severity into account when predicting mortality.

The initial step in prognostic model building is to identify clinically relevant candidate predictors for possible inclusion in the model, and this was achieved in the first five chapters of this thesis. The next steps in prognostic model building are to: 1) evaluate the quality of the collected data; 2) make data-handling decisions; 3) adopt a strategy for selecting important predictors and assign relative weights via regression analyses; and 4) perform internal validation and, if necessary, adjust for overfitting and optimism [223]. The sections below outline the recommended methods used for model building and internal validation.

7.2 Steps in building a prognostic model

Evaluate data quality – reliability of measurements

There are no established guidelines for the assessment of data quality in prognostic research. Ideally, predictors should be objective measurements with good reliability in settings of intended use [46]. If subjective measurements are included (e.g., imaging interpretation or SGA), it is logical to ensure an adequate degree of reliability.

Applications to GLIMPSE: Among the candidate predictors identified in Chapters 1-5, only the SGA is considered a subjective measurement. However, the SGA has been consistently shown to be a reliable nutrition assessment tool in general wards (Table 28) and even the ICU when administered to mechanically ventilated patients (kappa: 0.90) [84]. This reliability was also confirmed in this research programme, with good agreement between three ICU dietitians (weighted kappa: 0.85, n = 68, standard error = 0.079, p-value < 0.001) [2].

Table 30: Inter-rater reliability of SGA and 7-point SGA

Author Country	Tool	n	Types of patients	Number and type of assessors	Inter-rater reliability
Detsky et al. [261] Canada	SGA	59	Surgical patients	2 persons, profession not specified	Kappa: 0.72
Covinsky et al. [262] United States	SGA	21	Patients (> 70 years old) with > 3 days of stay in general medical unit	1 physician, 1 nurse	Kappa: 0.71
Nursal et al. [263] Turkey	SGA	2211	All patients excluding pregnant, psychiatric and critically ill patients	1 dietitian, 1 nurse	Kappa: 0.88
Baccaro et al. [264] Argentina	SGA	75	All patients in medical ward	5 physicians	Kappa: 0.75
Visser et al. [265] Netherlands	7-point SGA	22	Haemodialysis and peritoneal dialysis patients	4 nurses	Kappa: 0.72
Steiber et al. [266] Canada and United States	7-point SGA	76	Haemodialysis dialysis patients	54 dietitians	Kappa: 0.50

n: numbers of subjects; **SGA:** Subjective Global Assessment

Evaluate data quality – Missing data

Incomplete data sets are a common issue in all research, but these are unlikely to be completely missing at random [46]. Hence, the amount of missing data should be quantified and appropriately handled. One technique to manage missing data is to use multiple imputations to estimate the missing values from known predictors. However, such a technique relies on assumptions that cannot be substantiated, and the ramifications for the prognostic performance in real-life settings are questionable [223]. This may be the reason why the APACHE models [39, 160, 161] did not use multiple imputation techniques to handle missing data.

Applications to GLIMPSE: Similar to the APACHE models, multiple imputation was not performed for managing missing nutritional status in this study. More importantly, the characteristics of patients with missing nutritional status were either not associated with mortality and ICU length-of-stay, or were adjusted using the multivariable models.

Make data-handling decisions

Examples of data-handling decisions include: 1) generation of new predictors (e.g. the combination of height and weight to generate the body mass index); 2) combining ordinal predictors into lesser categories (e.g., disease stage); and 3) correct handling of continuous data (e.g., age). In the case of continuous data, the literature offers two recommendations. First, the linearity of the continuous predictor should be checked by transformations such as fractional polynomials or restricted cubic splines [43]. Second, it is preferable to keep continuous data in their original state as categorising them can result in loss of information. In addition, categorisation does not allow comparison with other studies or the conduct of meta-analysis since different cut-off points are frequently used in different studies [267]. *Applications to GLIMPSE:* Where possible continuous data were kept in their original state during the development of the prognostic model.

Select predictors

Before selecting predictors for the prognostic model, it is helpful to have an idea of the number of predictors that is appropriate to the study sample size. A prognostic model contains several predictors, and this inherently makes the sample size estimation challenging [47]. However, some guidelines are available from several earlier studies. In binary prognostic models, total sample size has little relevance to its predictive power. Instead, the events-per-predictor ratio is more important [268]. Peduzzi et al. [269] performed a simulation study and demonstrated that a ratio of approximately 10 to 15 events-per-predictor is adequate to produce a reasonably stable model. An alternative approach is for a model to contain at least 50 events as a base, and each predictor to have at least 8 events [270].

There is no consensus on the best approach for selection of candidate predictors. Two broad methods exist: full model or a predictor selection strategy [46], *Full model* – This method requires knowledge of the most promising candidate predictors, and all such predictors are included in the final model. This minimises predictor selection bias and the risk of overfitting [46]. *Predictor selection* – This technique can be undertaken in two ways, namely exclusive multivariable analysis or bivariable analyses followed by multivariable analyses. Both methods require a pre-defined nominal significance level for predictor selection, which can range from high significance (p-value ranging 0.01-0.05) to lower levels (p-value ranging 0.20-0.25). The former will result in fewer predictors, while the latter will yield more; but in all cases, there is a risk of overfitting when sample size is small [271].

In the case of exclusive multivariable analysis, predictors that are not significantly associated with the outcome (according to pre-defined nominal significant level) are excluded in the final model. Selection is automated in two manners, i.e., backward selection, and forward selection. In backward selection, the model starts by including all candidate predictors, and these are sequentially removed beginning from the predictor least associated with the outcome [46]. Conversely, in forward selection, the model begins by including the candidate predictor that has the strongest association with the outcome and sequentially adds the second most associated candidate predictor and so on. This is a less preferred method because, unlike backward selection, forward selection does not allow for simultaneous assessment of the synergistic predictive effects of all predictors [272]. However, when compared to backward selection, forward selection has a lower risk of multicollinearity [46]. In situations where multicollinearity is severe, the prognostic model is considered unstable as the variance of the coefficient estimates will be inflated, making the model overly sensitive to minor changes in the predictors.

An alternative to the exclusive use of multivariable analysis in the selection of candidate predictors, is to pre-select candidate predictors based on their bivariate associations with the outcome. In most cases, candidate predictors that are significantly associated with the outcome ($p < 0.05$) at the bivariate level are selected for inclusion in the multivariable analysis, where another round of selection will take place [46]. However, such pre-selection is discouraged, for three reasons [271]. First, important predictors may be erroneously eliminated during the

bivariable analyses, and this problem may even occur when the pre-defined nominal significance is increased to 0.25. Second, candidate predictors may correlate and serve as confounders with one another, and individual bivariable analysis will neither detect such associations nor execute proper statistical adjustment. Lastly, bivariable analyses may select candidate predictors that are collinear and cause multicollinearity in the prognostic model.

Regardless of the choice of analytical methods, multivariable analysis performs two functions. Firstly, it takes into account the effects of all candidate predictors and simultaneously performs adjustments to assign relative weights (regression coefficients) for each candidate predictor. In other words, the multivariable analysis estimates the effect of a candidate predictor on the outcome of interest (dependent variable) while keeping the other candidate predictors constant. Secondly, multivariable analysis estimates the baseline risk of patients. That is, when all candidate predictors equal zero, the baseline risk of patients is indicated by the intercept in the logistic regression.

Applications to GLIMPSE: To develop GLIMPSE, the full-model method was used, for two reasons. First, the full-model method has the lowest risk of predictor selection bias and overfitting, an inherent problem in studies with small sample size. Since the sample size of this research study was relatively small, the full model would help to minimize this risk. Second, automated stepwise selection of predictors would result in the inclusion of predictors that are unique to the logistics and infrastructure of the research site. For example, location before ICU admission can be determined by the ICU admission policy, logistics, or infrastructure of a hospital. Therefore, despite being a strong predictor in this research programme, location before ICU admission may have limited external validity in other hospitals.

To satisfy the recommendation of a stable model, the number of predictors in GLIMPSE will be determined by the event rate. Since the 28-day mortality rate in this research programme was 28.0 % (123 patients), GLIMPSE will contain at most 8 to 12 predictors, or 10 predictors according to Peduzzi et al. [269] and Green [270], respectively.

Developing a new prognostic model versus building on existing models

Developing a novel prognostic model with a set of entirely new and well-fitted predictors is likely to result in better prognostic performance compared to previous models. However, this may result in an overly optimistic model with good internal validity but lacking in generalizability. The premise of evidence-based medicine is to make informed decisions from as much information as possible. This notion is often violated when current prognostic models are deemed obsolete when they are found to be inferior during external validation, and consequently are replaced by entirely new models built from scratch [273]. This is counterintuitive to the notion of evidence-based medicine. Instead, existing prognostic models that lack external validity should be updated by combining them with new information as well as recalibrating them to local circumstances and settings. This may increase external validity and transportability of the model in new populations and settings [273].

Applications to GLIMPSE: In line with the principles of evidence-based medicine, GLIMPSE was not built from a set of entirely new predictors. Rather, predictors of GLIMPSE were restricted to parameters that have been shown to be predictive of mortality outcomes i.e., mNUTRIC score and SGA. In addition, other predictors with strong physiological rationale for their association with mortality outcomes will be included in GLIMPSE.

Perform internal validation

Internal validity is fundamental to all prognostic model since deficiency in this aspect precludes applicability outside the study population (external validity). Internal validity of a prognostic model is measured by its degree of overfitting.

Overfitting refers to the violation of the principle of parsimony (using the least number of independent variables to describe the dependent variable) during model building, hence yielding an overly optimistic model fit and resulting in worse prediction in independent data. That is, including predictors with no useful function in a prognostic model and/or using an overly sophisticated statistical model that will adapt to the data too closely [223, 274]. The inclusion of irrelevant predictors in a prognostic model has several repercussions as resources

will be wasted in measuring and recording these data. More importantly, the presence of superfluous predictors increases random variation in the coefficients fitted into the model, resulting in reduced prognostic performance [274]. In the case of the choice of statistical model, the use of models that are more flexible than required, may worsen performance. For example, in a dataset that conforms to a simple linear model, the use of a neural net model to accommodate a curvilinear relationship may result in worse performance compared to a simple linear model [274].

Overfitting can be determined in two ways. One is to: 1) randomly split the original dataset into a development sample (half to two-thirds of the dataset) and a validation sample; 2) develop a prognostic model from the development dataset; 3) apply the prognostic model to the validation dataset; and 4) compute the differences in discrimination and calibration accuracies between the development and validation dataset as these values will reflect the degree of overfitting. An alternative (preferred) technique is bootstrapping as the former method is statistically inefficient (since not all data not used in the development and validation of the prognostic model) and may suffer from replication instability in which different random split will result in differing prognostic models [46, 223]. In contrast to the method described above, bootstrapping utilises all data in the original study sample (OSS) to quantify the degree of optimism. This piece of information can be used to adjust the C-index (a measure of discrimination accuracy) to better reflect model performance in new samples [46].

Bootstrapping is a process in which bootstrap samples (BS) are randomly drawn (with replacement) repeatedly about 100 to 1000 times from the original study sample (OSS) to mimic a random draw from the larger source population [46]. Since the resultant BS will be similar but not identical to the OSS, the model developed from each BS may be different from the OSS and hence have different model performance (C-index). To quantify the degree of optimism, each bootstrap model is applied to the OSS, and the resultant model performance is compared to those of the bootstrap model. The average of all differences in model performance reflects the degree of optimism in the initially developed model from the OSS [46]. For example, the C-index of the model developed from the OSS is 0.8. The C-index of five models developed from five BS are 0.75, 0.69, 0.82, 0.81 and 0.71. Subsequently, the five models are applied to the OCC, and the resultant c-index are 0.8, 0.72, 0.79, 0.79 and 0.75, and the

differences in C-index when compared with the BS models are 0.05, 0.03, -0.03, -0.02 and 0.04 respectively. The average of these C-index differences is 0.014, and this reflects the degree of optimism.

Applications to GLIMPSE: The bootstrapping technique was used to determine the internal validity of GLIMPSE. A bootstrap with re-sampling will be used to determine the discrimination (C-index) and calibration accuracy (assessed graphically via a bias-corrected calibration curve) of GLIMPSE.

Sections 7.1 and 7.2 explained the rationale and methods that will be adopted in the development of GLIMPSE, respectively. Section 7.3 contains material from:

Lew CCH, Wong GJY, Cheung KP, et al. The association between nutritional adequacy and 28-day mortality in the critically ill is not modified by their baseline nutritional status and disease severity. Crit Care. 2019;23(1).

Contribution to the publication:

- Research design: 100%
- Data collection and analysis: 80%
- Writing and editing: 90%

I made a major contribution to the conception of the manuscript, design of the research, and acquisition, analysis, and interpretation of the data. I drafted the manuscript and revised it according to the recommendations provided by my co-authors and the peer reviewers.

7.3 Introduction

The optimal daily amounts of energy and protein that result in a lower mortality risk in critically ill patients remain uncertain. Heyland et al. [38] proposed that nutritional support may not benefit all patients, and consequently developed the Nutrition Risk in Critically Ill score

(NUTRIC) to identify patients who would derive the most benefit from nutritional support. This score was subsequently modified to exclude interleukin-6 [modified-NUTRIC (mNUTRIC)] and currently comprises variables such as age, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score (SOFA), length of hospitalization before admission to the Intensive Care Unit (ICU), and number of comorbidities [41]. None of these are nutritional parameters, and it is arguable that the mNUTRIC is a disease severity score. This concept is supported by data from a study by Lew et al. [5] wherein a poor concordance was demonstrated between the mNUTRIC score and the Subjective Global Assessment (SGA)–a validated nutritional assessment tool that has strong mortality prognostic value in critically ill patients [1, 2].

The mNUTRIC has a maximum score of 9, in which scores 0 to 4 and 5 to 9 are classified as low-mNUTRIC and high-mNUTRIC, respectively. Adequate energy and protein intakes were observed to benefit only high-mNUTRIC patients, with no effect on low-mNUTRIC patients [41, 153, 225]. However, several recent studies have reported conflicting results [230, 242]. Lew et al. [260] recently validated the mNUTRIC score and observed that the association between mNUTRIC score and 28-day mortality was modified by the timing and dose of nutritional support [260]. Specifically, the study suggested that early high energy and protein intakes were associated with a higher risk of 28-day mortality in high-mNUTRIC patients with short-term nutritional support (≤6 days), whereas the inverse was observed in those with longer-term nutritional support (≥7 days) [260]. However, the median mNUTRIC scores of these two groups of patients (receiving ≤6 days vs. ≥7 days of nutritional support) at ICU admission were similar, which suggested that mNUTRIC may be unable to identify patients who would either benefit from, or be harmed by early high energy and protein intakes.

It is unclear if the above results reflect the absence of nutritional parameters in the mNUTRIC score because intuitively, malnourished patients would be expected to require more energy and protein to overcome the deleterious effects of critical illness. Lew et al. [260] previously demonstrated that disease severity (measured by the mNUTRIC) and nutritional status (measured by the SGA) independently and in combination can predict mortality [2, 5]. A recent review also recommends simultaneous use of both the mNUTRIC and SGA for complete nutritional evaluation for the critically ill [275]. In light of this, the aim was to develop

a new prognostic model, namely the Global Index of Mortality Probability in the Severely ill (GLIMPSE) that combines both mNUTRIC and 7-point SGA to predict 28-day mortality. In addition, this study also evaluated the ability of GLIMPSE to identify patients who would benefit the most from early high energy and protein intakes.

7.4 Methods

Setting and Patient

This was a prospective observational cohort study conducted in the ICU (35 beds) of Ng Teng Fong General Hospital (Singapore). The ICU functions as a closed unit, in which board-certified intensivists and residents provide care for medical, surgical, trauma, cardiac, and neurological patients. Patients are classified as "critically ill" if they are mechanically ventilated and require the support of two or more organ systems. They are downgraded to high dependency status once they are extubated from mechanical ventilation.

To develop GLIMPSE, consecutive patients admitted between August 2015 and October 2016 were screened for enrolment. Patients who were at least 21 years old, had been admitted to the ICU at least 24 hours prior to the screening, and whose nutritional status was established within 48 hours were enrolled. Nutritional status was established by the 7-point SGA, and details have been previously published [2]. Briefly, each one-point decrease in the 7-point SGA (indicative of a greater degree of malnutrition) was associated with a higher risk of 28-day mortality [2]. [4]. Patients who were readmitted to the ICU within the same hospitalization were excluded.

The ability of GLIMPSE to identify patients who would derive the most benefit from nutritional support was validated in a subgroup of patients. These patients had experienced at least 48 hours of mechanical ventilation and were not pronounced moribund (had medical orders not to resuscitate or had poor prognosis) within 48 hours of ICU admission.

The Domain Specific Review Board approved this study (NHG DSRB Ref: 2014/00878), and informed consent was not required because no attempt was made to change the standard of care in the study.

Data collection

Patient demographics, admission diagnoses, adequacy of exclusive nutritional support (ENS), and mortality outcome were prospectively recorded in the electronic medical records and retrieved. Since mNUTRIC was not part of routine care, it was calculated at the end of the study. Details of the collection of energy and protein intakes via ENS have been previously published [260]. In brief, adequacy of nutrition support was calculated by dividing total enteral and/or parenteral nutrition (energy and protein) intake by number of days on ENS and expressed as a percentage of the goals established at ICU admission. This was recorded from ICU admission to a maximum of 14 days, unless death occurred earlier.

Development of GLIMPSE

Variables demonstrated to be associated with mortality outcomes in our previous studies were included in GLIMPSE. They include: 1) disease severity measured by mNUTRIC score [5]; 2) nutritional status measured by 7-point SGA [2]; and 3) cardiopulmonary resuscitation before ICU admission [2]. These predictors were fitted into a multivariable logistic model. This generated weighted coefficients and a constant that could be used to calculate the predicted mortality risk of patients. More importantly, a logistic model is required for the measurement of internal validity. The internal validity of GLIMPSE was assessed via a bootstrapping technique, in which 1,000 re-samples of the entire cohort were created to quantify the discrimination and calibration accuracy of GLIMPSE (R package version 3.5.1. http://CRAN.R-project.org/package=rms). Discrimination was assessed by using the C-index (adjusted for optimism via bootstrapping). Calibration was assessed graphically by preparing a bias-corrected calibration curve and assessing its slope.

Validity of GLIMPSE as an assessment tool for nutrition support

Lew et al. [260] showed that associations between early high energy and protein intakes and 28-day mortality in high-mNUTRIC patients with ≤6 days and ≥7 days of ENS were different (harm vs. benefit, respectively) and the mNUTRIC of these two groups of patients were similar [260]. The same approach was used in this study to determine the validity of GLIMPSE in the same subgroup of patients. First, the mortality risks of patients predicted by GLIMPSE were stratified into low- and high-GLIMPSE by using the Youden Index [12]. Second, given the prospective nature of this study, multivariable Cox proportional hazard regressions were used to determine associations between energy and protein adequacies and 28-day mortality, stratified by GLIMPSE risk groups and the duration of ENS exposure (≤6 days and ≥7 days). Statistical analyses were performed using STATA 14.2 (Stata Corp, College Station, TX, USA) and R package (version 3.5.1). For all comparisons, interactions, and associations, a p-value < 0.05 was considered statistically significant.

7.5 Results

There were 440 patients enrolled, and no patients were lost to follow-up (Figure 20). Mortality at day 28 following ICU admission was 28.0%. Survivors had lower disease severity, and were more likely to be well-nourished compared to non-survivors (Table 29). Data from a subgroup of the entire cohort of 252 patients were used to evaluate the ability of GLIMPSE to identify patients who will derive the most benefit from early high energy and protein intakes. Patients who were excluded had similar characteristics to those included in the validation group apart from a lower SOFA score (mean 8.1 versus 9.2, $p < 0.001$) and a higher number of comorbidities (median 3 versus 2, $p < 0.001$). Characteristics of the 252 patients were stratified by their duration of exposure to ENS (short- versus longer-term ENS). All characteristics in patients with short- and longer-term ENS were similar except for type of admission, number of comorbidities, and admission diagnosis.

The mean (SD) percentages of energy and protein relative to the requirements for the first six days of ICU admission in the validation group were 60.0% (23.6%) *[15.2 (6.5) kcal/kg]*

and 55.1% (24.5%) *[0.64 (0.31) g/kg]*, respectively. The actual energy and protein intakes are summarised in Table 30 and Figure 21. During the first six days of ENS, patients with longer-term ENS had significantly higher energy and protein intakes than those of the patients with short-term ENS (p-value: < 0.001 for both energy and protein). When stratified by nutritional status, the mean percentages of goal energy and protein intakes between the well-nourished and malnourished patients during the first six days of ENS (Energy: 63.4% vs. 58.8%, p-value: 0.172; Protein: 57.4% vs. 54.2%, p-value: 0.368, respectively) were not signficiantly different.

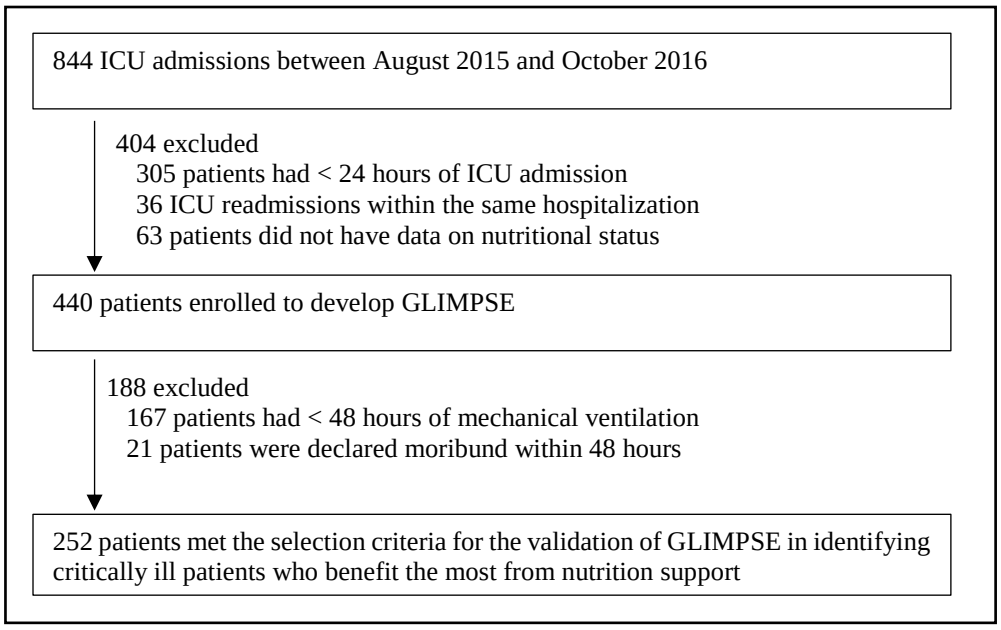


Figure 20: Enrollment of patients

Table 31: Characteristics of enrolled patients

Patient characteristics	Enrolled patients (n=440)	Survivors (n=317)	Non-survivors (n=123)	p-value	Short-term ENS (≤ 6 days) (n = 106)	Longer-term ENS (≥ 7 days) (n = 146)	p-value
Age (years)	61.4 (15.7)	59.3 (15.9)	66.8 (14.1)	<0.001	60.4 (16.9)	59.5 (15.5)	0.655
Male	259 [58.9]	192 [60.6]	67 [54.5]	0.244	63 [59.4]	92 [63.0]	0.564
BMI (kg/m^2)	24.4 {21.3, 28.2}	24.4 {21.2, 28.0}	24.2 {21.3, 28.6}	0.955	24.5 {21.2, 29.5}	24.6 {21.8, 28.4}	0.726
Location before adm				0.003			0.976
ED/HD/OT	357 [81.1]	268 [84.5]	89 [72.4]		88 [83.0]	121 [82.9]	
Wards	83 [18.9]	49 [15.5]	34 [27.6]		18 [17.0]	25 [17.1]	
Type of adm				0.006			0.001
Medical	293 [66.6]	199 [62.8]	94 [76.4]		80 [75.5]	79 [54.1]	
Surgery	147 [33.4]	118 [37.2]	29 [23.6]		26 [24.5]	67 [45.9]	
No of comorbidities	2.0 {1.0, 4.0}	2.0 {1.0, 4.0}	3.0 {2.0, 4.0}	0.069	3.0 {1.0, 4.0}	2.0 {1.0, 3.0}	0.002
LOS before ICU adm (days)	0.0 {0.0, 1.0}	0.0 {0.0, 1.0}	1.0 {0.0, 3.0}	0.009	0.0 {0.0, 1.3}	0.0 {0.0, 1.3}	0.730
APACHE II	24.5 (8.1)	22.6 (7.4)	29.5 (7.7)	< 0.001	25.4 (8.4)	24.7 (7.6)	0.543
SOFA	8.7 (3.8)	7.9 (3.5)	10.7 (3.8)	< 0.001	9.2 (3.7)	9.1 (3.8)	0.909
mNUTRIC	5.3 (2.1)	4.8 (2.1)	6.6 (1.5)	< 0.001	5.5 (2.3)	5.3 (2.0)	0.531
mNUTRIC ≥ 5 (high-mNUTRIC)	299 [68.0]	187 [59.0]	112 [91.1]	< 0.001	74 [69.8]	100 [68.5]	0.823
Malnutrition	123 [28.0]	72 [22.7]	51 [41.5]	< 0.001	31 [29.2]	35 [24.0]	0.347
Admission reasons				< 0.001			0.020
Cardiovascular	82 [18.6]	43 [13.6]	39 [31.7]		19 [17.9]	18 [12.3]	
Respiratory	84 [19.1]	68 [21.5]	16 [13.0]		24 [22.6]	21 [14.4]	
Sepsis	105 [23.9]	72 [22.7]	33 [26.8]		36 [34.0]	39 [26.7]	
Trauma	12 [2.7]	12 [3.8]	0 [0.0]		4 [3.3]	4 [2.7]	
Metabolic/Renal	8 [1.8]	8 [2.5]	0 [0.0]		2 [1.9]	2 [1.4]	
Gastrointestinal	42 [9.6]	29 [9.2]	13 [10.6]		3 [2.8]	8 [5.5]	
Post operation	13 [3.0]	12 [3.8]	1 [0.8]		4 [3.8]	3 [2.1]	
Orthopaedics	7 [1.6]	6 [1.9]	1 [0.8]		1 [0.9]	2 [1.4]	
Neurological	87 [19.8]	67 [21.1]	20 [16.3]		13 [12.3]	49 [33.6]	
CPR before ICU adm	53 [12.1]	17 [5.4]	36 [29.3]	< 0.001	18 [17.0]	18 [12.3]	0.297
Length of MV (days)	2.0 {1.0, 5.0}	2.0 {1.0, 4.0}	3.0 {2.0, 6.0}	<0.001	3.0 {2.0, 4.0}	7.0 {4.0, 13.0}	<0.001
ICU LOS (days)	2.0 {2.0, 5.0}	2.0 {1.0, 4.0}	3.0 {2.0, 6.0}	0.001	3.0 {2.0, 4.0}	7.0 {4.0, 12.0}	<0.001
Hospital LOS (days)	14.0 {7.0, 25.0}	15.0 {9.0, 33.0}	9.0 {4.0, 16.0}	<0.001	8.0 {4.0, 15.3}	24.0 {16.0, 45.0}	<0.001

Values are mean (standard deviation), median {interquartile range}, or count [percentage]. **adm:** Admission; **APACHE II:** Acute physiology and chronic health evaluation II; **BMI:** Body mass index; **CPR:** Cardiopulmonary resuscitation; **ED:** Emergency department; **ENS:** Exclusive nutrition support; **HD:** High dependency; **ICU:** Intensive care unit; **LOS:** Length-of-stay; **MV:** Mechanical ventilation; **mNUTRIC:** Modified nutrition risk in critically ill; **OT:** Operation theatre; **SOFA:** Sequential organ failure assessment

Table 32: Comparison of goal and achieved energy and protein intakes between 28-day survivors and non-survivors stratified by days of exclusive nutrition support

Nutrition parameters	All patients	Survivors	Non-survivors	p-value
	Short-term exclusive nutrition support (≤ 6 days)			
Energy				
Goal (kcal/kg)	25.7 (5.8)	25.5 (5.5)	25.9 (6.3)	0.680
Actual Intake (kcal/kg)	12.0 (6.6)	10.0 (6.0)	15.0 (6.4)	< 0.001
Actual intake (% goal/kg)	48.0 (24.9)	40.0 (22.4)	59.2 (24.1)	< 0.001
Protein				
Goal (g/kg)	1.14 (0.23)	1.14 (0.20)	1.15 (0.26)	0.779
Actual Intake (g/kg)	0.47 (0.29)	0.39 (0.26)	0.57 (0.30)	0.001
Actual intake (% goal/kg)	41.6 (25.0)	34.7 (21.6)	51.4 (26.4)	0.001
	Longer-term exclusive nutrition support (≥ 7 days)			
Energy				
Goal (kcal/kg)	25.6 (4.4)	25.9 (4.4)	24.8 (4.3)	0.166
Actual Intake (kcal/kg)	17.5 (5.3)	17.7 (5.2)	16.9 (5.7)	0.389
Actual intake (% goal/kg)	68.7 (18.2)	68.8 (17.8)	68.2 (19.5)	0.857
Protein				
Goal (g/kg)	1.19 (0.22)	1.20 (0.21)	1.15 (0.26)	0.281
Actual Intake (g/kg)	0.77 (0.25)	0.79 (0.24)	0.71 (0.28)	0.125
Actual intake (% goal/kg)	64.8 (19.1)	66.1 (18.9)	61.6 (19.4)	0.206

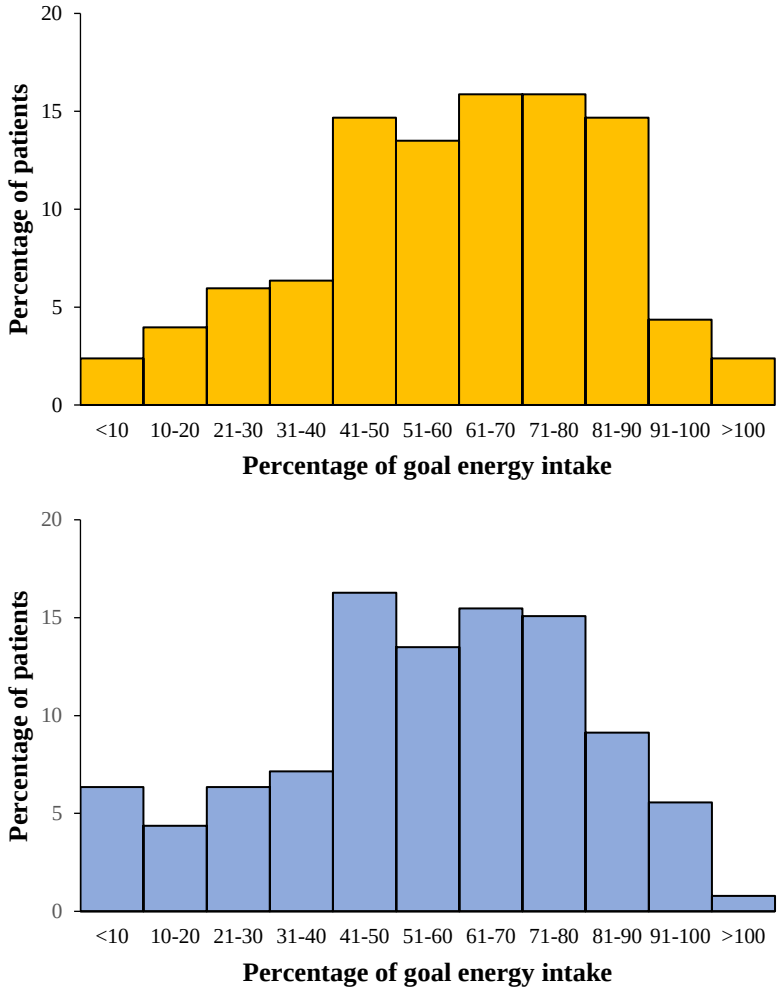


Figure 21: Distribution of the percentage of goal energy and protein intakes during the first 6 days of exclusive nutrition support

Development of GLIMPSE

Three predictors (mNUTRIC score, 7-point SGA, and exposure to cardiopulmonary resuscitation before ICU admission) were fitted into a multivariable logistic regression. All predictors were significant (p-value < 0.05). The resultant equation used to calculate the predicted 28-day mortality risk was −3.003 + (mNUTRIC × 0.477) + (7-point SGA × −0.166) + (exposure to cardiopulmonary resuscitation before ICU admission × 1.933). Internal validation in the model via 1000 bootstrap replicates revealed an adjusted C-index and max-rescaled R-square of 0.78 (95% CI: 0.73, 0.82) and 0.30, respectively. The bias-corrected calibration curve (Figure 2) suggested overall fair calibration accuracy (slope: 0.98).

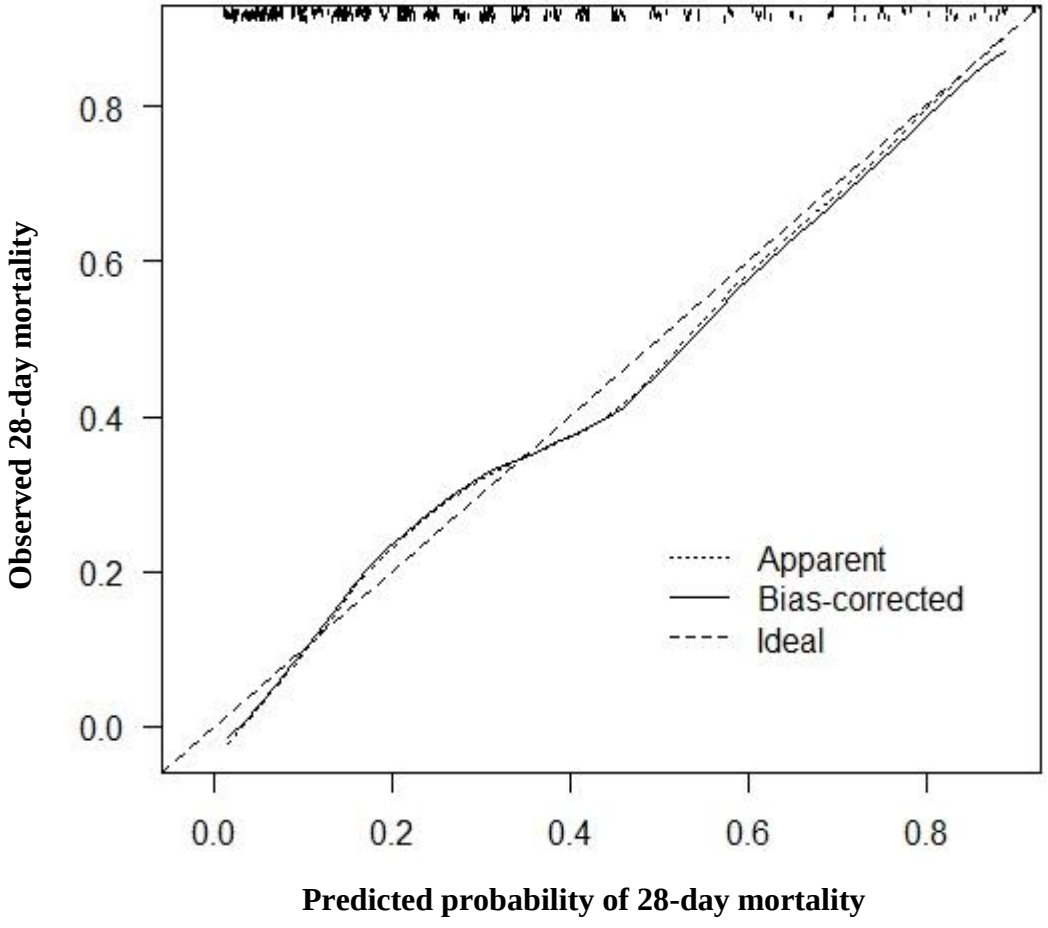


Figure 22: Bias-corrected calibration curve for the prediction of 28-day mortality

Validity of GLIMPSE as an assessment tool for nutrition support

The optimal cutoff point for defining low- and high-GLIMPSE was 20%, and the C-index, sensitivity, and specificity were 0.71, 87.8%, and 54.6%, respectively. The characteristics of patients classified as low- and high-GLIMPSE in the first day of ICU admission were all significantly different except for sex and body mass index (Table 31). However, the mean predicted mortality risks (standard deviation) in patients with short- and longer-term ENS were similar [32.2% (24.1%) vs. 27.8% (21.3%), respectively, p-value: 0.122].

In patients with short-term ENS, the association between energy and protein intakes and 28-day mortality during the first six days of ENS was examined in Cox regression models (Table 32). There were no interactions between the GLIMPSE groups and energy and protein intakes. Generally, there was a positive association between energy and protein intakes and 28-day mortality in both GLIMPSE groups, but it was statistically significant for patients with high-GLIMPSE only.

Similarly, the association between energy and protein intakes and 28-day mortality during the first 6 days of ENS was examined in patients with longer-term ENS (Table 32). There were no interactions between the GLIMPSE groups and energy and protein intakes. The associations between energy and protein intakes and 28-day mortality in patients with low- and high-GLIMPSE appeared to be opposite of each other, but only protein intake was significantly associated with 28-day mortality because each 10% increase in protein adequacy was associated with an 18% reduction in the hazard of 28-day mortality.

Table 33: Characteristics of patients classified as low- and high-GLIMPSE

Patient characteristics	Low-GLIMPSE (n = 188)	High-GLIMPSE (n=252)	p-value
Age (years)	53.6 (16.0)	67.2 (12.8)	< 0.001
Male	115 [61.2]	144 [57.1]	0.396
BMI (kg/m^2)	25.5 (6.3)	24.9 (5.8)	0.262
Location before adm			< 0.001
ED/HD/OT	169 [89.9]	188 [74.6]	
Wards	19 [10.1]	64 [25.4]	
Type of adm			< 0.001
Medical	104 [55.3]	189 [75.0]	
Surgery	84 [44.7]	63 [25.0]	
No of comorbidities	2.0 {1.0, 3.0}	3.0 {2.0, 4.0}	< 0.001
LOS before ICU adm (days)	0.0 [0.0. 1.0]	1.0 [0.0, 2.5]	<0.001
APACHE II	18.6 (5.2)	29.0 (6.9)	< 0.001
SOFA	6.4 (3.0)	10.3 (3.4)	< 0.001
mNUTRIC	3.4 (1.5)	6.7 (1.2)	< 0.001
mNUTRIC ≥ 5 (high-mNUTRIC)	55 [29.3]	244 [96.8]	< 0.001
Malnutrition	29 [15.4]	94 [37.3]	< 0.001
Predicted mortality risk	9.7 (5.0)	41.6 (19.5)	< 0.001
Admission reasons			< 0.001
Cardiovascular	22 [11.7]	60 [23.8]	
Respiratory	39 [20.7]	45 [17.9]	
Sepsis	26 [13.8]	79 [31.4]	
Trauma	11 [5.9]	1 [0.4]	
Metabolic/Renal	3 [1.6]	5 [2.0]	
Gastrointestinal	15 [8.0]	27 [10.7]	
Post operation	9 [4.8]	4 [1.6]	
Orthopaedics	3 [1.6]	4 [1.6]	
Neurological	60 [31.9]	27 [10.7]	
CPR before ICU adm	1 [0.5]	52 [20.6]	< 0.001
Length of MV (days)	2.0 {1.0, 4.0}	2.0 {1.0, 5.0}	0.039
ICU LOS (days)	2.0 {2.0, 5.0}	3.0 {2.0, 5.0}	0.381
Hospital LOS (days)	13.5 {7.0, 27.0}	14.0 {7.0, 24.0}	0.953

Values are mean (standard deviation), median {interquartile range}, or count [percentage].
adm: Admission; **APACHE II:** Acute physiology and chronic health evaluation II; **BMI:** Body mass index;**CPR:** Cardiopulmonary resuscitation; **ED:** Emergency department; **ENS:** Exclusive nutrition support; **HD:** High dependency; **ICU:** Intensive care unit; **LOS:** Length-of-stay; **MV:** Mechanical ventilation; **mNUTRIC:** Modified nutrition risk in critically ill; **OT:** Operation theatre; **SOFA:** Sequential organ failure assessment

Table 34: Association between energy and protein intakes and 28-day mortality as well as nutritional status stratified by days on exclusive nutrition support and GLIMPSE groups

Parameters	Short-term ENS (≤ 6 days)		Longer-term ENS (≥ 7 days)		p-value	
	Low-GLIMPSE * (n=36)	High-GLIMPSE * (n=70)	Low-GLIMPSE * (n=64)	High-GLIMPSE * (n=82)		
Energy intake each 10% of goal	1.22 (0.70, 2.17) p-value: 0.479	1.25 (1.10, 1.43) p-value: 0.001	1.37 (0.80, 2.34) p-value: 0.249	0.88 (0.74, 1.04) p-value: 0.138	0.673†	0.075‡
Protein intake each 10% of goal	1.19 (0.68, 2.10) p-value: 0.547	1.27 (1.09, 1.48) p-value: 0.004	1.09 (0.69, 1.74) p-value: 0.709	0.82 (0.70, 0.96) p-value: 0.015	0.754§	0.143**
7-point SGA-categories					0.480††	0.633‡‡
Well-nourished						
SGA-7	22 [61.1]	34 [48.6]	41 [64.1]	34 [41.5]		
SGA-6	8 [22.2]	11 [15.7]	18 [28.1]	18 [22.0]		
Mildly-moderately malnourished						
SGA-5	3 [8.3]	8 [11.4]	4 [6.3]	14 [17.1]		
SGA-4	2 [5.6]	7 [10.0]	1 [1.6]	9 [11.0]		
SGA-3	1 [2.8]	5 [7.1]	0 [0.0]	5 [6.1]		
Severely malnourished						
SGA-2		4 [5.7]		2 [2.4]		
SGA-1		1 [1.4]		0 [0.0]		

Values are hazard ratio (95% confidence interval) adjusted for days on exclusive nutrition support and count [percentage]
ENS: Exclusive nutrition support; **GLIMPSE:** Global index of mortality probability in the severely ill; **SGA:** Subjective global assessment
* Low- and high-GLIMPSE is defined as predicted mortality risk lower and greater than 20%, respectively
† Interaction between energy intake and GLIMPSE categories in patients with short-term exclusive nutrition support
‡ Interaction between protein intake and GLIMPSE categories in patients with short-term exclusive nutrition support
§ Interaction between energy intake and GLIMPSE categories in patients with longer-term exclusive nutrition support
** Interaction between protein intake and GLIMPSE categories in patients with longer-term exclusive nutrition support
†† Comparison of 7-point SGA-categories between low-GLIMPSE patients with short-term and longer-term ENS
‡‡ Comparison 7-point SGA-categories between high-GLIMPSE patients with short-term and longer-term ENS

7.6 Discussion

A new prognostic model (GLIMPSE) was developed by combining baseline nutritional status (measured by the 7-point SGA) and disease severity (measured by the mNUTRIC score) to predict 28-day mortality. Internal validation suggested that GLIMPSE had good discrimination and calibration accuracy and was able to identify patients at low- and high-risk of 28-day mortality. However, it was unable to differentiate patients who would benefit from or be harmed by early high energy and protein intakes.

Prognostic performance

The GLIMPSE model can be viewed as an extension of the mNUTRIC score. The latter had a C-index and max-rescaled R^2 of 0.65 and 0.57, respectively [41]. However, subsequent large multi-centre cohort studies (n > 1000) that sought to validate mNUTRIC demonstrated reduced prognostic performance, with the C-index and max-rescaled R^2 ranging from 0.65 to 0.7, and 0.09 to 0.16, respectively [225, 231]. In our study, GLIMPSE model demonstrated better prognostic performance than mNUTRIC. This may be attributed to the inclusion of strong independent predictors of mortality (nutritional status and CPR status) [2] to and the simultaneous adjustment of relative weights (regression coefficients) to each predictor via logistic regression to better quantify 28-day mortality risk. Despite its good prognostic performance, the GLIMPSE model was unable to identify patients who would benefit from or be harmed by early high energy and protein intakes. Specifically, early high energy and protein intakes were associated with higher mortality in high-GLIMPSE patients with short-term nutrition support while the opposite was observed in those with high-GLIMPSE and longer-term nutrition support. In these two groups of patients, mean predicted 28-day mortality risks were similar (32.2% versus 27.8%, respectively).

Validity of GLIMPSE in identify patients who would derive the most benefits from aggressive nutrition support

The GLIMPSE tool was developed because it was hypothesized that an integration of nutritional status with disease severity would identify patients who will derive the most benefit

from early high energy and protein intakes. However, this was not supported by the data in the current study. However, this was not supported by the data in the current study. The disparity between early high energy and protein intakes and 28-day mortality in patients with short- and longer-term ENS was unexpected, as was the lack of discrimination by the integration of nutritional status with disease severity in the GLIMPSE model. Further stratification of nutritional status in these two groups of patients also revealed that the associations between energy and protein intakes and 28-day mortality were independent of baseline nutritional status (Table 32). The plausible rationales for this observation will be explored in three parts:

- The mortality-modifying effects of energy and protein intakes on the association between disease severity and clinical outcomes.

- The mortality-modifying effects of energy and protein intakes on the association between nutritional status and clinical outcomes.

- The fate of energy and protein metabolism during the initial stage of critical illness

Modifying effects of energy and protein intakes on the association between disease severity and clinical outcomes

Several mNUTRIC validation studies suggested that higher average energy [41, 153, 225] and protein [225] intakes reduced the mortality risk of patients with high-mNUTRIC score. Since the mNUTRIC score has been demonstrated to be a disease severity score in Chapter 5 [5], the results of previous validation studies [41, 153, 225] could indicate that higher average energy and protein intakes may reduce the mortality risk of severely ill patients in the ICU.

However, the ability of mNUTRIC to identify patients who would benefit more from higher average energy and protein intakes was not a consistent finding in the literature. Arabi et al. [33] conducted a multi-centre study (PermiT) that specifically aimed at comparing the effects of permissive underfeeding and full-feeding on a range of clinical outcomes. This trial concluded that both feeding strategies were comparable for all measured outcomes, and this

conclusion generated much debate in the literature. One hypothesis was that consideration of the patients' nutrition risk by using the mNUTRIC score would have shown full-feeding to benefit patients with high-mNUTRIC score [276]. In response, two post-hoc analyses were conducted [237, 242]. In one, it was demonstrated that neither feeding strategies affected the clinical outcomes of patients with high-mNUTRIC score [237], while in another, patients with high-mNUTRIC score who received less than 12 days of full-feeding were at a significantly higher risk of 90-day mortality [242], a finding that is contrary to those of other validation studies. It is important to highlight that the findings provided by the post-hoc analyses of the PermiT trial [237, 242] can be considered more robust than other validation studies [41, 153, 225] since this trial was specifically designed to investigate the effects of different feeding strategies. In contrast, other mNUTRIC validation studies (except for Rahman et al. [41]) are observational in nature and may inherently be subject to residual confounding and indication bias. In the case of the post-hoc analysis conducted by Rahman et al. [41], the use of data from an RCT that was not designed to investigate the effects of full- versus permissive-underfeeding as well as the lack of robust statistical analysis (discussed in Chapter 6) could explain the favourable results towards the mNUTRIC score.

The inconsistency of the mNUTRIC score in identifying patients who would derive the most benefits from aggressive nutrition support was also demonstrated in a recent observational study. Lee et al. [230] conducted a prospective observational study to determine the association between energy and protein intakes and 60-day mortality. Adequate nutrition support (defined as having received more than 66.7% of energy and protein goals) did not significantly reduce the mortality risk of patients with high-mNUTRIC scores. Instead, adequate nutrition support was associated with significantly higher mortality in patients with low-mNUTRIC scores.

Apart from the mNUTRIC score, data from the EPaNIC post-hoc analysis also provided evidence for the lack of association between energy and protein intakes and time to live discharge from the ICU regardless of disease severity [246]. Patients in the post-hoc analysis were stratified into four groups according to their degree of disease severity quantified by the APACHE II score. Thereafter, the effects of late parenteral nutrition (withholding for one week) and early parenteral nutrition (which resulted in a higher total energy and protein intake) on time to live discharge from the ICU were compared across the four groups. It was observed

that disease severity did not affect the association between early parenteral nutrition and longer ICU length-of-stay.

Overall, it is clear that the modifying effects of energy and protein intake on the association between disease severity and clinical outcomes are inconsistent. This could explain why GLIMPSE had good mortality prognostic performance but did not identify patients who would derive the most benefit from nutrition support. A common limitation of GLIMPSE, mNUTRIC, and APACHE II is the inability to characterise the dynamic disease progression of critically ill patients. For example, patients admitted with diabetic ketoacidosis and severe pancreatitis may have the same GLIMPSE, mNUTRIC, and APACHE II scores, but the patient with diabetic ketoacidosis would have a rapid metabolic recovery while the insult suffered by the patient with severe pancreatitis may worsen. This reflects the inability of prognostic scores in taking into account the differing pathophysiology and progression of diseases. Therefore, the same nutrition support intervention rendered to patients with similar disease severity measured at baseline would have differing effects.

The modifying effect of a progressive deterioration in clincial status on the association between energy intake and hospital mortality was demonstrated in a recent retrospective cohort study in ICU patients with acute lung injury [277]. Patients in this study had their SOFA scores sequentially recorded for the first seven days following the diagnosis of acute lung injury. Thereafter, they were stratified into those with improved organ functions (day-7 SOFA score < baseline) and those with worsened organ functions (day-7 SOFA score > baseline) in the statistical analysis. This study demonstrated that high energy intake was significantly associated with increased odds of hospital mortality in patients with worsened organ functions (adjusted OR: 4.22 (95% CI: 202–8.78) while this was not significant in patients with improved organ functions (adjusted OR: 1.87 (95% CI: 0.90–3.87) [277].

Modifying effects of energy and protein intakes on the association between nutritional status and clinical outcomes

Chapters 1 and 3 demonstrated the association between malnutrition and a higher risk of mortality. Therefore, urgent nutrition support, which often translates to early high energy

and protein intakes, is recommended for malnourished critically ill patients because it confers clinical benefits [278, 279]. However, this has not been examined in RCTs performed in ICUs because this sub-group of patients is often excluded due to ethical reasons. Furthermore, results of the this present study suggest that the association between malnutrition and higher risk of mortality may not be modified by higher energy and protein intakes. This section aims to explore the modifying effects of energy and protein intakes on the association between nutritional status and clinical outcomes reported in recent literature.

Most RCTs that investigated the effects of various doses of energy and protein intakes (e.g., full-, permissive-, or trophic feeding) on clinical outcomes in the critically ill did not use validated nutrition screening or assessment tools to measure the baseline nutritional status of subjects [11-13, 18, 31-34, 280, 281]. This precludes the ability to perform statistical stratification or adjustment to explore if the interventions have a different effect on malnourished patients. Although some RCTs did perform nutrition screening or assessment at baseline [115, 247], the interactions between nutritional risk (or status) and interventions were not analysed, except for the EPaNIC [14] and PEPaNIC [282] studies.

The EPaNIC trial is one of the few RCTs that measured and considered baseline malnutrition risk in their analysis. In the EPaNIC study [14], baseline malnutrition risks of subjects were measured using the NRS-2002. Despite the possibility of misclassifying nutritional status as a result of using a nutrition screening tool instead of a validated nutrition assessment tool (e.g. SGA), this study demonstrated that the effect of nutrition support on time to live discharge from the ICU was independent of the baseline malnutrition risk of patients. That is, patients at risk of malnutrition who received higher energy and protein (via early parenteral nutrition) did not have shorter ICU length-of-stay. This was also the case for the PEPaNIC trial [282]. Baseline malnutrition risk in the pediatric population was quantified by the STRONGkids score, and similar to the EPaNIC trial, children at risk of malnutrition did not benefit from higher energy and protein intakes provided by early parenteral nutrition. Instead, children at risk of malnutrition and receiving lower energy and protein during the first seven days of ICU admission (due to the withholding of parenteral nutrition) had lower odds of infection. However, the reasons for the above observations in the EPaNIC and PEPaNIC studies are unclear.

In the current study, baseline nutritional status of critically ill patients did not appear to modify the association between energy and protein intakes and 28-day mortality. This result is congruent with a recent retrospective cohort study that also demonstrated that baseline nutritional status measured by the SGA did not modify the association between energy intake and hospital mortality [277]. Although it is possible that an association could be present in the longer term (e.g., 6-month mortality), a more plausible reason for the lack of interactions between nutritional status, energy and protein intakes, and 28-day mortality could be the fate of energy and protein metabolism during the initial stage of critical illness.

Fate of energy and protein metabolism during the initial stage of critical illness

This section explores plausible reasons for the lack of treatment effects of nutrition support in critically ill patients. It is not intended to be an exhaustive review of the literature, and it is recognised that the concepts outlined are controversial. Therefore, this section sets out to generate hypotheses for future research.

Fate of energy and protein metabolism in the state of malnutrition in critically ill patients

Malnutrition is defined as "a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" [283]. To effectively treat malnutrition (a state of depleted fat-free mass and body cells), one must efficiently utilise the repleted nutrients provided by nutrition support for either anabolism or to attenuate further catabolism.

At the initial phase of critical illness, patients are often in an overtly inflammatory and catabolic state where levels of glucagon, catecholamines, and cortisol are considerably raised, resulting in anabolic resistance [284]. Therefore, energy and protein provided at this stage are unlikely going to be effectively used for anabolism or attenuation of catabolism [285-288]. This possible rationale is further strengthened by a recent study that examined the skeletal muscle metabolic phenotype during the initial phase of critical illness [289]. It was revealed that intramuscular inflammation and altered hypoxic signalling during the initial phase of

critical illness may impair lipid oxidation and reduce intramuscular adenosine triphosphate. These processes prevent anabolic restoration, reduce the bioavailability of adenosine triphosphate for muscle protein synthesis and hence lead to skeletal muscle wasting. More importantly, these process may not be modified by higher energy intake during the initial phase of critical illness [289].

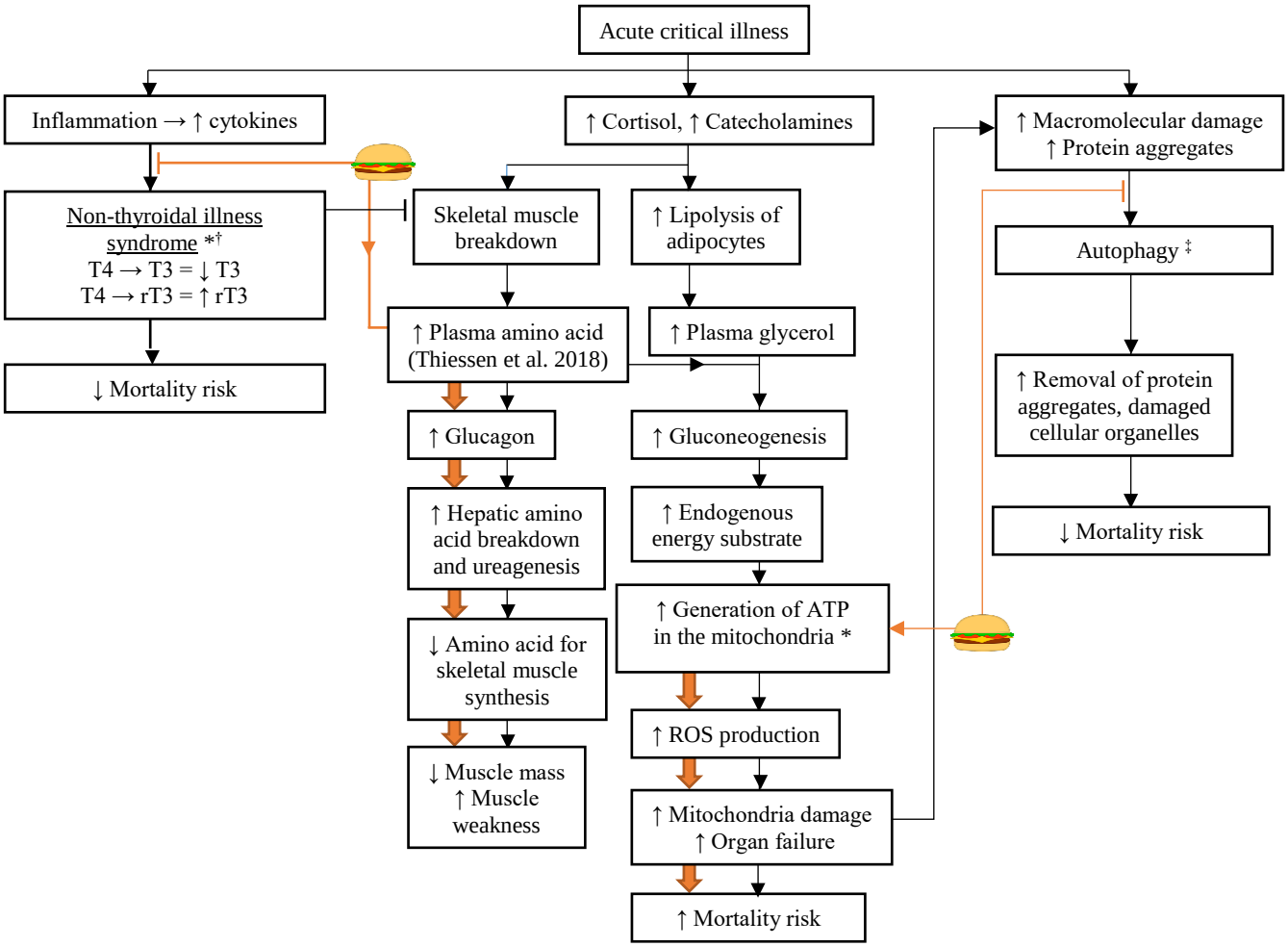
Results outlined in this present study suggest that the baseline nutritional status of critically ill patients may not significantly change the fate of energy and protein metabolism during the first six days of ENS. It is more plausible that the rate of inflammatory resolution is the primary determinant of how high energy and protein intakes may benefit or harm patients. That is, high energy and protein intakes were positively associated with 28-day mortality in patients with short-term ENS because they were in a heightened inflammatory state. In contrast, high energy and protein intakes were inversely associated with 28-day mortality in patients with longer-term ENS because they were either in a less inflamed stated or had only a brief period of heightened inflammation. Hence, these patients benefited from higher energy and protein intakes.

Patients in the ICU are heterogeneous, and they have varying degrees of inflammatory response to critical illness. Rehou et al. [290] conducted a cohort study that compared the acute phase response of 149 burn patients. This study demonstrated that elderly patients had poorer cardiac and metabolic responses as well as lower inflammatory reactions to burn injury as compared to adult patients. In addition, Molinger et al. [291] at the 17th Congress of the European Shock Society presented the results of a longitudinal observational study that used a non-invasive assessment to compare the muscle histology of 25 patients on day 1, 4, and 10 from ICU admission. The study demonstrated that changes in muscle architecture and muscle wasting are highly pronounced and accelerated in septic patients. However, patients with neurotrauma have considerably blunted responses. These results suggest that the metabolic consequences and inflammatory responses of various critical illness can differ. Therefore, patients with different critical illness can have different responses to early higher energy intake. Incidentally, a large proportion of patients (i.e., longer-term ENS) who benefited from early higher energy and protein intakes were admitted for neurological reasons, and this is in contrast

to the higher number of septic patients in the group (short-term ENS), in which the same nutrition support strategy was associated with higher mortality risk.

Other nutrition-related processes that affect the fate of energy and protein metabolism in critically ill patients

Among the numerous processes that occur during the acute phase of critical illness, three major processes related to nutrition are described (and often discussed separately) in the literature: 1) non-thyroidal illness syndrome (NTIS); 2) heightened inflammation; and 3) induction of autophagy. Figure 25 integrates these processes to illustrate how they increase the chance of survival, and how high energy and protein intakes during this stage may increase mortality and morbidity risk.



* McKeever et al. [292]
† Fliers et al. [293]
‡ Rosenthal et al. [294]

Figure 23: Purported consequences of high energy and protein intakes (orange lines) at the acute phase of critical illness

Note: Thick lines depict the relative amplification of pathway
↑: increase; ↓: decrease; **ATP**: Adenosine triphosphate; **ROS**: Reactive oxygen species; **rT3**: Reverse tri-iodothyronine; **T3**: Tri-iodothyronine; **T4**: Prohormone thyroxine

Non-thyroidal illness syndrome

The thyroid gland secretes hormones that play a major role in the regulation of energy metabolism. During critical illness, high levels of cytokines such as tumour necrosis factor, interleukin-1, and interleukin-6 are secreted which induce a condition termed non-thyroidal illness syndrome (NTIS). This is characterised by decreased plasma levels of tri-iodothyronine (T3) and prohormone thyroxine, increased plasma reverse T3, and normal or slightly decreased thyroid-stimulating hormone [293]. It is claimed that this hormonal environment is a beneficial adaptation to critical illness to promote survival as lower levels of T3. This may be an attempt by the body to decrease energy expenditure so as to conserve energy and prevent protein breakdown [293]. Attenuation of protein breakdown is especially crucial as increased skeletal muscle breakdown leads to high level of plasma amino acids, and will lead to: 1) higher glucagon production, and 2) more substrates for gluconeogenesis. *Higher glucagon levels*: Glucagon increases the breakdown of amino acid in the liver, and this reduces the supply of amino acid for muscle protein synthesis [284]. *Increased substrates for gluconeogenesis*: Higher levels of endogenous energy substrates increase the generation of adenosine triphosphate in the mitochondria, and this can have a negative impact during the acute phase of critical illness. During the acute phase, the electron transport chain may produce abnormally high amounts of reactive oxygen species, which can reduce mitochondria function and consequently hinders adenosine triphosphate production. These processes may increase cell death and risk of multi-organ failure [292]. Taken together, NTIS reduces muscle breakdown and production of reactive oxygen species during the acute phase of critical illness.

Heightened inflammation

In the presence of high cortisol and catecholamine in the acute phase of critical illness, increased skeletal muscle and adipocyte breakdowns occur [284, 295]. Furthermore, catecholamines may stimulate glucagon release by activating the beta receptors of alpha cells. These processes provide a substantial amount of endogenous energy substrates (glucose from gluconeogenesis, amino acids from protein breakdown, and free fatty acids from adipolysis) vital for energy production, a process that is not suppressed by exogenous energy administration [287, 288].

Induction of autophagy

Emerging evidence suggests that a process termed "autophagy" may be crucial to the recovery of critical illness-induced organ failure [296]. A well-recognised form of autophagy is macroautophagy, where isolation membranes in the cytoplasm encapsulate damaged intracellular contents (e.g., organelles and protein aggregates) and deliver them to the lysosomes for degradation [297]. Macroautophagy may help increase survival in the acute phase of critical illness as it is the only process that can remove intracellular contents such as damaged mitochondria, intracellular microorganisms, and protein aggregates [297]. Autophagy is stimulated in the presence of damaged intercellular content, exercise, and particularly in starvation [294, 297].

The beneficial effects of inducing autophagy were demonstrated in the EPaNIC trial [14]. In this study, early high energy and protein intakes resulted in poor clinical outcomes (increased ICU length-of-stay and infection risk) whereas the inverse was observed in patients with lower energy and protein intakes [14]. These findings, corroborated by mechanistic sub-studies in EPaNIC [246, 298], demonstrated that inducing autophagy by delaying the provision of parenteral nutrition benefits critically ill patients.

The suggested benefits of autophagy are not without controversy. Opponents argue that autophagy is unlikely to be the only physiological process that determines clinical outcomes in critically ill patients. Although autophagy is an essential means of eliminating protein aggregates to promote survival, it must be balanced with the mTOR pathway as the latter is involved in protein synthesis and prevents excessive autophagy and muscle wasting [299]. Unrestrained autophagy can lead to excessive degradation of cytosolic proteins and organelles, leading to apoptosis, necrosis, and cell death [299]. Given that the interactions between autophagy and mTOR are complex and not well understood, opponents argue that it is premature to withhold nutrition support at the acute phase of critical illness for the sole purpose of preserving autophagy [299].

Suggested consequences of high energy and protein intake during the acute phase of critical illness

Currently, the phases of critical illness are arbitrarily divided into two phases: acute (a highly catabolic and inflammatory state), and late (a more anabolic and less inflammatory state) [300]. The typical duration of acute phase ranges from three days [259] to a week [243, 244, 246, 277]. In practice a time interval is used to demarcate the phases because, at present, there are no biomarkers that accurately quantify the degree of inflammation [156, 300]. Since the number, type, and degree of insults for each critically ill patient can differ widely in the ICU, it is no surprise that some patients will be in a prolonged acute state while others progress quickly into the late phase. This has significant ramifications for patient responses to early high energy and protein intakes because patients with prolonged acute phase may be harmed while those with quick progression to late phase will potentially benefit [300]. This notion may in part explain the mixed results (harm [14, 247], no effect [29, 33], and benefit [17, 19]) found in RCTs that evaluated the effects of full- and permissive underfeeding during the first week of ICU admission.

A recent retrospective observational study [277] provides more insights into a possible explanation for the mixed results observed in RCTs. Peterson et al. [277] demonstrated that the association between energy intake (during the first seven days following intubation) and hospital mortality was modified by the degree of organ failure. Specifically, high energy intake was associated with higher odds of hospital mortality in patients with severe organ failure than in patients with less organ failure (measured by the SOFA score). Results of this study suggest that the mixed findings of previous trials may be explained by the varying degree of organ failure (which may reflect the severity of inflammation) of recruited patients. Interestingly, this association was not modified by patients' nutritional status, a result similar to the findings of the current study.

As illustrated in Figure 25, high energy and protein intakes during the acute phase of critical illness in severely ill ICU patients: 1) attenuate NTIS, 2) increase plasma amino acid, and 3) hinder autophagy. *Attenuation of NTIS* – Administration of exogenous energy and protein during the acute phase of critical illness has been shown to attenuate NTIS [301].

Consequently, energy metabolism may be less suppressed, and more exogenous macronutrients metabolised in the mitochondria to produce ATP. This may increase the amount of reactive oxygen species and accordingly reduce mitochondria function and increase the risk of cell death and multi-organ failure [243]. *Increased plasma amino acids*: This further stimulates glucagon production, which increases hepatic amino acid breakdown, leading to a reduced supply of amino acid for skeletal muscle synthesis [302]. Furthermore, recent studies demonstrated that administration of exogenous amino acid does not reduce muscle wasting [286, 302], increased ureagenesis (indicating an inefficient use of amino acid) [29, 303-305], and may lead to muscle weakness [298]. *Hindered autophagy*: It has been hypothesized that reduced autophagy during the acute phase of critical illness leads to higher mortality risk [294]. Administration of exogenous amino acid impedes autophagy and hence hinders the clearance of damaged cellular organelles and protein aggregates. However, this process is partially mitigated by the attenuation of NTIS [292] because T3 has been shown to stimulate autophagy, and more importantly, mitochondrial biogenesis [306]. It is claimed that this process not only aids the body to overcome the inhibiting effects of exogenous amino acid on autophagy but also improves the body's ability to metabolise exogenous nutrient (and hence lesser reactive oxygen species) with the synthesis of new mitochondria [292].

Why high energy and high protein intakes were not associated with harm or were even beneficial in some studies

The discussion above supports permissive underfeeding at the acute phase of critical illness because full-feeding may be associated with poorer clinical outcomes. However, this should be balanced against the overall evidence in the literature. When compared with patients who received lower energy and/or protein intakes in the first few days of ICU admission, some studies demonstrated the benefits of early higher intakes [19, 115] whereas others do not show either harm or benefit [29, 281]. Notably, a large multi-centre RCT that recruited 3,957 patients from 46 Australian and New Zealand ICUs demonstrated that achieving energy goals at day-2 of ICU admission did not lead to any mortality differences compared to patients with lower energy intake [281]. These studies provided clinical evidence that refutes the purported harm associated with early full-feeding. However, there is a lack of pre-planned mechanistic studies

describing the patients' biological responds to feeding which would clarify why some patients are harmed while others benefit from full or permissive underfeeding.

A possible explanation is that the duration of the acute phase of critical illness may vary with some patients in a prolonged acute phase while others may have early resolution of inflammation and arrive at a late phase more rapidly. Since there are no biomarkers to define the different stages [156, 300] and severity scores such as admission APACHE II and SOFA scores cannot accurately quantify the dynamic inflammatory response of patients during the course of their ICU admission, it is open to speculation that the mixed results in RCTs could be explained by the different metabolic and inflammatory states. That is, trials that demonstrated no difference between higher and lower nutrients intakes might have a similar number of patients who were in the acute and late phase, whereas trials with positive results may have had a majority of the patients with quick resolution of inflammation (late phase) and hence can efficiently utilise energy and protein for recovery.

Two RCTs provided some signal of benefits when higher energy and protein are provided in a less inflammatory state [307, 308]. The NOURISH [307] and EFFORT [308] trials recruited malnourished patients (diagnosed by the SGA) and patients at risk of malnutrition (classified by the NRS-2002) from the general ward, respectively. Both studies demonstrated that higher energy and protein intakes significantly reduced mortality risk. Results of these studies suggest that patients in a less inflammatory state may be more susceptible to nutrition repletion [300], and nutrients provided with the appropriate timing may yield a more pronounced benefit.

Critical appraisal of the internal validity as well as strengths and limitations of GLIMPSE in predicting 28-day mortality

It is crucial to critically appraise the methods used in the current study to identify deficiencies that may explain the results and guide future work. To achieve this, a structured critical appraisal framework recommended by the National Health and Medical Research Council [309] (i.e., Graphic Appraisal Tool for Epidemiological – GATE – studies) [310] was adopted to evaluate the internal validity and the limitations of GLIMPSE in predicting 28-day

mortality. The evaluation criteria for internal validity are broadly classified into four domains: Participants, Exposure and Comparison, Outcomes, and Time.

Table 35: Critical appraisal for internal validity in prognostic studies – Participants [310]

Items	Criteria	Checklist
a)	What were the key selection (inclusion and exclusion) criteria? Were they well-defined and replicable?	☺
b)	Were inclusion and exclusion criteria appropriate given the study question?	☺
c)	Were participants at a common point in the course of their disease?	☺

a) The selection criteria are outlined and these were broad, well-defined, and replicable.

b) Since the study sought to develop and validate GLIMPSE in a heterogeneous ICU population, it was intentional that the inclusion criteria be broad. In addition, as it was essential to compare the results of this present study with other studies [41, 153], exposure to > 48 hours of mechanical ventilation and ENS were the inclusion criteria. In addition, as with other studies [41, 230], patients who were declared moribund within 48 hours of ICU admission were excluded. This was because moribund patients often receive little ENS and death in these patients is most likely to result from severe disease rather than underfeeding. The above selection criteria are replicable and appropriate for the study question.

c) All patients were enrolled within 48 hours of ICU admission. Hence, patients were enrolled at a common point in the course of critical illness.

Table 36: Critical appraisal for internal validity in prognostic studies – Exposure and comparison [310]

Items	Criteria	Checklist
d)	What were the prognostic groups? Were they well defined and replicable?	☺
e)	Was the measurement of variables similar and valid in all groups?	😐
f)	Were different prognostic groups similar at the start except for prognostic factors? If not, were differences stratified or adjusted for in analyses?	😐
g)	Were all participants analysed in groups to which they were initially assigned?	☺
h)	Were participants, health workers, and researchers blind to prognostic factors?	😐
i)	Were group treated equally?	😐
j)	Were prognostic factors re-measured during follow-up, and were there important changes?	☹

d) *Measurement of baseline nutritional status* – The 7-point SGA was used within 48 hours of ICU admission to classify the nutritional status of critically ill patients into well- and malnourished groups. Internal reliability measured by Kappa statistics demonstrated good agreement between assessors (weighted kappa: 0.85, n = 68, standard error = 0.079, p-value < 0.001) [2]). Furthermore, previous studies also revealed that the 7-point SGA had good reliability [265, 266]. *Measurement of baseline disease severity* – In the case of the mNUTRIC score, computation was solely based on objective parameters. Therefore, the prognostic groups in this present study can be considered well-defined and replicable.

e) *Measurement of baseline nutritional status* – Measurement of baseline nutritional status was identical in all patients as the 7-point SGA was the only nutrition assessment used in this present study. However, the validity of the 7-point SGA may be limited by its ability to identify patients with low muscularity. Recent studies revealed that low muscularity in critically ill patients is associated with prolonged duration of mechanical ventilation and hospitalisation, as well as increased risk of infection and mortality [311-314]. Compared with objective measures of muscularity (dual-energy X-ray absorptiometry, magnetic resonance imaging and computed tomography), the SGA may have poorer accuracy due to its subjective nature. Furthermore, in the current

obesity pandemic, the use of a subjective method to assess muscularity poses a greater challenge for the detection of low muscularity in obese patients (sarcopenic obesity). This is evidenced by Sheean et al. [111] in which the SGA did not detect low muscularity. Specifically, more than half of the patients classified by the SGA as "well-nourished" had low muscularity, and this misclassification was more common in males and in people who are overweight or obese. Other studies conducted outside of the ICU also revealed that the SGA does not consistently identify patients with low muscularity. For instance, there was only fair concordance [kappa: 0.342, (95%CI: 0.185, 0.499)] between malnutrition diagnosed by the SGA and low muscularity classified by bioimpedence analysis in surgical patients [315]. This was similar in patients with liver cirrhosis (kappa: 0.28) in which low muscularity was classified by computed tomography [316]. *Measurement of baseline disease severity* – Disease severity, as quantified by the mNUTRIC score, was identical in all patients. Previous studies [38, 41, 153, 224-226, 228, 231] and Chapter 5 [5] have demonstrated that the mNUTRIC score has excellent and consistent validity in quantifying disease severity.

f) Besides the common prognostic factors (baseline nutritional status and disease severity), the admission diagnoses of patients can affect their mortality risk [2]. However, the admission diagnoses were not included in the GLIMPSE model because of the small number of patients in some of the categories. Nevertheless, the internal validation study demonstrated that the GLIMPSE model has good discrimination and calibration accuracy despite lacking admission diagnoses.

g) The statistical analyses were based on the baseline nutritional status recorded in the electronic medical records. In addition, variables required to compute the mNUTRIC score were also recorded in the electronic medical records. Therefore, all participants were analysed in the groups to which they were initially assigned.

h) All healthcare professionals providing care for the critically ill patients in this present study were blinded to the objectives of the studies, with the exception of the ICU dietitians who performed the nutrition assessment and rendered the nutrition support

for the critically ill. Therefore, treatment bias seems unlikely although it could not be entirely ruled out.

i) In the ICU, patient care can be classified into medical treatment, nursing care, and nutrition support. *Medical treatment and nursing care* – Since the physicians and nurses were blinded to the objectives of this present study, it is likely that standard medical treatments and nursing care were provided to all critically ill patients. *Nutrition support* – Since the ICU dietitians were not blinded to the objectives of the study, there is a likelihood that more attention may be given to the nutrition support rendered to malnourished patients. However, this may not be the case for severely ill patients because the mNUTRIC score was retrospectively computed at the end of the study.

j) *Measurement of baseline nutritional status* – The nutritional status of the critically ill was not re-measured at the end of the study. It is likely that some well-nourished patients would become malnourished during their stay in the ICU. Patients with a longer duration of ICU admission are at higher risk of iatrogenic malnutrition as most of them would only receive about 56% and 52% of their estimated energy and protein requirements, respectively [7]. This may result in an under-estimation of the association between malnutrition and mortality outcomes. *Measurement of baseline disease severity* – Disease severity was not re-measured during follow-up as the mNUTRIC score was designed to quantify disease severity at day-1 of ICU admission [38]. More importantly, most patients at the 28th day from ICU admission would have been discharged from the ICU and hence preclude the calculation of the Sequential Organ Failure Assessment scores and APACHE II scores – both required to calculate mNUTRIC.

Table 37: Critical appraisal for internal validity in prognostic studies – Outcomes [310]

Items	Criteria	Checklist
k)	What outcome measures were used? Were they well defined and replicable?	☺
l)	How complete were the follow-ups? Was this sufficient? How many dropouts were there?	☺
m)	Was outcome assessment blind?	☺

k) The outcome measure was 28-day mortality, and it is well-defined and reproducible.

l) Some patients were excluded due to missing 7-point SGA data. Although several of their characteristics were significantly different from those patients with 7-point SGA data, these were adjusted using the multivariable models (i.e., SOFA and number of comorbidities). Aside to patients with missing 7-point SGA data, all enrolled patients were followed for up to one year from their ICU admission, and none was lost to follow-up, thus minimising attrition bias.

m) Mortality at the 28th day of ICU admission is an objective measure and hence do not need to be blinded.

Table 38: Critical appraisal for internal validity in prognostic studies – Time [310]

Items	Criteria	Checklist
n)	Was follow up time sufficiently long to detect important prognostic factors?	😐

n) It is unclear if the follow-up period was adequate to detect the impact of energy and protein intakes on mortality. Nonetheless, the 28-day mortality was chosen in order to compare the findings of the study with previously published data.

Strengths

In summary, the methods used to develop GLIMPSE have a number of strengths. *Participants* – The selection criteria were broad, well-defined, and replicable. In addition, consecutive enrollment of subjects minimised selection bias. *Exposure and comparison* – Classification of baseline nutritional status was standardised, and there was evidence of good inter-reliability between assessors. Having nutritional status classified within 48 hours of ICU admission also minimised the risk of reverse causality bias. *Outcomes* – The outcomes were objective, well-defined, and replicable. Since there was complete follow-up, the risk of attrition bias was minimised.

Limitations

A number of limitations require consideration. *Participants* – Although the key selection criteria were well-defined and reproducible, the resultant case-mix of participants is unique to the current study- namely a single-centre observational study conducted at NTFGH. The GLIMPSE model may not be applicable to patients who are admitted primarily for orthopaedic reasons, metabolic/renal, trauma, respiratory support post-surgery, or gastrointestinal conditions as their prevalence were relatively low (1.6%, 1.8%, 2.7%, 3.0%, and 9.6%, respectively. Instead, it would be more applicable to patients with sepsis (23.9%), neurological (19.8%), respiratory (19.1%), and cardiovascular (18.6%) conditions (Table 29). In addition, the prevalence of severe malnutrition (3.0%) was also very low in the current study. Hence, the prognostic ability of GLIMPSE may not apply to ICUs where there is a very high prevalence of severe malnutrition [37, 76]. Furthermore, the applicability of GLIMPSE is also limited by the availability of clinicians who can competently perform the 7-point SGA.

Exposure and comparison – The drawbacks were mainly centred around the validity of the 7-point SGA in classifying nutritional status as well as the lack of blinding of ICU dietitians to the objectives of this present study. With respect to the 7-point SGA, while it is the recommended bedside nutrition assessment tool [1], the risk of misclassifying critically ill patients with low muscularity as "well-nourished" [111] may limit the validity of the 7-point SGA. Therefore, subjective assessment of nutritional status in critically ill patients should be supplemented by objective measurements. A potential assessment tool is inexpensive, non-invasive and can be conducted by the bedside is ultrasonography of the quadricep muscles. Recent studies conducted in critically ill patients have consistently reported that this technique has good intra- and inter-reliability [317-319]. However, more work is needed to standardise measurement techniques and sites to improve the diagnosis of low muscularity in critically ill patients [320]. In the case of the lack of blinding, although it is possible that malnourished patients are reviewed more frequently, there were no significant differences in mean percentage of goal energy and protein intakes of these patients when compared to their well-nourished counterparts during the first six days of ENS (Energy: 63.4% vs. 58.8%, p-value: 0.172; Protein: 57.4% vs. 54.2%, p-value: 0.368, respectively).

Outcomes – The outcome measure of this present study was limited to mortality. Having measured patient-centred outcomes such as physical functionality and quality-of-life post-discharge would provide a more holistic insight. However, such measurements are not routine and would require informed consent. This is likely to reduce participation and itself increase the risk of selection bias. In addition, there were insufficient resources for such measurements.

7.7 Conclusion

The GLIMPSE model integrates parameters of disease severity and nutritional status and demonstrates good prognostic performance in the prediction of 28-day mortality in critically ill patients. However, the model is unable to identify patients who would derive the most benefit from early high energy and protein intakes. The modifying effects of nutrition support appeared to be independent of the baseline nutritional status and disease severity of critically ill patients.

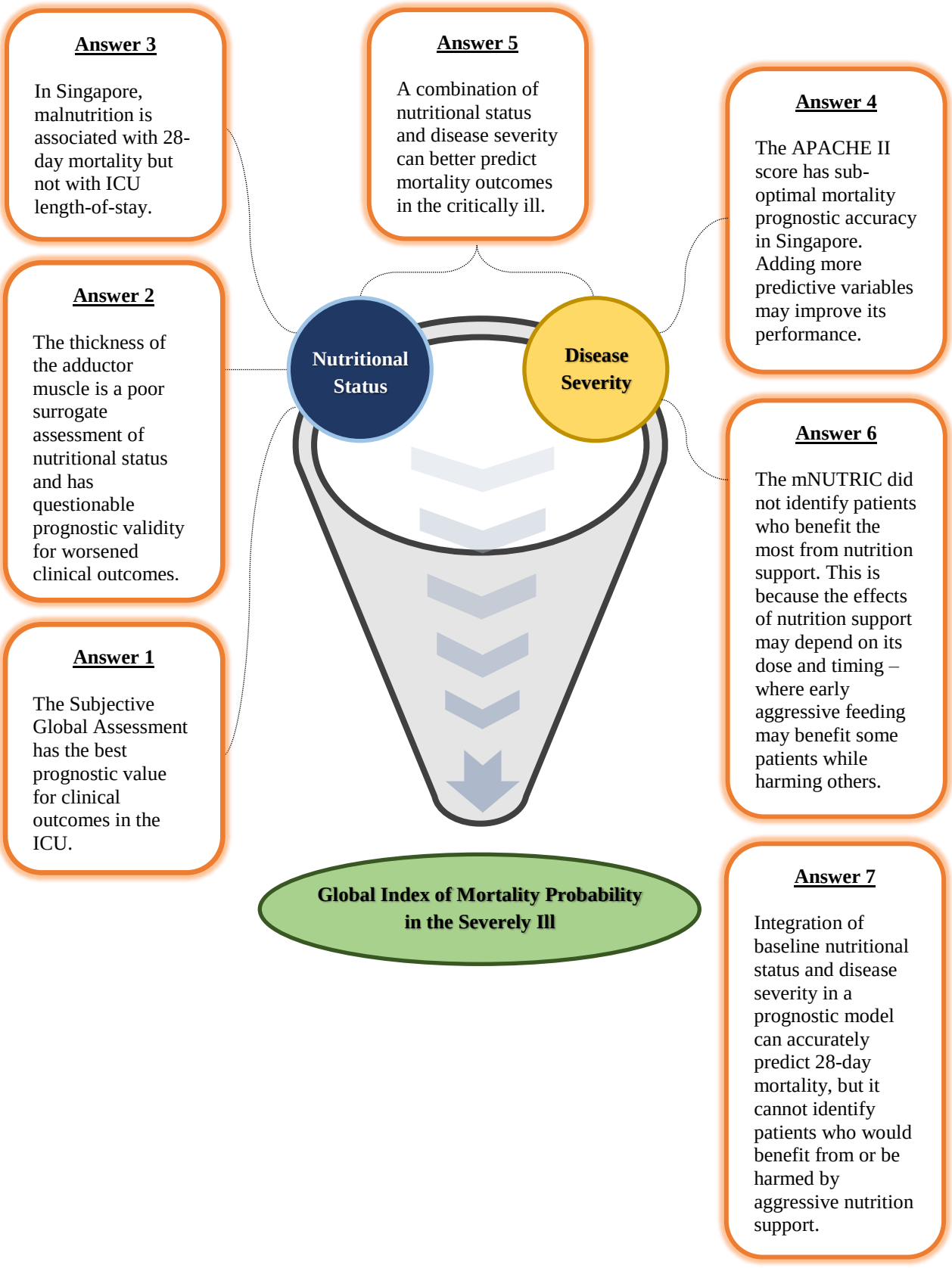


Figure 24: Conceptual framework for the development of an assessment tool that accounts for both baseline nutritional status and disease severity in critically ill patients – Research Question 7

Chapter 8: Overall discussion and conclusion

8.1 Summary of findings and original contribution to knowledge

The objective of this research programme was to develop a prognostic model (GLIMPSE) that integrates baseline nutritional status and disease severity to: 1) improve the prognostication of clinical outcomes in critically ill patients; and 2) identify patients who would derive the most benefits from aggressive nutrition support in the ICU. It was hypothesized that: 1) the integration of baseline nutritional status and disease severity in a prognostic model can better predict 28-day mortality in critically ill patients; and 2) that an accurate quantification of the risk of 28-day mortality could aid clinicians in identifying patients who require aggressive nutrition support at day-2 of their ICU admission (predictors of GLIMPSE, i.e., mNUTRIC score, require at least 24 hours of ICU admission to be computed).

The research journey started off with the identification of a nutrition assessment tool with good prognostic validity for poor clinical outcomes in the ICU. This was achieved via a systematic review that evaluated the prognostic value of a myriad nutrition screening and assessment tools used in the ICU [1]. Among them, the SGA was identified as having the most consistent prognostic validity for poor outcomes such as increased ICU length-of-stay, ICU readmission, incidence of infection, and risk of hospital mortality. However, several pitfalls were identified in the primary studies, which reduced the prognostic validity of the SGA. Hence, an original study (Chapter 3) was conducted to address these limitations and consequently ascertain a more valid estimate of the association between malnutrition (diagnosed by 7-point SGA) and 28-day mortality as well as ICU length-of-stay [2]. This study not only validated the positive association between malnutrition and 28-day mortality but also demonstrated a dose-respondent association between them. The robust statistical analysis also refuted the previously established association between malnutrition and ICU length-of-stay. In addition, this study revealed that the prevalence of malnutrition could be lower than what was reported in the literature at the time when the systematic review [1] was published (28% instead of 38% to 78%), suggesting that each ICU should perform its own measurements to guide their

nutrition screening and assessment policies. As a result of the original study [2] and systematic review [1], the 7-point SGA was chosen to be part of the GLIMPSE model.

Table 39: Original contribution to knowledge – 1 and 2

No.	Contribution
1	The prevalence of malnutrition is highly varied in the critical care setting (28% to 78%) [1, 2].
2	There is a dose-respondent association between the severity of malnutrition and 28-day mortality, but this was not the case for ICU length-of-stay [2].

It was anticipated that some patients would be deemed unfit to provide vital information for a detailed nutrition assessment in the first 48 hours of ICU admission. Therefore, an alternative surrogate of nutrition assessment that does not require self-reported information (e.g., diet and weight history) was examined. At the initial period of this research programme, considerable attention was given to the thickness of the adductor pollicis muscle as some studies suggest that it is indicative of nutritional status and prognostic of mortality outcomes in critically ill patients [37]. However, the systematic review [3] outlined in Chapter 2 concluded that the thickness of the adductor pollicis muscle has very poor concordance with the SGA and that its prognostic validity for mortality outcomes in critically ill patients is questionable. Furthermore, recent studies revealed that the thickness of the adductor pollicis muscle has a weak correlation with lean body mass [139-141]. Given these limitations, measurement of the adductor pollicis muscle was excluded as a candidate predictor, and the only nutrition parameter included in GLIMPSE was the 7-point SGA.

Table 40: Original contribution to knowledge – 3

No.	Contribution
3	The thickness of the adductor pollicis muscle has not only a limited role in nutrition assessment, but also questionable prognostic validity for worsened clinical outcomes in critically ill patients [3].

Upon identification of a nutrition assessment tool (the 7-point SGA) with strong prognostic validity, the research proceeded to determine the validity of two common assessments used to measure disease severity. The first is the APACHE II score. An original study was conducted [4], and the APACHE II score was demonstrated to have poor calibration accuracy, and this did not improve with primary recalibration efforts. Therefore, APACHE II may require secondary recalibration in larger studies (preferably multi-centred) and/or additional predictors to improve its prognostic performance. The second is the mNUTRIC score. This score is considered a nutrition screening tool in the literature [279] but appears to be a disease severity score. Hence, an original study was carried out to determine the concordance between mNUTRIC and SGA [5]. It was concluded that they have very poor concordance and that mNUTRIC is in fact a score that quantifies disease severity rather than nutrition risk. The study also showed that a combination of mNUTRIC (a measure of disease severity) and SGA (a measure of nutritional status) better discriminate patients who are at a higher risk of mortality. This signalled that Hypothesis 1 (i.e. integration of baseline nutritional status and disease severity in a prognostic model can better predict 28-day mortality in critically ill patients) is likely true. However, since data on energy and protein intakes were not available at that point in time, Hypothesis 2 could not be tested.

Table 41: Original contribution to knowledge – 4, 5, and 6

No.	Contribution
4	Despite good discriminative value, APACHE II has poor calibration accuracy in Singapore, and this did not improve with recalibration efforts [4].
5	Rather than being a nutrition risk score, the mNUTRIC is a valid disease severity score with consistent and robust mortality prognostic validity [5].
6	A combination of mNUTRIC and SGA can better discriminate patients who are at a higher risk of mortality [5].

Up to this point, there were evidence from new RCTs (PermiT [33], INTACT [247], PEPaNIC [282], NephroProtect [303], or Refeeding Syndrome Trial [250]) demonstrating that aggressive nutrition support resulting in higher energy intake did not translate to better clinical outcomes in critically ill patients. However, these findings did not affect Hypothesis 2 of this research programme as the RCTs (except INTACT [247]) did not use any validated nutrition

assessment tool to measure baseline nutritional status. Instead, they used a nutrition screening tool [282] (the STRONGkids score [321] which may inherently misclassify nutritional status), excluded patients with low body mass index [29], or did not perform either of the aforementioned [33]. This precludes the application of their results in malnourished ICU patients.

The critical turning point of this research programme was when the post-hoc analysis of the INTACT trial [243] and the subsequent cohort study were published [244]. These studies were conducted by experienced research and clinical dietitians, and it was demonstrated that the timing and dose of energy and protein intakes had significant effects on mortality outcomes in critically ill patients diagnosed with acute lung injury. That is, early exposure to high energy and protein intakes were associated with higher mortality while the opposite was observed at the later stage of acute lung injury. Given these novel findings, an original study was conducted (Chapter 6) to determine if the results could be replicated in the cohort of critically ill patients enrolled in this research programme. The study demonstrated that the timing and dose of nutrition support could influence the outcome of critically ill patients with high-mNUTRIC scores. In patients with high-mNUTRIC scores and short-term ENS (≤ 6 days), early high energy and protein intakes were positively associated with 28-day mortality, while the association between early high protein intake was inverse in patients with longer-term ENS (≥ 7 days). However, mNUTRIC was unable to identify patients who will benefit from or be harmed by early high energy and protein intakes [260]. Since the mNUTRIC does not contain nutrition parameters, it was believed that the integration of baseline nutritional status and disease severity would enable identification of patients who would derive the most benefits from early high energy and protein nutrition support.

Table 42: Original contribution to knowledge – 7

No.	Contribution
7	In patients with high-mNUTRIC scores and short-term ENS (≤ 6 days), energy and protein intakes were positively associated with 28-day mortality risk. In contrast, protein intake was inversely associated with 28-day mortality in patients with high-mNUTRIC and required longer-term ENS (≥ 7 days). Since the mean mNUTRIC scores in these two groups of patients were similar, mNUTRIC was unable to differentiate those who may benefit from or be harmed by early high energy and protein intakes [260].

Consequently, the GLIMPSE model was developed in Chapter 7, and robust internal validation via the bootstrapping technique demonstrated that the model has good discrimination and calibration accuracy for 28-day mortality. However, similar to mNUTRIC, the model was unable to identify patients who would derive the most benefits from early high energy and protein intakes as it appears that the effects of early high energy and protein intakes are independent of baseline nutritional status. In other words, GLIMPSE is an improved mortality prognostic model that accounts for baseline nutritional status but lacks the ability to identify patients who will benefit from or be harmed by early aggressive nutrition support.

Table 43: Original contribution to knowledge – 8

No.	Contribution
8	Integration of baseline nutritional status and disease severity in a prognostic model can accurately predict 28-day mortality but cannot identify patients who would benefit from or be harmed by aggressive nutrition support [322].

The associations between early high energy and protein intakes and 28-day mortality were different in high-GLIMPSE patients with short- and longer-term ENS. In high-GLIMPSE patients with short-term ENS (≤6 days), each 10% increase in goal energy and protein intake were significantly associated with an increased hazard of 28-day mortality. In contrast, each 10% increase in goal protein intake during the first 6 days of ENS in high-GLIMPSE patients with longer-term ENS (≥7 days) was significantly associated with a lower hazard of 28-day mortality.

The above results may be explained by the predominant metabolic state (i.e., catabolism versus anabolism) at the initial phase of nutrition support since this will dictate the fate of exogenous macronutrient metabolism. *Catabolism* – During the acute phase of critical illness, raised levels of glucagon, catecholamines, and cortisol may result in anabolic resistance [284]. Therefore, energy and protein provided at this stage may not be effectively used for anabolism or attenuation of catabolism [285-287]. This is illustrated in recent studies in which early high protein intake during the acute phase of critical illness led to increased ureagenesis (reflecting inefficiency in protein metabolism [29, 303-305]). Furthermore, early high energy and protein

intake was associated with poorer clinical outcomes such as prolonged ICU length-of-stay and increased risk of infection [14] as well as a greater degree of muscle and functional loss [286, 289, 298]. Mechanistically, these results may be attributed to hindered autophagy [297, 298], attenuation of the non-thyroidal illness syndrome [292], or intramuscular inflammation and altered hypoxic signalling, which consequently reduces the bioavailability of the intramuscular adenosine triphosphate needed for muscle protein synthesis [289]. *Anabolism* – By contrast, during the later phase of critical illness, inflammation and the levels of hormones responsible for catabolism gradually abate, which may result in more efficient use of energy and protein for anabolism and recovery [323].

The number, type and degree of insults for each critically ill patient differ vastly in the ICU. Therefore, some patients will be in a prolonged acute state (catabolic) while other progress quickly into the late phase of critical illness (anabolic) [323]. From the literature, it may be deduced that the acute state can be as short as three days [259] or as long as seven days [243, 244, 246]. In the acute state, high energy or protein intake were shown to worsen clinical outcomes while the same at the later stage were shown to have clinical benefits [243, 244, 246, 259]. Variability in the duration of the acute state could explain the different effects of early high energy and protein intakes in our study. That is, the positive association between energy and protein intakes and 28-day mortality in high-GLIMPSE patients with short-term ENS may reflect the consequence of early high energy and protein intakes in an overt state of catabolism while the negative association in patients with longer-term ENS may suggest an early resolution of catabolism and hence energy and protein could be efficiently used for anabolism.

8.2 Implications for practice

By integrating the results of this research programme with evidence provided by published studies, critical care clinicians should:

1) Use mNUTRIC or GLIMPSE to classify patients into low- and high-risk and focus their nutrition support efforts on high-risk patients. This is because it has been consistently demonstrated that low-risk patients are likely unaffected by the dose of energy and protein intakes [41, 153, 225].

2) In high-risk patients, provide about 50% of the energy and protein goals in the early periods of ICU admission and gradually increase their amounts in accordance to clinical indicators of inflammation resolution, including down-trending in high-sensitivity C-reactive protein and insulin resistance (improved glycaemic control in patients without diabetes [324]) or improvement in organ functions (down-trending in sequential SOFA scores) [277] and levels of transthyretin [288].

    a. The above recommendation for energy intake is similar to the recent ESPEN guidelines (Guidelines 17 and 19), which state that patients should receive lower energy (< 70% of measured or estimated energy requirement) in the acute phase of critical illness, and intake can progressively be increased to meet energy goal [249].

    b. The above recommendation for protein intake is similar to that offered in two recent publications. Preiser [325] summarised the controversies surrounding the optimal protein dose and recommended a cautious approach to protein provision (0.3 to 0.8 gram protein/kg/day at the acute phase of critical illness). Similarly, the ESPEN guidelines (Guideline 22) state that protein provision should be gradually increased, with the ultimate goal of 1.3 gram protein/kg/day [249].

3) Before ICU discharge, use the SGA to identify malnourished patients who require post-ICU intensive nutrition support. Evidence provided by the NOURISH [307] and EFFORT [308] trials suggest that higher energy and protein intakes may significantly reduce the mortality risk of malnourished patients.

8.3 Future studies

Causal inference between malnutrition and clinical outcomes

Malnourished critically ill patients are under-represented in most of the nutrition support trials conducted in the ICU. This is because most trials did not use validated nutrition screening or assessment tools to measure the baseline nutritional status of subjects [11-13, 18,

31-34, 280, 281] or they excluded patients with low body mass index [12, 29]. Therefore, the applicability of the results in this population of patients is unknown. Although this research programme may somewhat fill up the aforementioned knowledge gap, a well-conducted RCT will still be needed to provide a higher level of evidence. This is in part due to the limitations of the current study design. That is, quick accumulation of energy and protein deficits may accelerate the deterioration of nutritional status. Thereby, causing well-nourished patients to be malnourished during their stay in the ICU. As patients' nutritional status was only measured once at baseline, the evolving nutritional status of well-nourished patients may confound the results of this research programme. Therefore, it is vital for future RCTs to only include malnourished patients at baseline to avoid this pitfall. This sample restriction technique was used in the NOURISH [307] and EFFORT [308] trials, and nutritional interventions were demonstrated to be effective.

Instead of measuring the effect of nutritional interventions on mortality outcomes, future studies should focus on functional outcomes as there may be a higher potential for efficacy [326, 327]. A recent systematic review evaluated the robustness of power calculations in 10 RCTs of nutritional interventions. It concluded that all trials are underpowered because the predicted effect sizes of the interventions were overestimated. The systematic review further demonstrated that 50,000 patients would be required to show a 1% difference in mortality if their baseline mortality rate was 20% and type I and II errors were set at 0.05 and 0.2, respectively [327].

Effects of more extended periods of nutrition support in critically ill patients

Critically ill patients may respond better to nutritional repletion at the later stage of critical illness [300]. Ironically, this is also a period where most patients will be extubated from the mechanical ventilator with simultaneous removal of the feeding tube. Several studies have demonstrated that patients post mechanical ventilation or after ICU discharge have variable but generally sub-optimal nutritional intakes [82, 328, 329]. Two studies consistently showed that oral intake in the first week of ICU discharge is less than 50% of energy and protein requirements [82, 328]. It was also demonstrated that a combination of tube feeding with oral intake could significantly help patients meet energy and protein requirements [329]. Therefore,

future trials should explore innovative feeding strategies to boost nutritional intake post-extubation and examine its effect on functional outcomes. These studies should also include an adequate number of malnourished patients so that pre-planned post-hoc analysis can be performed to compare the effects of higher energy and protein intakes in well- and malnourished patients discharged from the ICU.

External validation of the GLIMPSE model

The GLIMPSE model was developed from a relatively small population of critically ill patients housed in a single centre. Therefore, it is vital for the GLIMPSE model to be validated in a larger sample of patients from multiple centres to evaluate its external validity.

Revision of the GLIMPSE model

While scores such as mNUTRIC and GLIMPSE use patients' baseline parameters to predict mortality, these scores do not provide insights into the disease progression of different conditions as well as patients' response to the ongoing medical and nutrition interventions. There is an urgent need for future studies to identify methods to accurately define the duration of the different phases of critical illness because patients with the same demographics as well as disease type and severity may have different responses to inflammation. Some patients will have a better capacity to quickly resolve inflammation while others will fare worse. Therefore, the revised GLIMPSE model should not be a static score but a dynamic one. Indeed, Mayaud et al. [330] developed a mortality prediction model using dynamic information (e.g. physiological parameters before, during and after a hypotensive episode as well as exposure and types of medical treatment) and demonstrated that it outperformed static models such as the APACHE IV and Simplified Acute Physiology Score.

Recent literature reveals several promising parameters that are dynamic by nature and hence could be considered for the revised GLIMPSE model (GLIMPSE-QUARTSS). The parameters include baseline and sequential measurements of: **qua**driceps muscle thickness, C-**r**eactive protein, **t**ransthyretin, **S**OFA score, and muscle glycogen **s**tores (QUARTSS).

Quadriceps muscle thickness may be used along with the SGA to diagnose malnutrition at baseline. This technique is especially useful in overweight and obese patients because the assessment of muscularity via SGA-physical examination is often inaccurate in this group of patients [111]. Besides baseline assessment, sequential measurements of quadriceps muscle thickness can be performed to monitor the degree and rate of muscle atrophy as the degree of muscularity in critically ill patients is associated with prolonged duration of mechanical ventilation and hospitalisation, as well as increased risk of infection and mortality [1-4]. These measurements can also reflect the progression and severity of disease because Puthucheary et al. [286] observed that the number of organ failure in critically ill patients was inversely related to the thickness of the quadriceps muscle.

The recent ESPEN group for ICU guidelines recommends simultaneous and sequential measurements of C-reactive protein and transthyretin in the ICU to evaluate patients' response to nutrition therapy [331], and an established algorithm is recommended to aid interpretation [332]. Indeed, Berger et al. [288] conducted an RCT and demonstrated that adequate nutrition support from day-4 of ICU admission resulted in better clinical outcomes, and transthyretin was demonstrated to be responsive to nutrition support. That is, transthyretin increased significantly faster in patients who received higher caloric and protein intake.

A recent retrospective study analysed the sequential SOFA score of patients and stratified the analysis by the trend of their scores. The study suggests that higher energy and protein intake is associated with lower mortality in patients with decreasing SOFA, whereas the same is associated with higher mortality in patients with increasing SOFA. This observation suggests that sequential SOFA score has the potential of identifying the optimal time and dose of nutrition support in critically ill patients. But given the limitation of the retrospective study design, this method of assessment requires further validation.

Another possible dynamic measurement is sequential quantification of muscle glycogen via ultrasonography. Ultrasound-measured muscle glycogen was suggested to be a measurement of muscle injury and metabolic state since glycogen depletion may lead to muscle damage and reflect catabolism [333]. Conversely, the replenishment of muscle glycogen may be an indication of metabolic recovery, reflecting the transition from a catabolic to an anabolic

phase of critical illness [333]. Although this hypothesis is theoretically sound, more studies are needed to validate this method of assessment.

8.4 Conclusion

With the belief that each critically ill patient's energy and protein needs are based on their unique characteristics, this thesis sets out to develop a prognostic model (GLIMPSE) that characterises patients according to their baseline nutritional status and disease severity. A series of prospective association studies were conducted, and it was demonstrated that: 1) there is a dose-respondent association between the severity of malnutrition (diagnosed by the SGA) and 28-day mortality [2]; and 2) mNUTRIC is a valid disease severity score with consistent and robust mortality prognostic validity [5]. These findings led to the development of GLIMPSE, in which baseline nutritional status and disease severity were integrated into a logistic model, and a robust validation study demonstrated that GLIMPSE could accurately quantify 28-day mortality risk. However, this model was unable to identify patients who would benefit from aggressive nutrition support as high energy and protein intakes were positive and inversely associated with 28-day mortality in patients with identical mortality risk. Mechanistic evidence provided by the literature suggests that energy and protein metabolism during the acute phase of critical illness can differ across patients, and this determines how higher intakes can affect clinical outcomes. However, there is a lack of metabolic biomarkers that can be used to guide the nutrition support prescription. In conclusion, each critically ill patient is unique, and it takes more than baseline nutritional status and disease severity to determine energy and protein needs. More studies are required to better understand the complex interactions between the metabolic processes during the acute phases of critical illness so that individualised nutrition therapy can be provided to bring about the best clinical outcomes.

Examine everything carefully; hold fast to that which is good

1 Thessalonians 5:21

Appendix-1

PubMed search conducted on 1st August 2014

No	Search terms	Results
#1	Malnutrition[Mesh] OR "Nutritional Status"[Mesh] OR "Nutrition Assessment"[Mesh] OR "Protein-Energy Malnutrition"[Mesh] OR malnutrition[tiab] OR malnourish*[tiab] OR undernutrition[tiab] OR undernourish*[tiab] OR underfeeding[tiab] OR nutritional deficienc*[tiab] OR nutrition deficienc*[tiab] OR protein energy malnutrition[tiab] OR protein calorie malnutrition[tiab] OR nutrition assessment[tiab] OR nutritional assessment[tiab] OR nutrition status[tiab] OR nutritional status[tiab] OR nutrition risk[tiab] OR nutritional risk[tiab]	155216
#2	"Questionnaires"[Mesh] OR questionnair*[tiab] OR screen*[tiab] OR assess*[tiab] OR scale[tiab] OR score*[tiab] OR checklist[tiab] OR form[tiab] OR tool[tiab] OR tools[tiab] OR evaluation[tiab] OR rating[tiab] OR monitor*[tiab] OR index[tiab] OR indices[tiab]	4947279
#3	#1 AND #2	44548
#4	Intensive Care[Mesh] OR "Intensive Care Units"[Mesh] OR "Critical Care"[Mesh] OR critical illness*[tiab] OR critically ill[tiab] OR surgical intensive care[tiab] OR medical intensive care[tiab] OR respiratory care unit[tiab] OR special care unit[tiab]	114331
#5	#3 AND #4	747
#6	#5 NOT "Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescen*[tiab] OR child*[tiab] OR infant*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR pregnant OR pregnanc*	523
#7	#6 NOT "addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]	487
#8	Filters: Humans; English	399

CINAHL search conducted on 1st August 2014

No	Search terms	Results
#1	(MH "Malnutrition") OR "Malnutrition" OR (MH "Protein-Energy Malnutrition+")	4,943
#2	(MH "Nutritional Status") OR "Nutritional Status" OR (MH "Nutritional Status: Nutrient Intake (Iowa NOC)") OR (MH "Nutritional Status: Food and Fluid Intake (Iowa NOC)") OR (MH "Nutritional Status: Energy (Iowa NOC)") OR (MH "Nutritional Status: Body Mass (Iowa NOC)") OR (MH "Nutritional Status: Biochemical Measures (Iowa NOC)") OR (MH "Nutritional Status (Iowa NOC)") OR (MH "Nutritional Assessment")	14,221
#3	#1 OR #2	17,242
#4	TI (malnutrition OR "nutritional status" OR "nutrition assessment" OR "protein energy malnutrition" OR malnourish* OR undernutrition OR undernourish* OR underfeeding OR "nutritional deficienc*" OR "nutrition deficienc*" OR "protein calorie malnutrition" OR "nutritional assessment" OR "nutrition status" OR "nutritional status" OR "nutrition risk" OR "nutritional risk") OR AB (malnutrition OR "nutritional status" OR "nutrition assessment" OR "protein energy malnutrition" OR malnourish* OR undernutrition OR undernourish* OR underfeeding OR "nutritional deficienc*" OR "nutrition deficienc*" OR "protein calorie malnutrition" OR "nutritional assessment" OR "nutrition status" OR	8,054

	"nutritional status" OR "nutrition risk" OR "nutritional risk") AND (malnutrition OR "nutritional status" OR "nutrition assessment" OR "protein energy malnutrition" OR malnourish* OR undernutrition OR undernourish* OR underfeeding OR "nutritional deficienc*" OR "nutrition deficienc*" OR "protein calorie malnutrition" OR "nutritional assessment" OR "nutrition status" OR "nutritional status" OR "nutrition risk" OR "nutritional risk")	
#5	#3 OR #4	18,399
#6	(MH "Questionnaires+") OR "Questionnaires" OR (MH "Structured Questionnaires")	186,024
#7	TI (questionnair* OR screen* OR assess* OR scale OR score* OR checklist OR form OR tool OR tools OR evaluation OR rating OR monitor* OR index OR indices) OR AB (questionnair* OR screen* OR assess* OR scale OR score* OR checklist OR form OR tool OR tools OR evaluation OR rating OR monitor* OR index OR indices)	554,500
#8	#6 OR #7	629,451
#9	#5 AND #8	9,706
#10	(MH "Intensive Care Units+") OR (MH "Critical Care Nursing+") OR (MH "Critical Care+") OR "intensive care"	57,495
#11	TI ("intensive care" OR "intensive care unit" OR "Critical Care" OR "critical illness*" OR "critically ill" OR "surgical intensive care" OR "medical intensive care" OR "respiratory care unit" OR "special care unit") OR AB ("intensive care" OR "intensive care unit" OR "Critical Care" OR "critical illness*" OR "critically ill" OR "surgical intensive care" OR "medical intensive care" OR "respiratory care unit" OR "special care unit")	37,483
#12	#10 OR #11	63,464
#13	#9 AND #12	265
#14	TI (adolescent OR child* OR infant OR adolescen* OR infant* OR pediatr* OR paediatr* OR pregnant OR pregnanc*) AND AB (adolescent OR child* OR infant OR adolescen* OR infant* OR pediatr* OR paediatr* OR pregnant OR pregnanc*)	102,347
#15	#13 NOT #14 Limiters - English Language; Human	119

SCOPUS search conducted on 1st August 2014

No	Search terms	Results
#1	malnutrition OR "nutritional status" OR "nutrition assessment" OR "protein energy malnutrition" OR malnourish* OR undernutrition OR undernourish* OR underfeeding OR "nutritional deficienc*" OR "nutrition deficienc*" OR "protein calorie malnutrition" OR "nutritional assessment" OR "nutrition status" OR "nutritional status" OR "nutrition risk" OR "nutritional risk"	117625
#2	questionnair* OR screen* OR assess* OR scale OR score* OR checklist OR form OR tool OR tools OR evaluation OR rating OR monitor* OR index OR indices	5205732
#3	#1 AND #2	57051
#4	"intensive care" OR "intensive care unit" OR "Critical Care" OR "critical illness*" OR "critically ill" OR "surgical intensive care" OR "medical intensive care" OR "respiratory care unit" OR "special care unit"	1214252
#5	#3 AND #4	1879
#6	addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication	3718462

	Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]	
#7	#5 NOT #6, Limiters - English Language; Human	1028

Cochrane search conducted on 1st August 2014

No	Search terms	Results
#1	MeSH descriptor: [Malnutrition] explode all trees	2003
#2	MeSH descriptor: [Nutritional Status] explode all trees	1539
#3	MeSH descriptor: [Nutrition Assessment] explode all trees	649
#4	MeSH descriptor: [Protein-Energy Malnutrition] explode all trees	227
#5	malnutrition or "nutritional status" or "nutrition assessment" or "protein energy malnutrition" or malnourish* or undernutrition or undernourish* or underfeeding or "nutritional deficienc*" or "nutrition deficienc*" or "protein calorie malnutrition" or "nutritional assessment" or "nutrition status" or "nutritional status" or "nutrition risk" or "nutritional risk":ti,ab,kw (Word variations have been searched)	4686
#6	#1 or #2 or #3 or #4 or #5	6199
#7	MeSH descriptor: [Questionnaires] explode all trees	17372
#8	questionnair* or screen* or assess* or scale or score* or checklist or form or tool or tools or evaluation or rating or monitor* or index or indices:ti,ab,kw (Word variations have been searched)	451157
#9	#7 or #8	451238
#10	#9 and #6	4113
#11	MeSH descriptor: [Intensive Care] explode all trees	1159
#12	MeSH descriptor: [Intensive Care Units] explode all trees	2640
#13	MeSH descriptor: [Critical Care] explode all trees	1856
#14	"intensive care" or "intensive care unit" or "Critical Care" or "critical illness*" or "critically ill" or "surgical intensive care" or "medical intensive care" or "respiratory care unit" or "special care unit":ti,ab,kw (Word variations have been searched)	11586
#15	#11 or #12 or #13 or #14	11815
#16	#15 and #10	110
#17	MeSH descriptor: [Adolescent] explode all trees	76828
#18	MeSH descriptor: [Child] explode all trees	133
#19	MeSH descriptor: [Infant] explode all trees	13271
#20	MeSH descriptor: [Pediatrics] explode all trees	544
#21	MeSH descriptor: [Pregnant Women] explode all trees	97
#22	adolescent or child* or infant or adolescen* or infant* or pediatr* or paediatr* or pregnant or pregnanc*:ti,ab,kw (Word variations have been searched)	176459
#23	#17 or #18 or #19 or #20 or #21 or #22	176467
#24	#16 not #23	82

Appendix-2

PubMed search conducted on 2nd May 2015

No	Search terms	Results
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#2	("Questionnaires"[Mesh] OR questionnair*[tiab] OR screen*[tiab] OR assess*[tiab] OR scale[tiab] OR score*[tiab] OR checklist[tiab] OR form[tiab] OR tool[tiab] OR tools[tiab] OR evaluation[tiab] OR rating[tiab] OR monitor*[tiab] OR index[tiab] OR indices[tiab])	5,196,332
#3	#1 AND #2	91,873
#4	adductor pollicis[tiab]	1,048
#5	#3 AND #4	29

CINAHL search conducted on 2nd May 2015

No	Search terms	Results
#1	(MH "Malnutrition") OR "malnutrition" OR (MH "Protein-Energy Malnutrition") OR (MH "Nutritional Status") OR "Nutritional Status" OR (MH "Nutritional Status (Iowa NOC)") OR (MH "Nutritional Assessment") OR AB malnourish* OR TI malnourish* OR TI undernutrition OR AB undernutrition OR TI undernourish* OR AB undernourish* OR TI protein energy malnutrition OR AB protein energy malnutrition OR TI protein calorie malnutrition OR AB protein calorie malnutrition OR TI nutrition status OR AB nutrition status OR TI nutritional status OR AB nutritional status OR TI nutrition risk OR AB nutrition risk OR TI nutritional risk OR AB nutritional risk OR TI nutrition OR AB nutrition OR TI nutritional OR AB nutritional)	50,486
#2	(TI Questionnaires OR AB Questionnaires OR TI screen* OR AB screen* OR TI assess* OR AB assess* OR TI scale OR AB scale OR TI score* OR AB score* OR TI checklist OR AB checklist OR TI form OR AB form OR TI tool OR AB tool OR TI tools OR AB tools OR TI evaluation OR AB evaluation OR TI rating OR AB rating OR TI monitor* OR AB monitor* OR TI index OR AB index OR TI indices OR AB indices)	565,070
#3	#1 AND #2	17,750
#4	TI adductor pollicis OR AB adductor pollicis	39
#5	#3 AND #4	8

Scopus search conducted on 2nd May 2015

No	Search terms	Results
#1	(TITLE-ABS-KEY (malnutrition) OR TITLE-ABS-KEY ("Nutritional Status") OR TITLE-ABS-KEY ("Nutrition Assessment") OR TITLE-ABS-KEY ("Protein-Energy Malnutrition") OR TITLE-ABS-KEY (malnourish*) OR TITLE-ABS-KEY (undernutrition) OR TITLE-ABS-KEY (undernourish*) OR TITLE-ABS-KEY ("protein calorie malnutrition") OR TITLE-ABS-KEY ("nutrition status") OR TITLE-ABS-KEY ("nutrition risk") OR TITLE-ABS-KEY ("nutritional risk") OR TITLE-ABS-KEY (nutritional) OR TITLE-ABS-KEY (nutrition))	496,604
#2	(TITLE-ABS-KEY (questionnaires) OR TITLE-ABS-KEY (screen*) OR TITLE-ABS-KEY (assess*) OR TITLE-ABS-KEY (scale) OR TITLE-ABS-KEY (score*) OR TITLE-ABS-KEY (checklist) OR TITLE-ABS-KEY (form) OR TITLE-ABS-KEY (tool) OR TITLE-ABS-KEY (tools) OR TITLE-ABS-KEY (evaluation	12,940,626

	) OR TITLE-ABS-KEY (rating) OR TITLE-ABS-KEY (monitor) OR TITLE-ABS-KEY (INDEX) OR TITLE-ABS-KEY (indices))	
#3	#1 AND #2	179,475
#4	(TITLE-ABS-KEY ("adductor pollicis"))	1,198
#5	#3 AND #4	36

Ethics application

Study Reference Number: 2014/00878

Version Number: 1

Please select the appropriate form for submission to the DSRB. Please refer to the explanatory notes below if you need more information.

◉ DSRB Application Form 1 - Non Exempt Category ○ DSRB Application Form 2 - Exempt Category

Research activities in which the only involvement of human subjects will be in one or more of the following categories may be able to qualify for the Exempt category.

Please click on the DSRB Application Form 2 - Exempt Category option above to view the categories.

DSRB Application Form 1 - Non Exempt Category

Principal Investigators should use Application Form 1 if their research activity does not qualify under the Exempt Category. Application Form 1 should be used for submissions for the Full Board Review and Expedited Review.

DSRB Application Form 2 - Exempt Category

Research activities in which the only involvement of human subjects will be in one or more of the following categories may be able to qualify for the Exempt category.

IMPORTANT: The criteria for the Exempt category do not apply when the research activity:

(i) involves prisoners

(ii) involves children, when the research involves survey or interview procedures or observations of public behavior, except when the investigator(s) do not participate in the activities being observed

(iii) is a US FDA-regulated research activity.

Ethics Main Application Form (Section A - Study Title & Study Administrators)

A1 Please enter the full title for this study.

The development of Global Index of Mortality Probability in the Severely ill – a new perspective in mortality prognostication and nutrition support

A2 Study Administrators are persons who are responsible for administrative matters related to the Study. They can be the Study Coordinators, Research Nurses or Clinical Research Associates, and need not be part of the Study Team.

While the Principal Investigator remains the primary contact person, the DSRB may contact the Study Administrators for clarification of administrative matters related to the Study.

Study Administrators may also assist the PI in drafting the various online forms and reports, however, only the PI may 'submit' these online forms and reports to the DSRB.

This section is optional but PI's are encouraged to nominate at least one Study Administrator. You may assign Study Administrators for this study below.

Ethics Main Application Form (Section B - Study Team & Submission Domain)

B1 Study Sites & Study Team Members

All investigators who have a responsibility for the consent process and/or direct data collection for this study should be listed below.

Study Team Members with registered user account with us will be notified of their participation in this study when the Application is submitted.

For a Multi-centre study, please appoint a Site PI for each site (Mandatory).

The Principal Investigator will be the Site PI for their own Institution, and will also be the primary contact person for the DSRB.

(i) 'Overall Principal Investigator': Chin Han Charles Lew

(ii) Study Sites under the oversight of NHG DSRB Click here for help

	Study Site	Name	Study Role	Institution	Department	Min Training
1	Alexandra Hospital	Mr Chin Han Charles Lew	PI	Alexandra Hospital	Allied Health Division	Completed
2	Alexandra Hospital	Dr Ai Ping Chua	Co-Investigator	National University Hospital	Medicine	Completed
3	Alexandra Hospital	Mary Foong Fong Chong	Collaborator	Agency for Science, Technology and Research	Singapore Institute for Clinical Sciences	-
4	Alexandra Hospital	Michelle Miller	Collaborator	Flinders University	Nutrition and Dietetics	-

5	Alexandra Hospital	Robert Fraser	Collaborator	Flinders University	Gastroenterology and Hepatology	-
6	Alexandra Hospital	Dr Chee Keat Tan	Co-Investigator	Alexandra Hospital	Intensive Care Medicine	Completed
7	Alexandra Hospital	Dr Chuen Seng Tan	Co-Investigator	NUS - Saw Swee Hock School of Public Health	NUS - Saw Swee Hock School of Public Health	Completed

(iii) Other external Study Sites under the supervision of the 'Overall Principal Investigator' (eg. Nursing Home, Community Hospitals, Community Centres etc)

B2 External Study Site (for Institutions NOT under the oversight of NHG DSRB)

(i) Are there any other independent study sites by another PI which are conducting the same study?

◉ Yes No

B3 Research Specialty

Please select the Primary Specialty, and then choose the relevant Sub specialty that has been matched according to the Primary Specialty selected. If the Primary Specialty and/or Sub specialty cannot be found from the list, please choose 'Others' and specify.

No.	**Primary Specialty**	**Primary Sub Specialty**
1	Nutrition & Dietetics	Nutritional assessments

Please indicate/add Secondary Specialties.

No.	Primary Specialty	Primary Sub Specialty	Others
1	Respiratory & Critical Care Medicine	Others	

B4

i. Which Domain Specific Review Board (DSRB) is this application being submitted to?
DSRB Domain D

ii. Has the study been submitted to another IRB?

◉ No

○ Yes

iii. Has the application been previously rejected by any IRB? (Including NHG-DSRB)

- No
○ Yes

Ethics Main Application Form (Section C - Conflict of Interest Declaration)

With effect from 1 January 2015, all study team members involved in the design, conduct or reporting of the research are required to complete and endorse a Conflict of Interest Declaration Form annually to the DSRB Financial Conflict of Interest (FCOI) Secretariat. This declaration includes any conflicts of interest of their immediate family members (includes parents, siblings, spouse and each dependent child).

The annual Conflict of Interest Declaration Cycle will be from 01 Jan to 31 Jan of the year and the declaration will be valid from 1 Jan to 31 Dec of the same year. The Conflict of Interest Declaration Form may still be submitted beyond the Declaration Cycle.

However, the declaration will only be valid until the next Declaration Cycle. The Conflict of Interest Declaration Form can be downloaded from https://www.research.nhg.com.sg/wps/wcm/connect/romp/nhgromp/hspp/financial+conflict+of+interest/fcoi+policy

An updated Conflict of Interest Declaration Form must be submitted to the FCOI Secretariat as soon as possible but no later than 30 days if any of the circumstances relevant described herein change during the conduct of the research.

Mr Chin Han Charles Lew (Principal Investigator)

○ Yes • No

Dr AI PING CHUA (Co-Investigator)

○ Yes • No

Dr Chee Keat Tan (Co-Investigator)

○ Yes • No

Dr Chuen Seng Tan (Co-Investigator)

○ Yes • No

Please attach the Study Team Member List if there are any study team members (study coordinators, biostatisticians etc.) involved in the design, conduct and reporting of the research, who are not listed in Section B and C of the DSRB Application Form.

Ethics Main Application Form (Section D - Nature of Research)

This is a smart form. The choice you make here will determine which sections of the application form will appear.

Clinical Trials

Choose this if your research involves:

(1) Administering a drug, device, or biologic as part of the research intervention, or

(2) Performing surgical procedures as part of research intervention

Questionnaire/ Survey/ Interviews

Choose this if your research involves:

(1) Administering questionnaires/surveys/interviews. This type of research may also include a medical records review component.

Medical Records Review

Choose this if your research involves:

(1) Collection of data for a specific research project by review of medical records including results of routine diagnostic tests performed for standard clinical purposes

(2) Prospective and/or retrospective data collection

Clinical Research

Choose this if your research involves:

(1) Collection of blood by venepuncture, finger stick, etc or

(2) Prospective collection of biological specimen by invasive or non-invasive means including biopsies, FNAC's, fundoscopy etc or

(3) Collection of data through research procedures such as X rays, MRI, ultrasound, ECG, EEG, etc

or

(4) Any other research categories that are not listed in the options above.

D1 Please select one category that best describes your research activities.

- ○ Clinical Trials (which includes Drug, Device and Surgical-Procedure Trials)
- ○ Questionnaire/ Survey/ Interviews
- ○ Medical Records Review
- Clinical Research

Note: Clinical Trial Certificate from Health Sciences Authority might be required if you are testing the safety and efficacy of the medicinal product. You should check with HSA if you are unsure.

D2 Is this a US FDA IND/IDE study or data is intended to be reported to FDA in support of a IND/ IDE application?

- ○ Yes • No

Note: US FDA-regulated (IND) research activities cannot qualify for Exemption from DSRB Review and Waiver of Informed Consent. The application must be submitted using the DSRB Application Form 1 - Non Exempt Category.

D3 Is this study subjected to any of the following regulations:

- No ○ Yes

☐ US Code of Federal Regulations 45 CFR 46

☐ US Code of Federal Regulations 21 CFR 50

☐ US Code of Federal Regulations 21 CFR 56

☐ US Code of Federal Regulations 21 CFR 312

☐ US Code of Federal Regulations 21 CFR 812

☐ Others

Ethics Main Application Form (Section E - Study Funding Information)

E1 Who will be responsible for the payment and compensation of injury or illness arising from participation of subjects in the study?
The PI should ensure that insurance coverage is available to provide payment and compensation to research subjects for injury or illness arising from their participation in the study.

(Note: For investigator-initiated studies - Contact your OBR/CRU for more information on available NHG Clinical Trial Compensation Insurance Scheme.

For Sponsored Studies - Sponsors should be primarily responsible for ensuring that subjects receive payment and compensation in the event of injury or illness as a result of their participation in a research study.)

NHG Clinical Trial Compensation Insurance Scheme.

E2 Please give information regarding the study's funding source or Sponsor information.

- No funding is required for this study to be carried out ○ Pharmaceutical / Industry Sponsored

○ Grant

E3 Who will be responsible for research-related costs? For sponsored studies, please list the costs that will be borne by the sponsor. You may wish to attach the Financial Agreement / Clinical Trial Assurance if it is available. * Click here for help

No funding is required

Subject identification Log (Version 1).docx
Data collection form (Version 1).docx
Data collection form for nutritional assessment (Version 1).docx
Data collection form for nutrition support (Version 1).docx

Ethics Main Application Form (Section F - Research Methodology)

F1 Please provide an abstract of your proposed research (Up to 300 words).

Your abstract must contain:

Aims
Methodology
Importance of proposed research to science or medicine

Potential benefits & risks

BACKGROUND Mortality prognostic models such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), (1) Nutrition Risk in the Critically Ill Score (NUTRIC Score) (2), Simplified Acute Physiology Score 3 (SAPS 3) (3, 4), Multiple Organ Dysfunction Score (MODS) (5), and Sequential Organ Failure Assessment (SOFA) (6) are important in intensive care practice and research. In practice, Intensive Care Units (ICU) within and across institutions use such models for audits and performance comparisons. For research, mortality prognostic models are often used for patient selection, risk stratification and/or statistical adjustment. These help to reduce the confounding effects of disease severity on treatment outcomes. Like other public hospitals in Singapore, the ICU of Alexandra hospital uses the

APACHE II. This is of dire concern as the APACHE II (1) was validated in Singapore more than 20 years ago (7) and recent studies clearly showed that it has poor prognostic value (8, 9). Although there are other prognostic models (2-6) that could be used in place of the APACHE II (1), their prognostic value in the local setting is yet to be determined. Therefore, there is an urgent need to audit the performance of the APACHE II, and determine the most predictive prognostic model among existing models. If the performance of the APACHE II and other prognostic models are unsatisfactory, this quality improvement project aims to development of a new prognostic model [Global Index of Mortality Probability in the Severely ill (GLIMPSE)] to better quantify the hospital mortality risk of patients. Existing prognostic models (3-6) generally use conventional predictive variables such as physiological variables, medical history, admission diagnosis and/or medical treatment to predict mortality. In contrast, GLIMPSE will integrate conventional predictive variables with nutritional status and/or anthropometry measurement [measured by the 7-point Subjective Global Assessment (7-point SGA) (10) and/or the thickness of the adductor pollicis muscle (TAPM) (11) respectively] to better quantify hospital mortality risk. It is hypothesized that the inclusion of nutritional status and/or anthropometry measurement can improve mortality prognostication as recent studies have consistently shown that they are independently associated with mortality (11-13). Heyland, Dhaliwal (2) observed reduced odds of 28-day mortality when malnourished patients with high mortality risk were fed to requirement. However, the opposite was observed in well-nourished patients with low mortality risk. Since GLIMPSE integrates nutritional status and conventional predictive variables, it may also be used to determine if the benefits of meeting patients' caloric or protein requirements is dependent on their global mortality risk. This audit/ quality improvement project aims to 1) to audit the prognostic value of the existing models (1-6), and 2) improve prognostication of hospital mortality by developing and validating a new prognostic model (GLIMPSE). METHODOLOGY Variables needed to audit the existing prognostic models (1-6) are routinely measured and recorded in the ICU. An audit/ quality improvement project will be carried out to compare the prognostic value of the existing models (1-6). To improve the prognostication of hospital mortality, the most predictive prognostic model will be combined with nutritional status, malnutrition risk and/or TAPM as recent studies have demonstrated that they are independently associated with mortality (11-13).IMPORTANCE OF PROPOSED RESEARCH TO SCIENCE OR MEDICINE Public hospitals in Singapore use

the APACHE II for audits and comparisons of ICU performance. However, the latter may be inflated as recent studies have clearly shown that the APACHE II overestimates mortality risk (8, 9). Therefore, there is an urgent need to audit the performance of the APACHE II, determine a better predictive prognostic model (1-6) and develop a new prognostic model. For research, a model with good prognostic value will help to reduce the confounding effects of disease severity on treatment outcomes. POTENTIAL BENEFITS amp; RISKS. This audit/ quality improvement project will have all data and subjects de-identified. Hence, there is minimal risk for the patients.

F2 What are the Specific Aims of this study?

a) Audit the prognostic value of existing mortality prognostic models (1-6) for hospital mortality, ICU mortality, 28-day new ICU acquired infection, 28-day ventilator-free days as well as ICU and hospital length of stay. b) Improve prognostication of hospital mortality by developing and validating GLIMPSE (Global Index of Mortality Probability in the Severely Ill).c) Determine if calorie and protein intake modify the association between GLIMPSE score and hospital mortality. d) Determine the prevalence of malnutrition in the ICU.

F3 What is the Hypothesis of this study?

HYPOTHESES a) The existing mortality prognostic models (1-6) have poor discriminative value, calibration accuracy and association with hospital mortality, ICU mortality, 28-day new ICU acquired infection, 28-day ventilator-free days as well as ICU and hospital length of stay. b) GLIMPSE has better discriminative value and calibration accuracy for hospital mortality than existing models. c1) Amongst patients with low glimpse scores, achieving calorie and protein intake consistent with recommendations is positively associated with mortality risk. c2) Amongst patients with high glimpse scores, achieving calorie and protein intake consistent with recommendations is negatively associated with mortality risk. d) At least 30% of the critically ill patients are malnourished.

F4 Please briefly describe the background to the current study proposal. Critically evaluate the existing knowledge and specifically identify the gaps that the proposed study is intended to fill.

Limited data on the validity of existing mortality prognostic model used in the Singapore ICU: The APACHE II (24) was developed in 1985 and it was validated in Singapore in 1991 (7). As with all prognostic models that require constant re-calibration, newer versions of the APACHE were developed in 1991 (APACHE III) (14) and 2006 (APACHE IV) (15). In spite of the newer versions, Alexandra Hospital, like other public hospitals in Singapore continues to use the APACHE II for audits and comparisons of ICU performance. This is of dire concern as a study carried out in 2013 showed that the APACHE II overestimated mortality risk by up to 60% (8). This may decrease the validity of audits as an overestimation of mortality risk will inflate the performance of the ICU. The inaccuracy of the APACHE II was also clearly demonstrated in recent large RCTs (16-19) where similar APACHE II scores resulted in vastly different mortality rates (e.g. studies with APACHE II score of 22 had mortality rate ranged from 6% to 21%). Although the newer version of the APACHE II (i.e. APACHE III) may theoretically have better prognostic ability, a large multi-centered trial performed by Paul, Bailey (20) showed that its performance had also deteriorated significantly (20). This was largely due to advances in treatments during the 10 year period (2000-2009), and since the APACHE III model did not account for the treatment improvements, the reduction in mortality rates over time resulted in poor calibration accuracy. Instead of the APACHE model, there are other prognostic models (2-6) that could be used in the ICU. However, their prognostic value in the local setting is yet to be determined. Therefore, there is an urgent need to audit the performance of the APACHE II, and determine the most predictive prognostic model. Combining disease severity and nutritional status in mortality prognosis: The Subjective Global Assessment (SGA) (21) is a validated nutritional assessment tool that is widely used in the clinical setting. To date, there are five prospective studies that used the SGA to investigate the association between ICU malnutrition and mortality (11-13, 22, 23). Amongst them, three well-performed prospective studies found malnutrition to be independently associated with mortality (11-13). Although both Sungurtekin, Sungurtekin (23) and Coltman, Peterson (22) also prospectively demonstrated that malnutrition was associated with mortality, the conclusion could be strengthened if disease severity was

adjusted in the analysis. The collective evidence from the studies suggests that malnutrition is an independent predictor of mortality. Therefore, patients' nutritional status and disease severity measured by the most predictive existing mortality prognostic model could be combined to provide a global assessment of hospital mortality risk. The function of such a prognostic model [Global Index of Mortality Probability in the Severely Ill (GLIMPSE)] is similar to those of logistic euroSCORE (24) in cardiac trials. In this instance, the logistic euroSCORE is used in place of other prognostic models since cardiac patients require cardiac related variables to accurately quantify their mortality risk. On the same token, nutrition trials in the ICU should use a specific prognostic model that accounts for nutritional status when quantifying mortality risk. This is where GLIMPSE may be applicable. The GLIMPSE model may benefit future ICU nutrition trials as it accounts for nutritional status when quantifying baseline global mortality. The latter can be used for patient selection, risk stratification and/or statistical adjustment to reduce the confounding effects of disease severity on treatment outcomes. Heyland, Dhaliwal (2) observed reduced odds of 28-day mortality when malnourished patients with high mortality risk were fed to requirement. However, the opposite was observed in well-nourished patients with low mortality risk. Since GLIMPSE integrates nutritional status and conventional predictive variables, it may also be used to determine if the benefits of meeting patients' caloric or protein requirements is dependent on their global mortality risk. Limited data on the prevalence of malnutrition in the Singapore ICU: The prevalence of malnutrition in the ICU was found to vary widely, ranging from 23.3% to 78.0% (11-13, 22, 23). A local study which excluded critically ill patients found that 1 in 3 patients in the general ward was malnourished (25). For effective planning of manpower and resources, it is important to determine the prevalence of malnutrition in our ICU.

F5 Please provide a list of relevant references.

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical care medicine. 1985;13(10):818-29.2. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Critical care. 2011;15(6):R268.3. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1:

objectives, methods and cohort description. Intensive care medicine. 2005;31(10):1336-44.4. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive care medicine. 2005;31(10):1345-55.5. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Critical care medicine. 1995;23(10):1638-52.6. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/ failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine. 1996;22(7):707-10.7. Lee KH, Hui KP, Lim TK, Tan WC. Acute physiology and chronic health evaluation (APACHE II) scoring in the medical intensive care unit, National University Hospital, Singapore. Singapore medical journal. 1993;34(1):41-4.8. Kim JY, Lim SY, Jeon K, Koh Y, Lim C-M, Koh SO, et al. External validation of the acute physiology and chronic health evaluation II in Korean intensive care units. Yonsei medical journal. 2013;54(2):425-31.9. Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, Bosman RJ, Peelen L, et al. External validation of acute physiology and chronic health evaluation IV in Dutch intensive care units and comparison with acute physiology and chronic health evaluation II and simplified acute physiology score II. Journal of critical care. 2011;26(1):105. e11-. e18.10. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Journal of the American Society of Nephrology: JASN. 1996;7(2):198-207.11. Caporossi FS, Caporossi C, Borges Dock-Nascimento D, de Aguilar-Nascimento JE. Measurement of the thickness of the adductor pollicis muscle as a predictor of outcome in critically ill patients. Nutricion hospitalaria. 2012;27(2):490-5.12. Fontes D, Generoso SDV, Toulson Davisson Correia MI. Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients. Clinical nutrition. 2014;33(2):291-5.13. Sheean PM, Peterson SJ, Chen Y, Liu D, Lateef O, Braunschweig CA. Utilizing multiple methods to classify malnutrition among elderly patients admitted to the medical and surgical intensive care units (ICU). Clinical nutrition. 2013;32(5):752-7.14. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100(6):1619-

36.15. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Critical care medicine. 2006;34(5):1297-310.16. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA: the journal of the American Medical Association. 2013;309(20):2130-8.17. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385-93.18. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. The New England journal of medicine. 2011;365(6):506-17.19. Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive care medicine. 2011;37(4):601-9.20. Paul E, Bailey M, Van Lint A, Pilcher V. Performance of APACHE III over time in Australia and New Zealand: a retrospective cohort study. Anaesthesia and intensive care. 2012;40(6):980-94.21. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN Journal of parenteral and enteral nutrition. 1987;11(1):8-13.22. Coltman A, Peterson S, Roehl K, Roosevelt H, Sowa D. Use of 3 tools to assess nutrition risk in the intensive care unit. JPEN Journal of parenteral and enteral nutrition. 2014.23. Sungurtekin H, Sungurtekin U, Oner O, Okke D. Nutrition assessment in critically ill patients. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2008;23(6):635-41.24. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. European heart journal. 2003;24(9):881-2.25. Lim SL, Tong CY, Ang E, Lee EJ, Loke WC, Chen Y, et al. Development and validation of 3-minute nutrition screening (3-MinNS) tool for acute hospital patients in Singapore. Asia Pacific journal of clinical nutrition. 2009;18(3):395-403.26. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? Bmj. 2009;338.27. Khwannimit B, Bhurayanontachai R. The performance of customised APACHE II and SAPS II in predicting mortality of mixed critically ill patients in a Thai medical intensive care unit. Anaesthesia and intensive care. 2009;37(5):784-90.28. Fadaizadeh L, Tamadon R, Saeedfar K, Jamaati HR. Performance assessment of acute

physiology and chronic health evaluation II and simplified acute physiology score II in a referral respiratory intensive care unit in Iran. Acta Anaesthesiologica Taiwanica. 2012;50(2):59-62.29. Faruq MO, Mahmud MR, Begum T, Ahsan AA, Fatema K, Ahmed F, et al. A comparison of severity systems APACHE II and SAPS II in critically ill Patients. Bangladesh Critical Care Journal. 2013;1(1):27-32.30. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC bioinformatics. 2011;12:77.31. Hosmer DW, Lemesbow S. Goodness of fit tests for the multiple logistic regression model. Communications in Statistics-Theory and Methods. 1980;9(10):1043-69.32. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis: Springer; 2001.33. Ridgeway G. The state of boosting. Computing science and statistics. 1999:172-81.34. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition. 2004;20(10):843-8.

F6 Please submit a copy of at least two relevant papers.

NUTRIC Score.pdf

Paul 2012 - Performance of APACHE III over time in Australia and New Zealand a retrospective cohort stud.pdf

Sheean 2013 - Utilizing multiple methods to classify malnutrition among elderly patients admitted to the medical and surgical intensive care units (ICU).pdf

Fontes 2013 - Subjective global assessment: A reliable nutritional assessment tool to predict outcomes in critically ill patients.pdf

Caporossi 2012 - Measurement of the thickness of the adductor pollicis muscle as a predictor of outcome.pdf

F7 Please state concisely the importance of the research described in this application by relating the specific aims to the long term objectives.

We aim to audit the prognostic value of current mortality prognostic models (1-6), and improve prognostication of hospital mortality by developing and validating Global Index of Mortality Probability in the Severely Ill (GLIMPSE). Existing prognostic models generally use physiological variables, medical history, admission diagnosis and/or medical treatment to predict mortality. In contrast, GLIMPSE will integrate nutritional status and/or anthropometry measurement with conventional predictive variables to better quantify mortality risk. It is hypothesized that the inclusion of nutritional status and/or anthropometry measurement can improve mortality prognostication since recent studies have consistently shown that they are independently associated with mortality (11-13).

The improved prognostic value of GLIMPSE would reduce the confounding effects of disease severity on treatment outcomes and hence, improve the validity of audits and performance comparisons of the ICUs within and across institutions.

F8 Discuss in detail the experimental design and procedures to be used to accomplish the specific aims of the study. (If this study involves a retrospective medical record review, please specify the period of data collection.) Note: W.e.f. 15 July 2015, all research studies submitted from National University Hospital (NUH) involving the use of radioactive materials and/or radiation-emitting equipment WHICH DO NOT COMPLY WITH THE RSC GUIDELINES will need to obtain approval from the NUH Radiation Safety Committee (RSC) prior to commencement of the study. For a copy of the 'Radiation Safety Guidelines for NUH', please download from http://nuhs-portal/wbn/slot/ u3196/Clinical%20Research/Radiation%20Safety%20Research%20Guidelines%20for %20NUH %20(rev%20dec%2014)20150629.pdf. For more information, please contact NUHS Research Office (clinical_research@nuhs.edu.sg).

The audit will be conducted in a 74-bed ICU which provides care for patients from the surgical, medical, cardiology, neurology, and trauma discipline. Data collection period will be from 3rd August 2015 to 30th April 2017. We will periodically retrieve all required data

from the electronic medical record (EMR). We choose this form of data collection given the large number of ICU beds and limited manpower. DATA COLLECTION PROCEDURE All data required will be routinely measured and recorded in the EMR. For example, the EMR will automatically calculate and document the APACHE II as well as the daily calorie and protein intake of all patients. Data needed: All data needed for the audit/ quality improvement project are routinely measured and automatically recorded in the electronic medical records as part of standard care. None of the data needed for the audit/ quality improvement project are measured and recorded for the purpose of the audit/ quality improvement project. The data that would be retrieved are: neurological variables (Glasgow coma scale), cardiovascular variables (mean arterial pressure, heart rate, doses of vasopressors, pressure adjusted heart rate, and systolic blood pressure), renal variables (urine output, presence of acute kidney injury, and serum sodium, potassium, creatinine, pH, bicarbonate and urea), respiratory variables (respiratory rate, FiO2, PaCO2, and PaO2), haematological variables (haemoglobin, haematocrit, white blood count, platelets, and prothrombin time), hepatic variables (albumin and bilirubin), prior admission variables (location, use of vasopressin, and length of stay), variable at admission (reason for ICU admission, ICU admission diagnosis, presence of nosocomial infection and respiratory infection), surgical variables (nil surgery, emergency or elective surgery performed), comorbidities (presence of dialysis, respiratory disease, AIDS, metastatic cancer, cancer treatment, liver disease, NYHA class IV heart disease, haematological cancers, and total number of comorbidities), nutritional intake (enteral calorie and protein intake, parenteral calorie and protein intake, oral calorie and protein intake, duration of nil-by-mouth, clear feeds and/or full feeds, and diet type), glycaemic control variables (mean blood glucose levels, morning blood glucose levels, number of hypoglycaemic events, and insulin dose per day), other prognostic variables (temperature, presence of gastrointestinal bleeding, ICU readmission, and age), mortality outcomes (ICU and hospital), length of stay (ICU and hospital), nutritional variables (nutritional status and TAPM measurements), and other clinical outcomes (28-day ventilator-free days and 28-day new infection in the ICU).The following describes the data collection procedure:• On a quarterly basis, ICU patients who are discharged or died during their hospital stay will be identified via the hospital census. The Subject Screening and Enrolment Log will be used to identify cases that are eligible for the audit/ quality improvement project. • We have generated 10000 unique codes starting from 1000831 to 1010831 without duplicates. A unique code will

be assigned to each patient and it will be used in the Subject Screening and Enrollment Log.• Eligible patients will have their unique code, name, date of birth, Identity Card number, and medical record number recorded in the Subject Identification Log.• All the required information of eligible patients will be retrieved from the EMR and documented in the Data Collection Form, Data Collection Form for Nutrition Support and Data Collection Form for Nutritional Assessment. All three forms will not contain any subject identifiers. In order to increase the level of confidentiality, the unique codes on the three forms will be encrypted. To encrypt the unique codes, we will multiply the unique codes by a factor of five. Thereafter, five will be added to the derivatives. For example, a unique code of 1000831 on the Subject Screening and Enrollment Log will be recorded as 5004160 [(1000831 X 5) +5)] in the Data Collection Form, Data Collection Form for Nutrition Support and Data Collection Form for Nutritional Assessment. • A spreadsheet will be created to electronically record the data. Encrypted unique codes will be used in the spreadsheet to maintain confidentiality. To increase the accuracy of data entry, each variable in the spreadsheet will be programmed to have acceptable limits.

F9 Please provide details on sample size and power calculation and the means by which data will be analysed and interpreted (If applicable). * Click here for help

Sample size for the training set of GLIMPSE:• To develop and validate the GLIMPSE model, patients' data will be randomly split into training (80%) and validation (20%) sets respectively. According to our ICU census from 2011 to 2013, the mortality rate ranged from 10% to 20%. If there were to be 20 variables in the GLIMPSE model, and the mortality rate between 2015 and 2016 is 10%, 15% or 20%, we would require 2000, 1333 or 1000 subjects respectively. This is assuming that each prognostic variable requires at least 10 events (i.e. deaths) (26). Sample size for the validation set of GLIMPSE:• All the ICUs in the Singapore public hospitals use the APACHE II prognostic model (1). Hence, the published Area under the ROC (Receiver Operating Characteristic) curve (AUC) of the APACHE II will be used to calculate the required sample size. Given the deteriorating prognostic value of the APACHE (20), we limited our literature search in Scopus to articles published within the last 5 years (2009-2013). With "APACHE II" as the search term for article title, and limiting the subject area and language to "Medicine" and "English", we found 67 articles. Amongst them, only

five studies measured the AUC of the APACHE II in all critically ill patients (8, 9, 27-29). Expectedly, the AUC deteriorated from 0.915 in 2009 (27) to 0.729 in 2013 (8). If the mortality rate between 2015 and 2016 is 10%, 15% or 20%, we would require 182, 127 or 100 subjects respectively. This is derived from the pROC model (30) in R version 3.1.0 with the assumption that the AUC of the APACHE II is 0.75 (29) and the chances of committing a type 1 and type 2 error are 5% each. Total sample size of GLIMPSE:• Summing up the number of subjects needed for the training and validation set of GLIMPSE, we would require 2182, 1460 or 1100 subjects if the mortality rate between 2015 and 2016 is 10%, 15% or 20% respectively. According to our projection, there would be about 1200 and 1950 admissions in 2015 and 2016 respectively. Therefore, we would need about 1.5 years to have an adequate number of case-reviews. Data analysis:• Descriptive data will be summarized as mean (SD), median (interquartile range), or percentage as appropriate. Comparing of categorical variables will be carried out by Chi-square tests and continuous variables by Student t test and Mann-Whitney test.• Objectives (a): Discriminative value will be assessed via the area under the receiver operating characteristic curve (AUROC) whereas calibration accuracy will be assessed by the calibration curve, Hosmer-Lemeshow C and H test (31) as well as the standardized mortality ratio (SMR). Associations between continuous dependent variables and other independent variable will be assessed via a series of stepwise multiple linear regressions. Association between dichotomous dependent variables and other covariates will be assessed by multivariate logistic regression. • Objective (b): Patients' data will be randomly split into training (80%) and validation (20%) sets. To develop a parsimonious GLIMPSE model, two approaches will be adopted. In the first approach, disease severity measured by the existing prognostic models (1-6) will be used as composite scores. In the second approach, all patients' variables will be mutually exclusive. Both approaches will share identical subsequent statistical analyses to develop the final model. The final model of both approaches will be compared using the Akaike information criterion (AIC) to compare their overall fit and provide evidence to favour one model over another. Development of the GIMPSE model involves three steps. Firstly, the Chi-square test and t-test would be used respectively to identify categorical and continuous variables that are associated (i.e. $p < 0.20$) with hospital mortality. Thereafter, linearity of the relationships between the identified continuous candidate variables and hospital mortality will be checked using restricted cubic regression splines (32). Variables with nonlinear relationship will have appropriate cut-off points

identified by knots, resulting in mutually exclusive categories of continuous variables. In the case of categorical variables, they will be collapsed according to their univariate hospital mortality levels using multidimensional tables and clinical judgement as appropriate. Thereafter, regression trees (33) will be applied to identify the appropriate cut-off points. Secondly, since the data may be clustered due to the different specialized ICUs, the GLIMPSE model will be developed by including all identified candidate variables in a multivariate logistic regression with robust variance estimators. This is to provide better variance estimates and confidence intervals. In addition, given that each candidate variable may modify the effects of another candidate variable, interactions will be checked in a series of stepwise regressions. If interaction is detected and the model with solely additive effects did not achieve acceptable calibration, interaction effects will be included. The a priori criteria for model performance will be = 0.75 for AUROC, $p > 0.05$ with the Hosmer-Lemeshow goodness-of-fit statistics, and slope and intercept that do not significantly differ from 1 and 0 respectively on the Hosmer-Lemeshow decile calibration plot. Lastly, the model with the overall best fit as evident by the AIC will be the final model for validation evaluation. To validate the latter, the final model will be applied to the validation set. Discriminative value will be assessed via the AUROC and calibration accuracy will be assessed by the calibration curve, Hosmer-Lemeshow C and H test (31) as well as the SMR. The a priori criteria for model performance in the validation set will be identical to those of the training set. Objective (c): In view of the on-going debate on the efficacy of enteral and parenteral nutrition (17, 18, 34), data analyses will be stratified into two groups. The first group will be patients who were provided with parenteral nutrition, either solely or in combination with enteral nutrition, and the second group will comprise of patients who were provided with enteral nutrition, either solely or in combination with diet. To examine if hospital mortality risk could be modified by the percentage of calorie and protein requirement received, logistic regression with the percentage of calorie and protein requirement received, GLIMPSE score and their product as continuous covariates will be used to generate two plots – one for percentage of calorie requirement received, the other for percentage of protein requirement received. The two plots will be used to determine if the percentage of calorie and protein requirement received modifies the association between GLIMPSE score and hospital mortality. Since the timing of feed initiation (< 48 vs > 48 hours) may be a possible confounder, it will be included as a covariate in the logistic regression. To assess the presence of interaction, a likelihood ratio

test will be performed. • Objective (d): Prevalence of "well nourished" (7-point SGA score < 3), "moderately malnourished" (7-point SGA score 3-5), severely malnourished (7-point SGA score > 5), and those who are both moderately and severely malnourished (7-point SGA score > 2) will be summarized. Prevalence of malnutrition will be stratified by discipline (i.e. medical vs surgical). A bi-nomial test will be carried out to determine if the prevalence of malnutrition is significantly more than 30%.

F10 List all activities that are carried out as part of research in this study. Please state/list all procedures involved in this research study and attach the data collection form (if any) which will be used for DSRB review. The data collection form should be attached under "Attachments" tab, Section "Others". Click on the help link to view the guidelines on using identifiers in the data collection form. * Click here for help

On a quarterly basis, ICU patients who are discharged or died during their hospital stay will be identified via the hospital census. Their variables will be extracted from the electronic medical records.

F11 List all activities that are performed for routine diagnostic or standard medical treatment as part of the subject's standard care. All research-related activities should not be stated in this section.

All data required are automatically recorded in the EMR. For example, patients' APACHE II (1) scores are automatically calculated and recorded at the 24th hour of ICU admission. The hospital's policy requires the dietitian to measure and record the TAPM (11) and the results of the 7-point SGA (10) of all patients within 72 hours of ICU admission. In addition, the calorie and protein intake of all patients are calculated and recorded in the EMR on a daily basis until they are discharged from the ICU.

F12 Please describe the subject's visits (frequency and procedures involved). For studies with multiple visits, please attach study schedule. (If applicable)

All required data will be collected from the electronic medical records. Hence, they will not require any study visits as they would have been discharged or demised during data collection.

F13 Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

Given the new EMR system, there may be some initial challenges in data extraction. However, the PI will work closely with the IT team to reduce the complexity of data extraction.

F14 What are the Potential Risks to Subjects?

There is no more than minimal risk to the subjects since the audit/ quality improvement project is purely observational by nature. All data required will be routinely collected and recorded in the electronic medical records. No form of intervention would be rendered outside of standard care. We are confident that encryption of the unique codes will ensure the highest level of patient confidentiality.

F15 What are the Potential Benefits (direct as well as indirect) to subjects? Indirect benefit may refer to the medical knowledge gained in the future, from the research.

Subjects are unlikely to benefit from the audit/ quality improvement project. However, the data provided by the subjects will aid in the validation of existing mortality prognostic models, and the development and validation of a new mortality prognostic model.

F16 Preliminary Studies / Progress Reports. Please provide an account of the Principal Investigator's preliminary studies (if any) pertinent to this application.

An audit was conducted between 24/02/2014 to 27/03/2014. The prevalence of malnutrition was 40.7% (mild-moderate malnutrition and severe malnutrition were 30.5% and 10.2%

respectively). Measurements of TAPM (11) on the right (RH) and left hand (LH) could not be performed on 28.9% and 22.0% of the patients respectively. This was mainly due to the intravenous cannulas there were obstructing the area above the adductor pollicis muscle. The mean ± SD (95% CI) TAPM for the RH and LH were 22.1 ± 4.7mm (20.7 – 23.6) and 20.9 ± 5.4 mm (19.3 – 22.5) mm respectively. This is significantly different from the results of Caporossi, Caporossi (11) where the mean ± SD (95% CI) TAPM for the RH and LH were 16.0 ± 5.8 mm (15.3 – 16.7) and 15.0 ± 5.8 mm (14.3 – 15.7) mm respectively. These results clearly showed the need for the determination of TAPM distribution within Asian subjects. There were 16 patients on enteral nutrition support. The mean ± SD (95% CI) for the amount of calories and protein received were 18.8 ± 4.1 kcal/day (15.81-21.73) and 0.9 ± 0.37 g protein/kg/day (0.8-1.07).

F17 What is the estimated timeline for this study? Click here for help

Estimated Start Date: 03-Aug-2015
Estimated End Date: 28-Apr-2017

F18 Does this study have a Study Protocol? Note: For Clinical Trials, investigators are required to submit a Study Protocol for review.

○ Yes • No

F19 The PI is responsible for ensuring that all Study Subjects give informed consent before enrolling into the study.

Please select all the applicable consent scenarios.

○ Informed Consent will be taken for all study subjects.

• Waiver of Informed Consent is requested for all study subjects.

○ A combination of both Informed Consent and Waiver of Consent is required for different study populations

Ethics Main Application Form (Section H - Recruitment Details)

H1 How will potential subjects be identified? (Please tick all the applicable boxes)

☐ Referral by attending healthcare professional ☑ Patients of study team

☑ Databases

i. Which of the following databases will be used? (Please tick all the applicable boxes)

☐ Laboratory Records

☐ Pharmacy Records

☐ Operating Theatre Records

☐ DRG Codes

☐ Standing databases/other department's databases

☑ Medical Records

c. Please elaborate how the names and NRIC of subjects be obtained by you to extract the records form the Medical Records Office.

All patients admitted into the ICU are referred to the dietitian. Since the hospital policy requires the dietitian to perform and document the findings of the 7-point SGA (11) and TAPM (12) for all patients within 72 hours of ICU admission, the subjects' name and identification card number will be recorded in the dietetics module of the electronic medical records.

☐ Other Data Sources

☐ Other methods of subject identification

H2 Who will make the first contact with subject (Enter NA if not applicable)? * Click here for help

NA

H3 How will the subject be contacted (Enter NA if not applicable)? * Click here for help

For the purpose of routine nutritional assessment, dietitians working in the ICU will sometimes contact patient's main care giver to gather pertinent information that cannot be obtained from patients. Since nutritional assessment is part of standard care, dietitians would by default be able to contact patient's main care giver for the sole purpose of nutritional assessment.

H4 Will any advertising / recruitment materials be used to recruit research subjects? * Click here for help

○ Yes • No

H5 Will any other recruitment strategies be used? (Eg. Talks in public places, societies etc.)

○ Yes • No

H6 What is the Recruitment Period (if applicable)? Please provide us with the approximate recruitment period. Click here for help

Start Date: 03-Aug-2015
End Date: 28-Apr-2017

H7 Please indicate the length of time of the subject's direct involvement in the study. E.g. For clinical visits, examinations etc. (If applicable)

All required data will be collected from the electronic medical records. Hence, they will not require any study visits as they would have been discharged or demised during data collection.
Ethics Main Application Form (Section I - Study Sites & Recruitment Targets)

I1 Please state the target number of research subjects to be recruited for each study site in Singapore. If the exact numbers are not available, please give an approximate number range in the Recruitment Target Minimum and Maximum columns.*

Please note that recruiting subjects beyond the Max. No. without DSRB's approval would constitute a Non-Compliance. If you intend to recruit beyond the Max. No., please submit a study amendment to increase the recruitment target.

For the distribution of Males, Females and Children to be recruited into the study, please use the Recruitment Target Max. No. to provide an approximate distribution ratio.

(Go back to Section B1 to add additional study site)

	Study Site	Recruitment Target Min	Recruitment Target Max	Males	Females	Children
1	Alexandra Hospital	1100	2182	1091	1091	0

I2 Is this study part of an international study?

○ Yes • No

Ethics Main Application Form (Section K - Research Participant Characteristics)

K1 Please list the inclusion criteria for research subjects in this study. Note: For global studies, please modify the criteria according to local regulations (e.g. persons below the age of 21 are considered minors in Singapore and would require parental consent prior to participation).

Patient is 21 years old or older Patient was not transferred from other hospital Patent did not have a "Do not resuscitate" status within24 hours of admission

K2 Please list the exclusion criteria for research subjects in this study. Please state clearly, if pregnant women will be excluded from the study.

For objective (c), patient did not receive immuninutrition and had more than 3 days of length of stay in the ICU

K3 Please state the age group of the research subjects.

Lower Age limit 21 Lower Age option years

Upper Age limit 120 Upper Age option years

K4 Are there any recruitment restrictions based on the gender of the research subjects?

○ Yes • No

K5 Are there any recruitment restrictions based on the race of the research subjects (e.g. only Chinese subjects will be included in this study)? If 'Yes', please provide a rationale for this race restriction.

○ Yes • No

K6 Do the potential research subjects have a dependent relationship with the study team (E.g. doctor-patient, employee-employer, head-subordinate, student-teacher, departmental staff relationship)? Note: If you have selected that subjects are 'Patients of study team' in Section H1, then the answer should be 'Yes'. * Click here for help

- Yes

If 'Yes', please describe how the study team will manage the dependent relationship to prevent coercion or undue influence.

Since we are requesting for a waiver of consent, the dependent relationship of the patient and the study team will not cause undue stress for the subject to provide consent. Most importantly, no form of intervention outside of standard care will be administered as this is purely a observational audit, and data collection will only be conducted when patient is discharged or demised.

○ No

K7 Does the study involve any vulnerable research participants? * Click here for help

◉ Yes

Please select all the applicable categories.

☐ **Pregnant Women, Foetuses and Neonates**

☐ **Children (persons who are less than 21 years of age)**

☐ **Prisoners**

☑ **Cognitively Impaired persons**

☐ **Others (E.g. mentally disabled persons, or economically or educationally disadvantaged persons.)**

○ No

K8 Does the study involve any of the following?

☑ Inpatients ☐ Outpatients

☐ Healthy Volunteers ☐ Not applicable

Ethics Main Application Form (Section O - Research Participant - Cognitively-Impaired Persons)

O1 Is this research relevant to this group of subjects who are cognitively-impaired? If 'No', then it is recommended than the study be conducted in mentally competent subjects instead.

- Yes

Please state and justify the reasons for including cognitively impaired persons in this study.

The intent of Hospital mortality prognostic tools is to be used on critically ill patient, who are often cognitively impaired. Hence cognitively impaired subjects are circumstantial to the nature of our audit.

- ○ No

O2 Are adequate procedures for evaluating the mental status of prospective subjects employed to determine if they are capable of providing consent?

- ○ Yes
- No

Please justify the reason for not evaluating the mental status of the prospective subjects.

We are requesting for a waiver of consent. Hence, the mental status of the prospective subject is irrelevant to our audit.

O3 Will legally acceptable representatives (LARs) be approached to give consent on behalf of the individuals judged incapable of providing consent?

○ Yes

• No

Please justify:

We are requesting for a waiver of consent. Hence, we will not be approaching the LAR to obtain consent.

O4 Will a separate Assent Form be used for cognitively impaired persons?

○ Yes, assent will be obtained.

• No, assent will not be obtained.

If 'No', please provide justifications for not obtaining assent from subjects.

We are requesting for a waiver of consent. Hence, assent from subject is irrelevant to our audit.

O5 If a subject is incapable of giving valid consent, will his/her objection to participation be overridden?

◉ Yes

Please provide justification for overriding the subjects' objection to participate

We are requesting for a waiver of consent.

O6 Will an advocate or consent monitor be appointed to ensure that the preferences of potential subjects are elicited and respected?

○ Yes • No

Please justify the reason for not appointing an advocate or consent monitor.
We are requesting for a waiver of consent.

O7 Will an advocate or consent monitor be appointed to ensure the continuing agreement of subjects to participate, as the research progresses?

○ Yes • No

Please justify the reason for not appointing an advocate or consent monitor to ensure the continuing agreement of subjects to participate as the research progresses.
We are requesting for a waiver of consent.

O8 Will the patient's physician or other health care provider be consulted before any individual is invited to participate in the research?

○ Yes • No

Please justify the reason for not consulting the subjects' physician or health care provider.
We are requesting for a waiver of consent so that all subjects can be included in our audit.

This is to reduce bias and preserve the scientific validity of our audit.
O9 Is there a possibility that the request to participate itself, may provoke anxiety, stress or any other serious negative response?

○ Yes • No

O10 Are there any other additional safeguards in place to protect the rights, safety and well-being of these vulnerable subjects?

• No ○ Yes

Kindly indicate the additional steps taken.

We are confident that encryption of the unique codes will reduce patients' risk to the minimal

Ethics Main Application Form (Section Q - Consent Process - Waiver of Consent)

Q NO. Informed consent will not be obtained from Research Participants before enrollment into the study.

The DSRB may waive the requirement to obtain informed consent if the DSRB finds that the study meets the following criteria:

Q1 The study poses no more than minimal risk to research subjects.
Please elaborate and justify why your study meets this criterion. * Click here for help

The objectives will be achieved via an audit/ quality improvement project. This is similar to the development of APACHE IV (15) and SAPS 3 (3, 4) (large international multi-centered studies) where informed consent was not required. The development of GLIMPSE involves no more than minimal risk to the subjects since the audit/ quality improvement project is purely observational by nature. All data required are clinically indicated, and would be measured and recorded in the electronic medical records regardless of the research. No form of intervention would be rendered outside of standard care. We are also confident that encryption of the unique codes will ensure the highest level of patient confidentiality.

Q2 Waiver of informed consent will not adversely affect the rights and welfare of research subjects? Please elaborate and justify why your study meets this criterion. * Click here for help

The data required for our audit/ quality improvement project are only collected after patients are discharged or demised. Hence, the information collected will not affect the clinical decision of the patients' care and will not deprive them of any clinical care that they would have already received.

Q3 The study cannot be practically conducted without the waiver of informed consent. (eg. the subjects are no longer on follow-up, lost to follow-up or deceased).

Please elaborate and justify why your study meets this criterion. * Click here for help

Our audit/ quality improvement project satisfied this criterion based on the epidemiological, ethical, and pragmatic considerations of our research. Epidemiological rationale: It is paramount for all patients admitted in the ICU to be subjects of our audit/ quality improvement project. This will preserve the scientific validity as the inclusion of all patients will enable accurate measurement of the absolute risk of mortality, infection and other outcomes of interest. This will also satisfy the first criterion of most critical appraisal standards for prognostic studies – i.e. "Was the sample of patients representative?" (Guyatt G, Rennie 2002). Most importantly, including all patients will reduce the bias caused by patients who refuse to consent. This is especially important in our case as the mortality rate of our critically ill patients is expected to be low (10-15%). Hence, any refusal of consent from patients where death is imminent, will result in the loss of important prognostic characteristics of mortality, and introduce bias to our audit/ quality improvement project. Another important reason for the waiver of consent is that some patients would demise soon after ICU admission. Therefore, there might not be enough time to seek consent. Ethical rationale: Related to the above mentioned rationale, it may not be appropriate to approach the legally acceptable representative (LAR) of patients who have passed away or when patients are gravely ill to seek consent. This is because the LAR could be overwhelmed by the ICU environment and the gravity of the prognosis of the patient. Hence, seeking consent at this time may cause undue emotional burden. We recognize that consent could possibly be sought from patients who survived the ICU. But this form of delayed consent will exclude patients who have demised in the ICU. We also recognize that we could sought consent from patients who are discharged. However, there is also a possibility that the patient has died post discharged, and calling the family to request for informed consent could again precipitate an emotional burden. Pragmatic rationale: From the sample size estimation, we would require between 1100 to 2182 subjects. Given the limited resources, we adopted a data collection method where the data of patients who were discharged or demised would be retrieved from the electronic medical records on a quarterly basis. Although we recognize that we could ask for informed consent

by calling the patients or their LAR, the logistical challenges and ethical considerations as mentioned above made this strategy less feasible.

Q4 Whenever appropriate, will the research subjects be provided with additional pertinent information after participation? * Click here for help

- No ○ Yes

Please elaborate.

The outcome of our audit/ quality improvement project would not have effect on the subjects as there is no anticipated benefit for them. Therefore, we do not foresee that we would provide any additional pertinent information to the subjects.

Q5 Do you have any additional comments supporting the waiver of informed consent? * If Yes.

Please describe.

- No ○ Yes

Ethics Main Application Form (Section R - Research Data Confidentiality)

R In general, to protect the Study Subject's confidentiality, research data should be coded, and the links between the Subject's identifiers and the codes should be stored separately from the research data.

R1 Will coded / anonymous research data be sent to the study sponsor (e.g. pharmaceutical-sponsored studies)?

- No, the study team would store all research data within the institution

i. Please state where the research data (soft copy and/or hardcopy) will be stored and indicate if the location storage is secured (i.e Password Protected PC or Laptop, data stored in physical location with lock and key access.)

Soft copy and hardcopy of the data will be stored in a password-accessed stand-alone computer and a locked cabinet at the Department of Dietetics and Nutrition respectively.

ii. Who will have access to the research data, and how will access to the research data be controlled and monitored? (Please state the personnel who will have access to the study data eg. PI, Co-investigator, study coordinator.) * Click here for help

PI will have the password and key to access the stand-alone computer and cabinet respectively. PI will review and monitor the data regularly.

iii. Are there any other measures in place to protect the confidentiality of the research data? * Click here for help

1) The password-accessed stand-alone computer and cabinet will only be accessed by the PI.2) The Data Collection Form, Data Collection Form for Nutrition Support and Data Collection Form for Nutritional Assessment will not have any identifiers. The forms will only contain the encrypted unique code. 3) Subject's identifier, which is tagged with his/her unique code, can only be found in the Subject Identification Log which will be password protected in the stand-alone password-accessible computer. Most importantly, the unique code in the Subject Identification Log will be different from the one on the Data Collection Form, Data Collection Form for Nutrition Support and Data Collection Form for

Nutritional Assessment, and only the PI will have the formula to decrypt the encrypted unique code.

iv. Are there any research data sharing agreements with individuals or entities outside the Institution, to release and share research data collected? * Click here for help

○ No

• Yes

Please describe the agreement. Submit a copy of the agreement if available.

Unidentifiable data will be shared with Assoc. Professor Tan from NUS in a password protected spreadsheet. Assoc. Professor Tan is the Biostatistian who would be providing statistical support. Unidentifiable and aggregated data will be share with SICS and Flinders University.

v. Describe what will happen to the research data when the study is completed. * Click here for help

Upon completion of data analysis, data will be stored for 6 years and thereafter permanently deleted.

○ Yes, the study team would send research data to the study sponsor

R2 Will any part of the study procedures be recorded on audiotape, film/video, or other electronic medium?

• No ○ Yes

Ethics Main Application Form (Section S - Biological Materials Usage & Storage)

S1 Will any biological materials (such as blood or tissue) be used as part of the study? This includes both prospectively collected and existing biological materials.

- No ○ Yes

Ethics Main Application Form (Section T - Data & Safety Monitoring)

The purpose of the Data and Safety Monitoring Plan is to ensure the safety and wellbeing of study subjects, and the integrity of the data collected for the study. Depending on the type and risk level of the study, this may include the Principal Investigator, experts within the department or institution, independent consultants or a combination of the said persons.

T1 Who performs the data and safety monitoring? If there is a Data Safety Monitoring Board (DSMB), please submit the charter of the DSMB. * Click here for help

PI will be solely responsible for the data.

T2 Please describe the frequency of review (e.g. daily, weekly, quarterly) and what data (e.g. adverse events/serious adverse events) will be monitored for safety. * Click here for help

Data will be reviewed quarterly. The audit is purely observational and monitoring of safety and adverse events are not part of the objective of our audit.

T3 How is data integrity monitored to ensure that study data is authentic, accurate and complete, and if the data correlates with the case report forms? * Click here for help

Data will be randomly audited for authentic, accurate and complete by the co-investigators.

T4 Please describe the stopping criteria for the research study based on efficacy, futility and safety criteria. * Click here for help

The adequate subjects are enrolled.

T5 Please state the route of dissemination of any data and safety information to the study sites, as well as the person/team responsible for doing so. * Click here for help

NA

Ethics Main Application Form (Section U - Principal Investigator's Curriculum Vitae)

This section shows the Principal Investigator's as well as Study Team Members' Curriculum Vitae.

Please ensure that the information shown here is accurate and up to date.

If the PI or Study Team Member Curriculum Vitae does not appear on the list, the team member needs to upload or update his/her CV, it could be done through his/her ROAM profile.

The DSRB will use the information contained here to assess the qualifications of the Principal Investigator and Study team members to carry out the Study as described in this Application.

	Study **Site**	Name	Study **Role**	**CV**
1	Alexandra Hospital	Mr Chin Han Charles Lew	PI	Charles_Lew_Curriculum_Vitae_for JGH.doc 11-Jun-201
2	Alexandra Hospital	Dr AI PING CHUA	Co-Investigator	CV for NHG research website_Jun2014.pdf 28-Jun-201
3	Alexandra Hospital	Mary Foong Fong Chong	Collaborator	
4	Alexandra Hospital	Michelle Miller	Collaborator	

5	Alexandra Hospital	Robert Fraser	Collaborator	
6	Alexandra Hospital	Dr Chee Keat Tan	Co-Investigator	CVtck%25202010[1][1].rtf 19-Nov-201
7	Alexandra Hospital	Dr Chuen Seng Tan	Co-Investigator	CV_Chuen_Seng_Tan.pdf 13-Dec-201

Ethics Main Application Form (Section V - Declaration of Principal Investigator)

Your DSRB Application is now complete and ready for submission.

Principal Investigator's Declaration

I will not initiate this study until I have received approval notification from the DSRB and all applicable regulatory authorities.

I will not initiate any change in the study protocol without prior written approval from the DSRB, except when it is necessary to reduce or eliminate any immediate risks to the Research Participants. Thereafter, I will submit the proposed amendment to the DSRB and all applicable regulatory authorities for approval.

I will promptly report any unexpected or serious adverse events, unanticipated problems or incidents that may occur in the course of this study.

I will maintain all relevant documents and recognise that the DSRB staff and applicable regulatory authorities may inspect these records.

I understand that failure to comply with all applicable regulations, institutional and DSRB policies and requirements may result in the suspension or termination of this study.

I declare that there are no existing or potential conflicts of interest for any of the investigators participating in this study and their immediate family members. If there are, I have declared them in the relevant section of this application form.

By checking the "I agree" box, you confirm that you have read, understood and accept the Principal Investigator's Declaration

☑ I have read and agree to the above declaration.

Principal Investigator: Chin Han Charles Lew

Data collection form

Subject ID: ___ ___ ___ ___ ___ ___ ___

Age: _____ **Gender:** Male / Female **Ethnicity:** Chinese / Malay / Indian / Others

Weight: _____ **Height:** _____

Hospital adm date: _____Time_____ **ICU adm date:** _____Time_____

Mechanical ventilation started before ICU admission: Yes / No

Admission Diagnosis: _____

ICU Admission reason

Non-operative patients

Cardiovascular
- □ Aortic aneurysm
- □ Cardiac arrest
- □ Cardiogenic shock
- □ Congestive heart failure
- □ Hypertension
- □ Rhythm disturbance
- □ Dissecting thoracic/ abdominal aneurysm
- □ Haemorrhagic shock/ hypovolemia
- □ Coronary Artery Disease

Respiratory
- □ Aspiration pneumonia
- □ Asthma/ Allergy
- □ Bacterial / Viral pneumonia
- □ COPD
- □ Pulmonary oedema (non-cardiogenic)
- □ Pulmonary embolism
- □ Post-respiratory arrest
- □ Respiratory neoplasm

Gastrointestinal
- □ GI Bleeding
- □ Hepatic failure
- □ Pancreatitis

Sepsis
- □ Sepsis
- □ Septic shock/ anaphylactic shock

Trauma
- □ Head trauma
- □ Multiple trauma

Neurologic
- □ Intracerebral haemorrhage
- □ Subdural haemorrhage
- □ Subarachnoid haemorrhage
- □ Seizure
- □ Stroke
- □ Focal neurologic deficit
- □ Coma
- □ Intracranial mass effect

Metabolic
- □ Diabetic ketoacidosis
- □ Drug overdose

Others
- □ Poisoning/ toxic

Major organ that led to admission
- □ Metabolic/Renal
- □ Respiratory
- □ Neurologic
- □ Cardiovascular
- □ Gastrointestinal

Surgical

Cardiovascular
- □ Peripheral vascular surgery
- □ Valvular heart surgery only
- □ Chronic cardiovascular disease

Respiratory
- □ Respiratory insufficiency after surgery

Gastrointestinal
- □ GI bleeding
- □ GI perforation/ obstruction
- □ GI surgery for neoplasm

Neurologic
- □ Craniotomy for neoplasm
- □ Craniotomy for ICH/ SDH/ SAH
- □ Laminectomy/other spinal cord surgery
- □ Haemorrhagic stroke

Trauma
- □ Head trauma
- □ Multiple trauma

Renal
- □ Renal surgery for neoplasm

Others
- □ Thoracic surgery for neoplasm

Major organ that led to admission
- □ Metabolic/Renal
- □ Respiratory
- □ Neurologic
- □ Cardiovascular
- □ Gastrointestinal

Note:
- A day starts from 00:00 to 23:59
- Mechanical ventilation start date can be at ED.

Co-morbidities: ☐ Yes ☐ No

If yes, check all that apply:

Myocardial
- ☐ Angina
- ☐ Arrhythmia
- ☐ Congestive heart failure (or heart disease)
- ☐ Myocardial infarction
- ☐ Valvular

Vascular
- ☐ Cerebrovascular disease (Stroke or TIA)
- ☐ Hypertension
- ☐ Peripheral vascular disease or claudication

Pulmonary
- ☐ Asthma
- ☐ Chronic obstructive pulmonary disease (COPD, emphysema)

Neurologic
- ☐ Dementia
- ☐ Hemiplegia (paraplegia)
- ☐ Neurologic illnesses (such as Multiple sclerosis or Parkinsons)

Endocrine
- ☐ Diabetes Type I or II
- ☐ Diabetes with end organ damage
- ☐ Obesity and/or BMI > 30 (weight in kg/(ht in meters)^2)

Renal
- ☐ Moderate or severe renal disease

Gastrointestinal
- ☐ Gastrointestinal Disease (hernia or reflux)
- ☐ GI Bleeding
- ☐ Inflammatory bowel
- ☐ Mild liver disease
- ☐ Moderate or severe liver disease
- ☐ Peptic ulcer disease

Cancer/Immune
- ☐ AIDS
- ☐ Any Tumor
- ☐ Leukemia
- ☐ Lymphoma
- ☐ Metastatic solid tumor

Psychological
- ☐ Anxiety or Panic Disorders
- ☐ Depression

Muskoskeletal
- ☐ Arthritis (Rheumatoid or Osteoarthritis)
- ☐ Connective Tissue disease
- ☐ Degenerative Disc disease (back disease or spinal stenosis or severe chronic back pain)
- ☐ Osteoporosis

Substance Use
- ☐ Heavy alcohol use or binge drinking history
- ☐ Current smoker
- ☐ Drug abuse history

Miscellaneous
- ☐ Hearing Impairment (very hard of hearing even with hearing aids)
- ☐ Visual Impairment (cataracts, glaucoma, macular degeneration)

Discipline:

Location at discharge:

Discharge Dx:

Cause of death:

Area	Item	Unit	Measurement
Before admission	Location before ICU admission	Nil	ED Wards OT Other hospital Other ICU
	Use of vaso-actives before ICU admission	Nil	Yes No
	CPR before ICU admission	Nil	Yes No
	Length of stay before ICU admission	days	
	Unplanned	Nil	Yes No
	No surgery	Nil	No surgery Emergency surgery Elective surgery
Comorbidities	AIDS	Nil	Yes No
	Dialysis	Nil	Yes No
	Respiratory disease (e.g. COPD)	Nil	Yes No
	Metastatic cancer	Nil	Yes No
	Currently on cancer treatment	Nil	Yes No
	Liver disease (e.g. cirrhosis)	Nil	Yes No
	NYHA class IV	Nil	Yes No
	Haematological cancer	Nil	Yes No
Notes and MAR	Gastrointestinal bleeding	1hr Before/ after	Yes No
	Dopamine	mcg/kg/min	Nil ≤ 5.0 5.1-15.0 >15.0
	Adrenaline / Epinephrine	mcg/kg/min	Nil ≤ 0.1 > 0.1
	Noradrenaline / Norepinephrine	mcg/kg/min	Nil ≤ 0.1 > 0.1
	Inotropes	Any dose of these?	Dobutamine, Vasopressin Phenylephrine / Nil
	AKI • Cr increased by ≥ 26.5 within 48hrs • Cr increased by 1.5 times from baseline • Urine output is <0.5 ml/kg/hr for 6 hours	Nil	Yes No
I/O	Urine output	ml / 24hr	< 200 < 500
Neuro	Lowest Glasgow Coma Scale	24 hrs	E: V: M: Total Time:
	Sedated throughout the 1st 24 hr of admission	24 hrs	Yes No
	GCS at ED		

	Item	Timing	Measurement	
Vitals	**Temperature (°C)**	24 hrs	Lowest:	Highest:
	Heart rate (Beats/ min)	24 hrs	Lowest:	Highest:
	Mean arterial pressure (mm Hg)	24 hrs	Lowest:	Highest:
	Respiration Rate	24 hrs	Lowest:	Highest:
	pH	24 hrs	Lowest:	Highest:
	PaO_2 (<50% FiO_2)	24 hrs	Lowest:	
	PaO_2 (≥50% FiO_2) (FiO_2 x 713) – PaO_2 – ($PaCO_2$ X 0.8)	24 hrs		Highest:
	PaO_2/FiO_2 Ratio (PaO_2: FiO_2:)	**24 hrs +/- 24 hrs**		**MV:** Yes No
Full Blood	**WBC**	24 hrs	Lowest:	Highest:
	Haemoglobin	24 hrs	Lowest:	Highest:
	Platelets	24 hrs	Lowest:	Highest: ±24:
Renal and liver panel	**Sodium**	24 hrs	Lowest:	Highest:
	Potassium	24 hrs	Lowest:	Highest:
	Bicarbonate	24 hrs	Lowest:	Highest:
	Creatinine	24 hrs	Lowest:	Highest: ±24:
	Urea	24 hrs	Lowest:	Highest:
	Albumin (g/L)	24 hrs	Lowest:	Highest:
	Bilirubin (umol/ L)Glucose	24 hrs	Lowest:	Highest: ±24:
	Blood glucose level (Highest)	24 hrs		
	Blood glucose level (Lowest)	24 hrs		
Outcomes	**ICU mortality**	Nil	Yes (Death date:_____Time:_____) No	
	Hospital mortality	Nil	Yes (Death date:_____Time:_____) No	
	28-day mortality	Nil	Yes (Death date:_____Time:_____) No	
	ICU discharge	Nil	Date:	Time:
	Hospital discharge	Days	Date:	Time:
	Mechanical Ventilator Start date	Date	Date:	Time:
	Mechanical Ventilator End date	Date	Date:	Time:

Room Air	= 21%	4 liters of oxygen	= 30%
1 liter of oxygen	= 23%	5 liters of oxygen	= 35%
2 liters of oxygen	= 25%	6 and 7 liters of oxygen	= 40%
3 liters of oxygen	= 27%	8, 9, and 10 liters of oxygen	= 49%

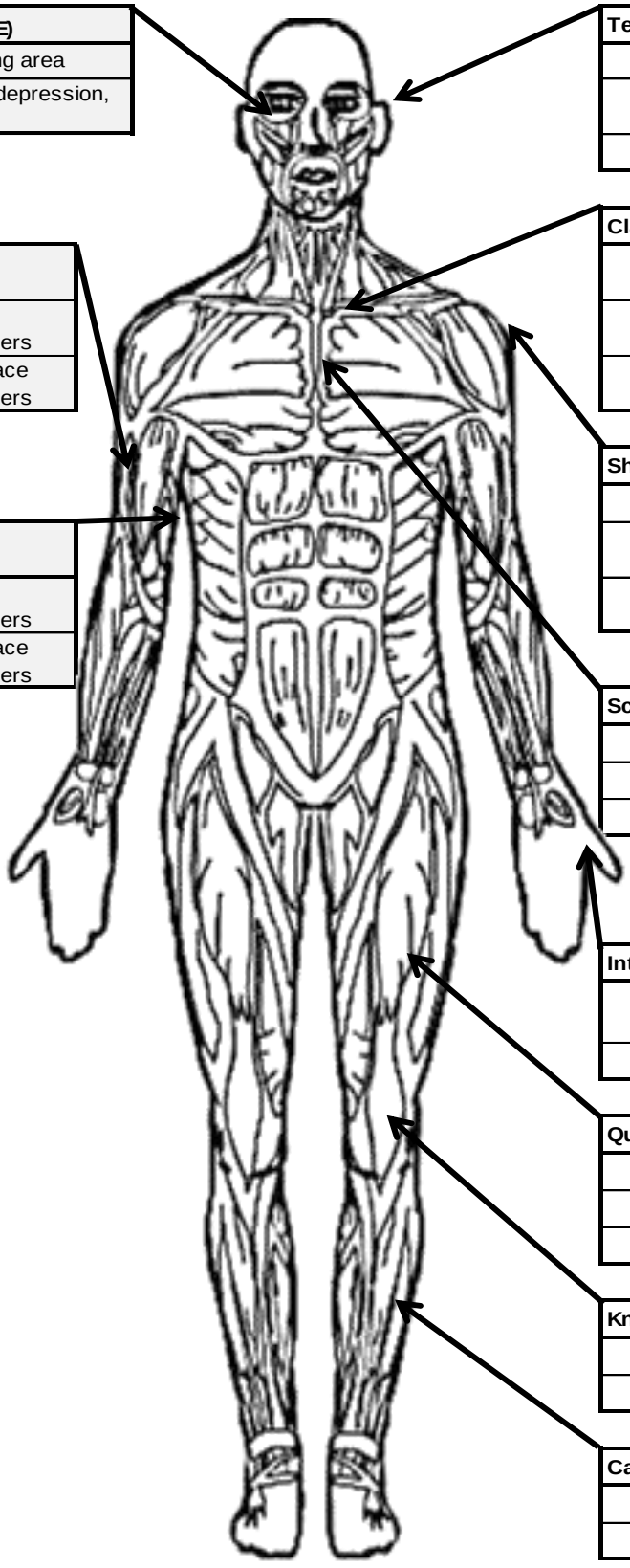
7-point Subjective Global Assessment

Weight History **Usual Wt:_____** **Current Wt:_____** **Weight loss _____ kg in the past 6 months** **7)** 0% **3)** 7 - < 10% **6)** < 3% **2)** 10 - < 15% **5)** 3 - < 5% **1)** > 15% **4)** 5 - < 7% **Note:** If weight is on increasing (↑) trend, add 1 point If weight is on decreasing (↓) trend, minus 1 point	7 6	5 4 3	2 1
Diet Intake **(Duration:_____)** **7)** Good (Full share of usual meal) **6)** Good (>3/4 share of usual meal) & no change **5)** Borderline (1/2 - 3/4 share of usual meal) but increasing **4)** Borderline (1/2 - 3/4 share of usual meal), no change/ decreasing **3)** Poor (< 1/2 share of usual meal) but increasing **2-1)** Poor (< 1/2 share of usual meal) no change/ decreasing or starvation (< 1/4 of usual meal)	7 6	5 4 3	2 1
GI symptoms (that persisted for > 2 weeks) Nausea:_____ Vomitting:_____ Diarrhoea:_____ **1)** No symptom **2)** Very few intermittent symptoms (1x per week) **3)** Some symptoms (2-3x per week) **4)** Some symptoms (1x per day) **5)** Some symptoms (2-3x per day) **6-7)** Some/ all symptoms (> 3x per day)	7 6	5 4 3	2 1
Functional status (nutrition related) **1-2)** Full functional capacity **3-5)** Difficulty with ambulation / normal activities **6-7)** Bed / chair-ridden	7 6	5 4 3	2 1
Muscle wastage **1-2)** Little or no depletion in all areas **6-7)** Severe depletion **3-5)** Mild to moderate depletion	7 6	5 4 3	2 1
Fat stores **1-2)** Little or no depletion in all areas **6-7)** Severe depletion	7 6		2 1
Oedema **1-2)** Little or no odema **6-7)** Severe oedema **3-5)** Mild to moderate oedema	7 6	5 4 3	2 1
Diagnosis Metabolic demand (stress) of primary condition:	Low	Moderate	High

Nutritional status: Well nourished / Mildly to moderately malnourished / Severely malnourished
Overall SGA rating: **1 2 3 4 5 6 7**

Fat Stores

Muscle Wastage



Below the eyes (E)	
	Slightly bulging area
	Hollow look, depression, dark circles

Triceps (Tr)	
	Large space between fingers
	Very little space between fingers

Biceps (Bi)	
	Large space between fingers
	Very little space between fingers

Temple (T)	
	Flat
	Slight depression
	Hollowing, depression

Clavicle (Cl)	
	Not visible (males) Not prominent (Female)
	Protrudes slightly
	Prominent bone

Shoulder (Sh)	
	Rounded
	No square look, protrudes slightly
	Square and prominent bone

Scapula / Ribs (Sc)	
	Bones not prominent
	Mild depression
	Prominent bone

Interosseous muscle (In)	
	Muscle protrudes could be flat in females
	Flat or depressed area

Quadriceps (Qu)	
	Rounded, no depression
	Mild depression, thin
	Depression on inner thigh

Knee (Kn)	
	Bones not prominent
	Bones prominent

Calf (Ca)	
	Well-developed
	Thin, no muscle definition

Posters

The Subjective Global Assessment (SGA) and Nutrition Risk in Critically ill score (NUTRIC) should both be used in the ICU

Charles Chin Han Lew[1,2], Ka Po Cheung[1], Mary Foong Fong Chong[3], Ai Ping Chua[4], Robert JL Fraser[5], Michelle Miller[2]

[1] Dietetics and Nutrition Department, Ng Teng Fong General Hospital (Singapore), [2] Discipline of Nutrition and Dietetics, Flinders University (Australia), [3] Saw Swee Hock School of Public Health, National University of Singapore (Singapore), [4] Department of Respiratory Medicine, Ng Teng Fong General Hospital (Singapore), [5] Department of Gastroenterology and Hepatology, Flinders University (Australia)

Introduction

The Subjective Global Assessment (SGA) and Nutrition Risk in Critically ill Score (NUTRIC) are validated tools that: 1) predict hospital mortality, and 2) identify patients that will benefit from nutrition support in the Intensive Care Unit (ICU).[1,2]

NUTRIC measures: Disease severity

SGA measures: Nutritional Status

Objectives

The study aimed to:

1) Determine the agreement between SGA and NUTRIC scores

2) Quantify their prognostic value for hospital mortality both independently and in combination

Methods

Data collection:

Enroll all patients (Aug 2015 to Oct 2016) → Perform SGA ≤ 48 hrs of ICU admission (Well- vs Mal-nourished) → Collect other known covariates of mortality → Calculate NUTRIC score after discharge (High-NUTRIC: 5-9 vs Low-NUTRIC: 0-4)

Statistical analysis:

Agreement	Discrimination	Hospital Mortality Risk
• Kappa statistics	• Area under the Receiver Operating Characteristic (ROC) curve	• Multivariate logistic regression

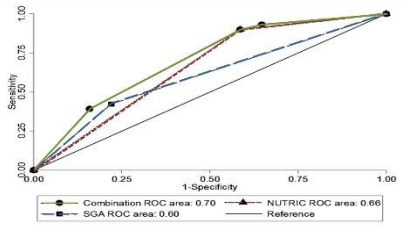


Figure 1: Receiver operating characteristic curve (ROC) for Nutrition Risk in Critically ill Score (NUTRIC), Subjective Global Assessment (SGA) and their combination for predicting hospital mortality

Results

There were 439 eligible patients, none was lost to follow-up and hospital mortality was 29.6%. The median (IQR) age (years), APACHE II and ICU length-of-stay (days) were 63.0 (52.0, 73.0), 24.0 (19.0, 30.0) and 2.0 (2.0, 5.0) respectively.

There was poor concordance between the SGA and NUTRIC (kappa statistics: 0.13, p-value < 0.001). However, the predictive abilities for hospital mortality were similar [C-statistics (95%CI): 0.60 (0.55, 0.65) for malnutrition and 0.66 (0.62, 0.70) for high-NUTRIC, p-value: 0.12]. The combination of SGA and NUTRIC had a significantly better predictive ability [0.70 (0.66, 0.75)] than either of these assessments alone (p-value: 0.002 and < 0.001 respectively) (Figure 1).

Multivariate logistic regression revealed that high-NUTRIC was associated with higher hospital mortality when compared to malnutrition. However, their combination had the highest adjusted odds for hospital mortality (Figure 2).

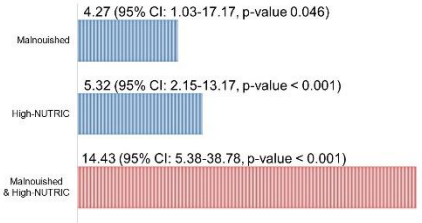


Figure 2: Adjusted odds ratio of the association between malnutrition, high-NUTRIC, and their combination with hospital mortality

Conclusion

Although individually, the NUTRIC and SGA assessments provide a fair prediction of hospital mortality, in direct comparison they have a poor agreement. Their combination however better identifies patients who are at higher risk of hospital death than either alone, suggesting performing both assessments concurrently may be useful to better guide the nutritional interventions in the ICU.

References

1. Lew, C.C.H., Yandell, R., Fraser, R.J., Chua, A.P., Chong, M.F.F. and Miller, M., 2017. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. *Journal of Parenteral and Enteral Nutrition*, 41(5), pp.744-758.
2. Heyland, D.K., Dhaliwal, R., Jiang, X. and Day, A.G., 2011. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Critical Care*, 15(6), p.R268.

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Performance of the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) in the prediction of hospital mortality in a mixed ICU in Singapore

Charles Chin Han Lew[1,2], Chee Keat Tan[3], Ai Ping Chua[4], Mary Foong Fong Chong[5] and Michelle Miller[2]

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[5] Saw Swee Hock School of Public Health, National University of Singapore (Singapore)

Introduction

The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) are commonly used in the ICU to predict hospital mortality. However their accuracy in Singapore remains questionable since they have never been validated locally with established statistical methods.

Objectives

The study aimed to determine the discriminative value, calibration accuracy and accuracy of prediction of the APACHE II and SOFA in predicting hospital mortality in a 35-bed mixed ICU.

Methods

All adult ICU patients who had ≥ 24 hours length-of-stay and admitted between August-2015 to October-2016 were included. For patients who were readmitted to the ICU during the same hospitalisation, only the data on the first admission were included. Data were prospectively recorded in the electronic medical records. The primary outcome was hospital mortality and all patients were followed until discharge or death.

The area under the receiver operating characteristic (ROC) curve was used to asses the discrimination, Hosmer-Lemeshow Chi-square C test for calibration, and Brier score for overall accuracy.

Results

There were 503 eligible patients (medical: 335, surgical: 168). Hospital mortality was 31.0% and none was lost to follow-up. The mean age (years), APACHE II, SOFA and ICU length-of-stay (days) were 61.2±15.8, 24.5±8.2, 8.6±3.8 and 4.5±7.7 respectively, and 89.9% received mechanical ventilation.

According to the Youden index, the best cut-off point for APACHE II and SOFA were 27 and 11 (sensitivity: 61.5%, 49.4%; specificity: 72.9%, 79.0%; correct classification: 69.4%, 69.8%) respectively.

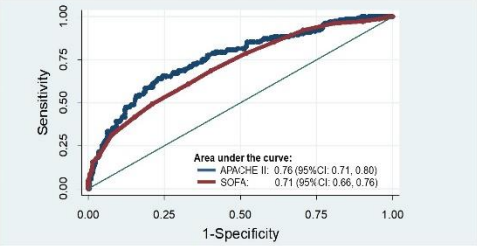

Figure 1: Receiver operating characteristic curve (ROC) for the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) in predicting hospital mortality

Discriminative value of the APACHE II was significantly better than the SOFA (p-value: 0.041) (Figure 1). Calibration for the APACHE II was poor (HL-C: 147.02, p-value: <0.001) and its calibration curve demonstrated an over-estimation of risk at all deciles (Figure 2). Calibration for the SOFA was good (HL-C: 4.02, p-value: 0.675). The Brier scores of the APACHE II and SOFA showed very poor overall accuracy of prediction (0.22 and 0.19 respectively).

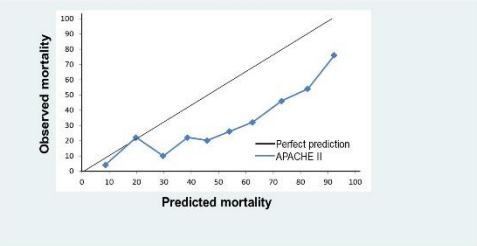

Figure 2: Calibration curve of the Acute Physiology and Chronic Health Evaluation II (APACHE II) in predicting hospital mortality across different risk strata

Conclusion

The overall validity of the APACHE II and SOFA in predicting hospital mortality was poor and one must exercise caution when using them for any clinical decision or quality evaluation. There is a dire need to recalibrate the APACHE II or develop a new prognostic model specifically for the local ICU population.

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The Association between Malnutrition and Mortality Outcomes amongst the Critically Ill: A Cohort Study and a Meta-analysis

Gabriel Jun Yung Wong[1,2], Jesslyn Chong[1], Ruey Jiun Lim[1], CK Tan[3], Ai Ping Chua[4], Mary Foong Fong Chong[5], and Michelle Miller[2], Charles Chin Han Lew[1,2]

[1] Dietetics and Nutrition Department, Ng Teng Fong General Hospital (Singapore)
[2] Discipline of Nutrition and Dietetics, Flinders University (Australia)
[3] Department of Intensive Care Medicine, Ng Teng Fong General Hospital (Singapore)
[4] Department of Respiratory Medicine, Ng Teng Fong General Hospital (Singapore)
[5] Saw Swee Hock School of Public Health, National University of Singapore (Singapore)

Introduction

Validity of the association between malnutrition and mortality outcomes in critically ill patients are hampered by several limitations in the literature. They include small sample size, possible treatment bias, and sub-optimal statistical adjustments of possible confounders. Since confounders are inherent to prognostic studies, optimal statistical adjustment is key to accurate quantification of the association between risk factors and the outcome of interest.

Objective

This study aimed to determine the association between malnutrition and hospital mortality amongst the critically ill via a large prospective cohort study and a meta-analysis.

Methods

This study was conducted between Aug-2015 and Oct-2016. All patients who had ≥ 24 hours length-of-stay in the 35-bed mixed ICU of Ng Teng Fong General Hospital had their nutritional status assessed by a dietitian using the Subjective Global Assessment (SGA) within 48 hours of ICU admission. Physicians and nurses were blinded from the objectives of the study to minimize the risk of treatment bias.

Detailed methodology of the systematic review has been published previously.[1] In brief, literature search was performed on 1st Aug-2014 in Pubmed, CNAHL, Scopus and Cochrane Library. Eligible studies were case-control or cohort studies, conducted the SGA within 48 hours of ICU admission and reported mortality outcomes. Results from previous studies and this cohort study were pooled in RevMan 5.

Results

The cohort study had 439 eligible patients (medical: 293, surgical: 156). Hospital mortality was 29.6% and none was lost to follow-up. The prevalence of malnutrition was 28.0%, of which 3.0% were severely malnourished. The median (IQR) age (years), APACHE II and ICU length-of-stay (days) were 63.0 (52.0, 73.0), 24.0 (19.0, 30.0) and 2.0 (2.0, 5.0), respectively. After adjusting for age; location, length-of-stay, and use of vasoactives and cardiopulmonary resuscitation before ICU admission; APACHE II; length of mechanical ventilation, and hospital and ICU length-of-stay, malnutrition was independently associated with hospital mortality [adjusted-OR of 3.38 (95%CI: 1.77-6.44)].

Malnourished ICU patients have increased odds of death

Well-nourished VS Malnourished

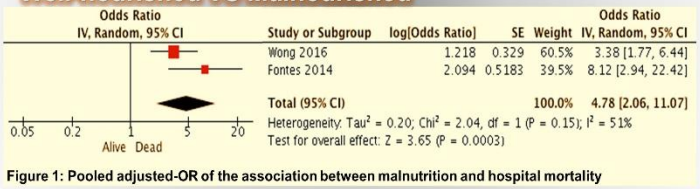

Figure 1: Pooled adjusted-OR of the association between malnutrition and hospital mortality

Literature search for the meta-analysis revealed 20 eligible studies out of 1168 studies.[1] Prevalence of malnutrition ranged from 38% to 78%. Only one study [2] had low risk-of-bias and was suitable for data pooling [n=185 adj-OR (95% CI) 8.12 (2.94-22.42) p-value <0.05]. The pooled adj-OR of the association between malnutrition and hospital mortality was 4.78 (2.06-11.07) p-value < 0.001. There was moderate heterogeneity where I^2 was 51% (Figure 1).

Conclusion

There is strong evidence that malnutrition diagnosed by the SGA is independently associated with hospital mortality. Given the variable prevalence of malnutrition, it is important for individual ICUs to determine their local prevalence. This may better guide resource allocation and improve the nutritional care of the critically ill.

References

1. Lew CCH, Yandell R, Fraser RJ, Chua AP, Chong MFF, Miller M. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit A Systematic Review. Journal of Parenteral and Enteral Nutrition 2016:0148607115625638.
2. Fontes D, Generoso Sde V, Toulson Davisson Correia MI. Subjective global assessment: a reliable nutritional assessment tool to predict outcomes in critically ill patients. Clin Nutr. 2014;33:291-5.

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Award and achievements

Best oral presentation

The original research in Chapter Six [260] was presented at the Congress of Parenteral and Enteral Nutrition of Asia 2018 and it was awarded the Best Oral Presentation.

THE 19th CONGRESS OF PENSA 2018

Parenteral and Enteral Nutrition Society of Asia in conjunction with The 17th Annual Congress of KSPEN

BEST ORAL PRESENTATION AWARD

Awarded to

Charles Chin Han LEW

Ng Teng Fong Hospital, Singapore

for the best oral presentation

Re-evaluation of the Modified Nutrition Risk in Critically Ill Score (mNUTRIC): Benefits of Energy and Protein Intake Vary with the Length of Nutrition Support in High-risk Patients

presented at the 19th Congress of Parenteral and Enteral Nutrition Society of Asia (PENSA 2018) in conjunction with the 17th Annual Congress of Korean Society for Parenteral and Enteral Nutrition (KSPEN) held in Seoul, Korea, June 13 - 16, 2018.

Ho-Seong HAN, MD, PhD
President of PENSA 2018

Kuk-Hwan KWON, MD, PhD
Chairman of the Executive Committee of KSPEN

I was also invited to present the following:

- Lew CCH: **Nutrition risk assessment in ICU**. *Presented at the 2nd Singapore Clinical Nutrition Meeting 2014, 26th – 27th April.*

- Lew CCH: **How to feed to target in ICU**. *Presented at the 3rd Singapore Clinical Nutrition Meeting 2016, 9th – 10th April.*

- Lew CCH: **The NUTRIC story: should all patients with high NUTRIC score receive aggressive nutrition support?**. *Presented at the 2nd Singapore Clinical Nutrition Meeting 2018, 14th – 15th April.*

ASPEN CE program

The systematic review in Chapter One [1] was chosen to be part of the ASPEN CE program. The email from ASPEN and details are below:

Journal of Parenteral and Enteral Nutrition <onbehalfof+jpen+nutritioncare.org@manuscriptcentral.com>
Tue 21/3/2017, 11:31 PMLew Chin Han Charles (JHS);charles.nutrition@gmail.com;tappende@illinois.edu;michelles@nutritioncare.org;brianw@nutritioncare.org;catherinew@nutritioncare.org
21-Mar-2017

Dear Dr. Lew:

I hope this message finds you well. In case you are not aware, JPEN provides readers with the opportunity to earn valuable CE credits by reading a preselected article and correctly answering some preapproved questions.

The good news is that Kelly Tappenden thinks your paper would make a great paper for the CE program. This will likely bring a lot of attention to your work because people will be claiming for the CE.

If you agree that this would be a great opportunity, please let me know as soon as possible but by no later than March 28th, 2017.

Attached is a document containing a questionnaire and other requirements for having your paper participate in the CE program. There is also a mandatory conflict of interest form that each of your co-authors would need to sign. CVs for all authors will also be required. We would need you to write up 5 questions along with the answers and return all of the required elements by no later than April 4th, 2017.

I have attached a template for how the questions should be structured, and I have taken the liberty of filling out the manuscript information for you (in blue) on the author questionnaire form.

Please let me know at your earliest convenience if you think this is something you would like to participate in.

Sincerely,

Sincerely,
Latoya Fladger
Journal of Parenteral and Enteral Nutrition

JOURNAL-BASED CE ACTIVITY INFORMATION

GENERAL INFORMATION

ASPEN prohibits programs that constitute commercial promotion. We support the *ACCME Standards for Commercial Support of Continuing Medical Education* in full. The standards for commercial support are located on the ACCME website at http://www.accme.org/dir_docs/doc_upload/68b2902a-fb73-44d1-8725-80a1504e520c_uploaddocument.pdf.

Journal Article Title The association between malnutrition and clinical outcomes in the Intensive Care Unit: A systematic review [JPEN-2015-07-183.R3]
Journal Article Authors *A current CV of the authors as well as disclosure/COI form must be provided* Charles Chin Han Lew, Rosalie Yandell, Robert JL Fraser, Ai Ping Chua, Mary Foong Fong Chong, Michelle Miller
Journal Article Issue (Minimum of Issue Month and Year and Page Numbers if Known) JPEN July 2017 Issue
Needs Assessment. Joint Commission Standard AOP 1.4 requires healthcare providers to identify patients who are at risk of malnutrition. The prevalence of malnutrition in the critical care setting can be as high as 78%, and it is associated with poorer clinical outcomes. However in clinical practice, it is unclear which nutrition screening or assessment tools should be used to identify risk of or presence of malnutrition.
Professional Practice Gap: 1. **Identified gap (Performance) –** There is a myriad of nutrition screening and assessment tools and clinicians may not be clear which is the most appropriate for the critical care setting. 2. **Educational Objectives:** a. Recognize the difference between nutrition screening and assessment b. Recognize the wide range of malnutrition prevalence rates in the critical care setting c. Identify the nutrition screening and assessment tools that have shown best validity in determining nutritional risk and diagnosing malnutrition in the critical care setting d. Describe the association between malnutrition and clinical outcomes in the critical care setting

3. **Expected outcome/desired result of providing the program**
    a. Clinicians will use the appropriate tools and routinely conduct nutrition screening and assessment in their intensive care units
    b. The Nutrition Risk Screening – 2002 and Subjective Global Assessment will be used to determine nutritional risk and diagnose malnutrition respectively.
    c. In light of the association between malnutrition and poorer clinical outcomes, clinicians will routinely identify malnutrition and provide nutritional interventions to achieve better clinical outcomes

4. **Content Focus** (select one)
    - Knowledge
    - Competence
    - Performance
    - Patient Outcome

Target Audience: Clinicians who are involved in nutrition support in the critical care setting

Education Design/Outcomes Evaluation

This program will be designed to change (please circle one):

- **Learner competence (changes in how to apply the knowledge to practice)**
- **Learner performance (changes in practice performance as a result of application of what was learned)**
- **Patient outcomes (changes in health status of patients due to changes in practice behavior)**
-

Evaluation Methods

Those who participate in the journal-based CE program must pass a post test and complete a program evaluation. Article authors must submit 5 learning assessment questions to be used for the post test. Learning assessment questions should have correct answers clearly marked when submitted. [See "Instructions for CE questions" document for template/instructions]

The Accreditation Council for Continuing Medical Education (ACCME) prohibits providers from asking commercial supporters to suggest topics or speakers for educational activities

Checklist of Items Needed from Authors:

- ❑ Current CV for each author
- ❑ Author disclosure/COI form completed
- ❑ Minimum of 5 learning assessment questions as related to the article with answers identified. *Questions should be related to the content presented in the article and should serve as a means to test the learners' comprehension of the topic or application of the information in the article, not just a regurgitation of information written in the article.*
- ❑ Authors can also be relied upon to help identify the needs assessment and practice gap data.

CE Assessment Items for *JPEN*

Participants in ASPEN's Journal CE Program must pass an assessment and complete a program evaluation after reading a CE article. To facilitate this program, the authors of a CE article must submit 5 learning assessment items to be used for the assessment. Authors must base their assessment items on learning objectives for the article and have correct answers clearly marked. For training resources to assist with the development of strong learning assessment items, please visit the following page:

www.nutritioncare.org/Continuing_Education/Faculty_Item_Writing_Training/

Article Title
The association between malnutrition and clinical outcomes in the Intensive Care Unit: A systematic review [JPEN-2015-07-183.R3]

Authors
Charles Chin Han Lew, Rosalie Yandell, Robert JL Fraser, Ai Ping Chua, Mary Foong Fong Chong, Michelle Miller

Learning Objectives
At the conclusion of the article, the learner will be able to:

1. Recognize the difference between nutritional screening and assessment

2. Recognize the wide range of malnutrition prevalence rates in the critical care setting

3. Identify the nutritional screening and assessment tools that have shown best validity in determining nutritional risk and diagnose malnutrition in the critical care setting

4. Describe the association between malnutrition and clinical outcomes in the critical care setting

Learning Assessment Items

1. Nutritional screening should be performed to diagnose malnutrition in the IC.U
    A. True
    B. False

2. The prevalence of malnutrition varies widely in the critical care setting.
    A. True
    B. False

3. In critically ill patients, which of the following nutritional screening tools has the best prognostic value for hospital mortality?
    A. Malnutrition Universal Screening Tool (MUST)
    B. Nutrition Risk Screening-2002 (NRS-2002)
    C. Short Nutritional Assessment Questionnaire (SNAQ)
    D. Prognostic Inflammatory and Nutrition Index (PINI)

4. In critically ill patients, which of the following nutritional assessment tools has the best prognostic value for hospital mortality?
    A. Mini Nutritional Assessment (MNA)
    B. Subjective Global Assessment (SGA)
    C. Malnutrition Clinical Characteristics (MCC)

5. The nutritional status of elderly patients in the ICU should be assessed by the Mini Nutritional Assessment.
    A. True
    B. False

Learning Assessment Answers

1. Answer = False; Rationale: Nutritional screening determines the risk of malnutrition, and cannot diagnose malnutrition as it inherently may misclassify patients' nutritional status. Therefore, patients who are at risk of malnutrition should thoroughly be evaluated using a nutritional assessment tool to diagnose malnutrition.

2. Answer = True; Rationale: The prevalence of malnutrition ranged from 38% to 78% in ICUs that include a heterogeneous group of patients. In view of this wide variation, it is important for individual ICUs to determine the local prevalence of malnutrition to guide their screening and assessment policy.

3. Answer = B; Rationale: Amongst the nutritional screen tools, the Nutrition Risk Screening-2002 demonstrated the best prognostic value. Patients with malnutrition risk have a higher rate of hospital mortality and a higher percentage of them would be discharged to nursing facilities.

4. Answer = B; Rationale: Malnutrition diagnosed by the Subjective Global Assessment (SGA) was associated with higher hospital mortality, longer ICU length of stay, increased incidence of infection and ICU readmission. In addition to its superior prognostic value, the SGA was also demonstrated to be a reliable nutritional assessment tool in mechanically ventilated patients.

5. Answer = False; Rationale: Although the Mini Nutritional Assessment (MNA) is the recommended nutritional assessment tool for elderly patients, it has limited prognostic value in the ICU. Except for postoperative complications, malnutrition diagnosed by the MNA was not associated with any other clinical outcomes.

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