Enhancing intensive care outcome prediction with nutrition information available at admission: An analytic observational study conducted in 31 intensive care units throughout Australia and New Zealand

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I declare that the research presented here is my own original work and has not been submitted to any other institution for the award of a degree.

Signed: ……

Date: ……

1. ABSTRACT

Background

At admission to an intensive care unit (ICU), patient data are collected to allow the objective estimation of risk of mortality. These risk estimates are used to stratify quality assurance projects and clinical research. The purpose of this study was to determine whether measures of nutrition status could add additional information to this risk stratification process.

Methods

At 31 ICU's throughout Australia and New Zealand, in addition to routine patient data, the following measures of nutrition status were collected: Triceps Skinfold Thickness, Mid Arm Muscle Circumference (MAMC), Body Mass Index (BMI), the Subjective Global Assessment (SGA) of Muscle Wasting and SGA Fat Loss.

Results

1,363 critically ill patients were enrolled. Controlling for severity of illness and other traditional risk factors, multivariable analysis revealed MAMC, SGA Muscle Wasting and SGA Fat Loss added significantly more information than BMI. With each measure, improved nutrition status was associated with improved outcome.

Conclusion

This analytic observational study demonstrates the existence of significant independent *associations* between a patient's nutrition status and outcome from critical illness. Future research should focus on determining whether this relationship is *causal*. For example, can improving nutrition status before ICU admission result in improved outcomes from critical illness?

2. AUTHORS CONTRIBUTION

The author was directly responsible for the design, conduct and analysis of this analytic observational study. She provided initial training and education to support collection of the specific bedside physical assessment and anthropometric measures of body composition collected at all 31 participating sites in a series of eight two-day study start-up meetings. In addition to initial training at start-up meetings, she conducted over 80 on-site education and monitoring visits. She also mentored and encouraged the research teams to continue to diligently collect the measures of body composition on all 1,363 participating patients. She created and published an Anthropometric Procedures Manual which was provided to all participating researchers to standardise collection.

2.1 Publications Arising from this Thesis

One scientific publication and one Anthropometric Procedures Manual have been published out of this PhD thesis to date.

Simpson F and Doig GS. Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: An analytic observational study." *Journal of Parenteral and Enteral Nutrition 2015; 39(3):313-321*. See Appendix A for authors' final version of this manuscript.

Simpson F and Doig GS. Anthropometric Procedures for a multi-centre randomised controlled trial: Early Parenteral nutrition vs. Standard care in patients not expected to be fed within 24 h of ICU admission. EvidenceBased.net, Sydney, Australia 2011. DOI:10:4451/EarlyPN_APM

See Appendix B for a copy of the Anthropometric Procedures Manual.

One poster has also been presented at an international meeting. A number of invited talks, which have discussed the anthropometric procedures included in the thesis, have also been given. See Appendix C for details.

3. ACKNOWLEDGEMENTS

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7. LIST OF ABBREVIATIONS

A-a	Alveolar-arterial
ANZICS CORE	Australian and New Zealand Intensive Care Society's Centre for Outcome and Resource Evaluation
APACHE	Acute Physiology and Chronic Health Evaluation
APS	Acute Physiology Score
aROC	Area under the receiver operating characteristic (curve)
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
$BMI_{categorical}$	BMI analysed as a categorical variable
$BMI_{continuous}$	BMI analysed as a continuous variable
CI	Confidence Interval
χ^2	Chi-squared
cm	Centimetre
CT	Computer Tomography
^0C	Degrees Celsius
DEXA	Dual Energy X-ray Absorptiometry
$Fi0_2$	Fraction of inspired oxygen
GCS	Glasgow Coma Scale
GOF	Goodness Of Fit
g/L	grams per Litre
ICU	Intensive Care Unit
IL	Interleukin
ISAK	International Society for the Advancement of Kinanthropometry
Kg/m_2	kilograms per meter squared

LR	Likelihood Ratio
MAP	Mean Arterial Pressure
Mm	Millimetre
mmHg	Millimetres of mercury
mmol/L	Millimoles per Litre
μMol/L	Micromoles per Litre
MNA	Mini Nutrition Assessment
MPM	Mortality Prediction Model
MPM II_0	Mortality Prediction Model version II, at admission
NIH	National Institutes of Health
OR	Odds Ratio
$Pa0_2$	Partial pressure of arterial oxygen
%	Percentage
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SGA	Subjective Global Assessment
SGA Fat Loss	Physical evidence of subcutaneous fat loss, defined using the SGA tool
SGA Muscle Wasting	Physical evidence of muscle wasting, defined using the SGA tool
TBN	Total Body Nitrogen
TBK	Total Body Potassium
WHO	World Health Organisation

8. INTRODUCTION

8.1 Background

Throughout Australia and New Zealand, a limited amount of readily available clinical information is collected at time of admission for each and every patient cared for in an Intensive Care Unit (ICU).[1] This information is used to objectively determine severity of illness and subsequent risk of poor outcome, which is of importance to support structured quality assurance projects and clinical research.[2-5] Severity of illness, and risk of poor outcome, can be calculated using a number of validated algorithms, including the Acute Physiology and Chronic Health Evaluation score, the Simplified Acute Physiology Score and the Mortality Prediction Model. However despite major differences in each scoring algorithm, they all bear one key similarity: none of the current severity of illness scores or models incorporates any elements of nutrition status.

Most elements of a comprehensive nutrition assessment require patient or surrogate family interviews to elicit historical information (diet history, history of weight change etcetera), which is not routinely available early in ICU stay when patients are ventilated and sedated. However, simple physical assessment and anthropometric measures of body composition, which are accepted to assess specific domains of nutrition status, can be easily undertaken at the patients' bedside, early in ICU stay.

The purpose of this multi-centre analytical observational study is to determine whether specific key measures of nutrition status can add additional information to a widely used method of outcome prediction for critically ill patients.

8.2 ICU outcome prediction: Severity of illness scores and models

Numerous scoring systems and models have been developed in order to measure severity of illness *at time of ICU admission* and predict subsequent patient outcomes. The

most widely used and validated at this point in time are the Acute Physiology and Chronic Health Evaluation (APACHE), the Simplified Acute Physiology Score (SAPS) and the Mortality Prediction Model (MPM). Since their initial publication, all of these prediction models and scores have been updated.

APACHE, SAPS and MPM differ widely in the methodology used to collect data and estimate risk, however there are some similarities. Using logistic regression, all combine physiological variables and/or measures of treatment with pre-intensive care measures of chronic health, in order to calculate a mortality risk estimate.

8.2.1 APACHE

In 1981 the APACHE scoring system was first published by Knaus et al.[6] Its primary purpose was to classify groups of ICU patients with regards to outcome rather than to guide individual patient decisions. The APACHE classification system was composed of two parts: an Acute Physiology Score (APS) designed to reflect the patients' acute illness, and a pre-intensive care health score representing the patient's health status before hospital admission. The scoring system was designed to include only objective data that was routinely collected in the ICU, and to be highly generalisable to a wide range of critically ill patients.

Thirty four physiological variables were included in the APS: heart rate, mean blood pressure, right atrial pressure/central venous pressure, electrocardiogram evidence of acute myocardial infarction, electrocardiogram arrhythmias, serum lactate, blood pH, total respiratory rate, P(A-a)O_2 at 100% Fi02 *OR* P(A-a)O_2, $PaCO_2$, urine output/day, serum blood urea nitrogen, serum creatinine, serum amylase, serum albumin, total bilirubin, serum alkaline phosphatase, anergy via skin testing, haematocrit, total white blood cell count, platelets, prothrombin time in seconds, blood positive culture, fungal positive culture, rectal

temperature, serum calcium, serum glucose, serum sodium, serum potassium, serum bicarbonate, serum osmolarity, and Glasgow Coma Scale (GCS) score.

Recognition that some patients can enter the ICU with significant preadmission disease burden led the APACHE investigators to incorporate a preadmission health status ranking into the final APACHE classification. Four chronic health categories were available: Category A was used to indicate excellent preadmission health; Category B indicated a mild to moderate limitation in activity due to a chronic medical condition; Category C indicated a chronic disease which seriously restricted but did not incapacitate patient activity; and Category D indicated a severe restriction of activity due to chronic disease. A final APACHE classification was then formulated for each ICU patient from the numerical sum of the APS and the preadmission health status categorisation (A to D).

The APACHE scoring system was used to classify 582 ICU admissions at a single American ICU. No predictive performance statistics such as area under the receiver operating characteristic curves (aROC) and Hosmer Lemeshow goodness of fit (GOF) statistics were reported in this initial APACHE manuscript.

8.2.2 APACHE II

In 1985 the APACHE classification system was refined in order to simplify the scoring system and to statistically validate its predictive performance.[7] The overall APACHE II score was made up of the sum of three different scores; the APS recorded from data obtained in the first 24 hours of ICU admission, an age-related score, and a chronic health score. The APACHE II score was then used to predict hospital mortality by including the score in a regression equation with each patient's emergent surgical status and primary reason for ICU admission.

All 34 physiologic variables included in the APS component of the APACHE score were considered for inclusion in the APS component of the APACHE II score.[7] Physiologic variables that were not routinely collected in the ICU were removed from APACHE II (e.g. skin testing for anergy). Serum albumin, serum glucose, urine output and central venous pressure were not found to increase the explanatory power of the model during multivariate analysis and hence were also excluded. Other changes from the original APACHE APS component included the removal of blood urea nitrogen in favour of serum creatinine and the removal of serum bicarbonate in favour of blood pH. In contrast to APACHE, the final APS component of the APACHE II score included 12 variables, rather than 34. The twelve physiologic variables were: temperature; mean arterial pressure; heart rate; respiratory rate; oxygenation (A-a gradient or $Pa0_2$); blood pH or serum bicarbonate if there were no arterial blood gases available; serum sodium; serum potassium; serum creatinine; haematocrit; white blood cell count; and GCS score.

As well as reviewing which APS variables were included in APACHE II, the authors also revised the APS thresholds and weightings. In addition to calculating an APS from twelve physiologic variables, the APACHE II score also allocated points for increasing age, admission due to elective or emergent surgery, and evidence of chronic health states prior to hospital admission. The addition of the APS points, age points, and chronic health points generated a total APACHE II score. Scores ranged from 0-71, with the worst or most deranged value sought for each variable.

In order to predict the risk of hospital mortality for groups of ICU patients, the authors assigned each patient a primary reason for ICU admission from a list of 45 diagnoses, categorised into non-operative and operative admissions. Where a specific patient was unable to be categorised, they were allocated to one of five general organ failure categories.[7] The

APACHE II predictive equation for each patient was then calculated using a regression equation.

Thirteen ICU's across America contributed 5,030 patients to the development study. Patients who underwent coronary artery bypass grafts were excluded from analysis. Using the development dataset, the accuracy of the APACHE to the APACHE II predictive equation was compared using logistic regression. A final aROC of 0.863 for APACHE II and 0.851 for APACHE was reported. A validation dataset was not used for comparisons.

The APACHE II predictive equations have been published in the public domain, allowing for calculation of an individual patient's risk of outcome without paying any fees.

8.2.3 APACHE III

In 1991 the APACHE III scoring system was developed to improve on the hospital risk prediction of the previous APACHE II scoring system.[8] The authors sought to re-evaluate the selection of physiologic variables included in the scoring system, revise the weightings attributed to each included variable, improve the representativeness of the patients included in the reference database, address issues of timing of APACHE III collection, increase the size of the reference database, and clarify whether APACHE III was able to estimate the risk of mortality in *individuals* as well as in defined patient *groups*. A series of detailed articles describing APACHE III's development are available.[9-13]

The final APACHE III system consisted of two components: 1) an APACHE III score and, 2) an APACHE III predictive equation. The APACHE III score consisted of 17 APS variables, patient age, and presence of chronic health states, and provided initial risk stratification within independently defined patient groups. The APACHE III predictive equation incorporated the APACHE III score, treatment location immediately prior to ICU

admission, and reference data on major disease categories to calculate hospital mortality risk for individual patients.

The final APACHE III physiologic variables included twelve variables from the previous APACHE II physiology score (pulse rate, mean blood pressure, temperature, respiratory rate, partial pressure of arterial oxygen ($Pa0_2$)or alveolar-arterial (A-a) gradient, haematocrit, white blood cell count, serum creatinine, serum sodium, pH, GCS score (and age), and five new variables (blood urea nitrogen, urine output, bilirubin, glucose and serum albumin).[8] Serum potassium and serum bicarbonate, previously included in the APACHE II score, were excluded from the APACHE III score. The definition of the GCS score was also revised. A score of zero to 252 points was possible for the APS component of the APACHE III score.

Whilst the APACHE III score also allocated points for increasing patient age, more age categories were created, and greater weighting was given to older adults (zero points for patients aged ≤44 years, to 24 points for patients aged ≥85 years).

Seven chronic health states were included in the final APACHE III score, all affecting the patients' immunological status and all meeting the statistical requirements for inclusion (acquired immunodeficiency syndrome, lymphoma, hepatic failure, solid tumours with metastasis, immuno-compromise, leukemia/multiple myeloma, and cirrhosis). Where a patient had multiple chronic health states the health state with the highest risk points contributed to the APACHE III score. Chronic health points were not allocated for elective surgery ICU admissions, as the authors discovered they did not improve the explanatory power within elective admissions. A score of zero to 23 points was possible for the chronic health component of the APACHE III score.

Forty hospitals contributed 17,440 patients to the development database. Patients', who remained in the ICU for less than four hours, were admitted with burn injuries, were

admitted with chest pain or who were less than 16 years were excluded from data collection. Based on data recorded on the first day of ICU stay, the aROC of the APACHE III predictive equation was 0.90 using the development dataset. The aROC of the APACHE II predictive equation for the same development dataset was 0.85.

The APACHE III predictive equations were *not* published in the public domain, which means that risk of outcome cannot be calculated for individual patients without paying a fee to the private license holders.

8.2.4 APACHE IV

In 2006, the authors developed the APACHE IV.[14] The existing APACHE III APS variables and weights were retained, with a focus on developing new predictor variables using more recent patient data and statistical modelling techniques. The APACHE IV predictive equation for critically ill patients has been published in the public domain.

Development of APACHE IV predictive equation for critically ill patients

The following data collected on day one of ICU stay was included in the APACHE IV predictive equation: age, pulse rate, mean blood pressure, temperature, respiratory rate, $Pa0_2/Fi0_2$ ratio (or $P(A\text{-}a)0_2$ for intubated patients with an $Fi0_2 \geq 0.5$), haematocrit, white blood cell count, creatinine, urine output, blood urea nitrogen, sodium, albumin, bilirubin, glucose, acid base disturbances, GCS score, chronic health variables (evidence of cirrhosis, hepatic failure, immune-suppression, lymphoma, leukemia or myeloma, metastatic tumour and acquired immunodeficiency syndrome), ICU admission diagnosis categories (116 categories), ICU source of admission categories (hospital floor, emergency room, operating theatres/recovery room, step-down unit, direct ICU admission, other ICU, other hospital, or other admission source), length of hospital stay prior to ICU admission, emergency surgery

(yes/no), inability to assess GCS score (yes/no), thrombolytic therapy for patients with acute myocardial infarction (yes/no), and need for mechanical ventilation. The worst value was taken for all acute physiology variables.[14]

One hundred and four ICU's across 45 unique hospitals submitted ICU patients to the overall development and validation APACHE IV databases. The randomly selected development dataset was created using 60% (66,270/110,558) of all entries and the validation dataset was created using 40% (44,288/110,558) of all database entries.

Using the validation dataset, the APACHE IV model for ICU patients had an aROC of 0.88. Calibration was also reported to be acceptable using the Hosmer Lemeshow GOF test (χ^2_{10df} = 16.8, P = 0.08).

Development of APACHE IV predictive equation for coronary artery bypass graft patients

A separate predictive equation was designed for use with patients admitted to ICU after coronary artery bypass grafts. Data elements collected and used in the APACHE IV predictive equation for coronary artery bypass graft patients include: age, APS variables, emergency surgery (yes/no), prior coronary artery bypass graft surgery (yes/no), female gender (yes/no), number of grafts, internal mammary artery graft (yes/no), myocardial infarction during current hospitalisation (yes/no), length of stay before ICU admission, diabetes (yes/no). All data was obtained from day one of ICU stay.[14]

The APACHE IV database included 9,180 patients. The predictive performance of the APACHE IV predictive equation for coronary artery bypass graft patients was not provided by the authors.

8.2.5 MPM

In 1985 Lemeshow *et al*. developed a multiple logistic regression model to predict hospital mortality from data obtained at ICU admission, later known as the Mortality Probability Model (MPM).[15] In contrast to other prediction models such as APACHE, the MPM used statistical techniques to determine variable weights rather than by assigning weights by expert consensus.

The final admission MPM model included the following variables: age, systolic blood pressure, number of organ failures, infection, type of admission (emergent or elective), level of consciousness (coma or deep stupor versus other), medical or surgical admission, cancer, and number of organ system failures.[15] Although measures of functional status were collected and considered for entry into the model, they were not included in the final model and no further details regarding this decision are provided in the publication.

Seven hundred and thirty seven patients from one general surgical and medical ICU were included in the MPM admission development database. Patients undergoing cardiac surgery, requiring coronary care or admitted with burns were excluded, as were patients under the age of 14 years. The authors reported good fit using the Hosmer Lemeshow GOF statistic ($_{8df,}$ P = 0.3871). No discrimination statistics were reported.

In 1988, Lemeshow *et al.* revised the MPM at admission model.[16] The primary endpoint remained hospital mortality. Twenty six variables were collected at time of ICU admission and assessed for inclusion in the final model. The final MPM at admission model included 11 variables: level of consciousness, type of admission (elective or emergency), cardiopulmonary resuscitation prior to admission (yes/no), cancer as part of the present problem (yes/no), history of chronic renal failure, infection, age, previous ICU admission within the last six months (yes/no), heart rate at ICU admission, surgical service at ICU admission, systolic blood pressure.[16]

Two thousand, six hundred and forty four patients from a single general medical and surgical ICU were included in the development database. Patients undergoing cardiac surgery, admitted with burns or requiring coronary care were excluded, as were patients under the age of 14 years. The MPM at admission model was found to have good fit as measured using the Hosmer Lemeshow GOF statistic (P=0.53). No aROC was reported.

8.2.6 MPM II_0

In 1993 a revised and updated version of the MPM model at admission was published and designated MPM II_0.[17] The final MPM II_0 consisted of 15 variables (coma or deep stupor, heart rate, systolic blood pressure, age, chronic renal insufficiency, cirrhosis, metastatic neoplasm, acute renal failure, cardiac dysrhythmia, cerebrovascular accident, gastrointestinal bleeding, intracranial mass effect, cardiopulmonary resuscitation prior to admission, mechanical ventilation, non-elective surgery admission) which were all highly significantly associated with mortality ($P < 0.001$). If variables were found to be missing at the time of the score calculation, they were assumed to be within the normal range and imputed as 'normal' at time of calculation.

The MPM II_0 database contained 19,124 patients admitted to ICUs across 12 countries. Of these patients, 12,610 were randomly selected for the development database, with 6,514 patients included in the validation database. Patients admitted to a medical or surgical ICU participating hospital were eligible for entry as long as they were older than 18 years, or not admitted due to burns, cardiac surgery or requiring coronary care. The MPM II_0 discriminated well between patients who lived and died with an aROC of 0.837 in the developmental database. The Hosmer Lemeshow GOF test also indicated that the model was well calibrated ($P = 0.623$) and that there was not a large discrepancy between observed and expected mortality. With regards to the validation database, the aROC was 0.824 and the P-

value for the Hosmer Lemeshow GOF test was 0.327, with the authors reporting the model validated well due to both good discrimination and calibration.

8.2.7 SAPS

The Simplified Acute Physiology Score (SAPS)[18] aimed to reduce the workload required to collect variables for the calculation of other scores, such as APACHE.[6] SAPS focused on 14 physiological variables routinely available in the medical record thus increasing the speed of data collection.[18] Unlike the APACHE[7;8;14] and MPM versions,[15-17] SAPS was designed to generate an overall score, rather than to produce a model used to predict mortality.

SAPS included: age, heart rate, systolic blood pressure, body temperature, spontaneous respiratory rate, ventilation or continuous positive airway pressure, urinary output, blood urea, haematocrit, white blood cell count, serum glucose, serum potassium, serum sodium, serum bicarbonate, and GCS score. Like the APACHE APS, the most abnormal value documented within the first 24 hours of ICU stay contributed to SAPS.[18]

Six hundred and seventy nine patients admitted to eight ICU's across France were included in the developmental database. Model calibration and discrimination was not reported. No predictive performance statistics were reported.

8.2.8 SAPS II

In 1993, Le Gall *et al.*[19] developed and validated SAPS II in 137 medical and surgical ICU's across 12 countries. Scoring SAPS II was estimated to take no more than 5 minutes per patient, with the score developed to fit groups rather than individual patients.

Of the 37 variables considered for inclusion in SAPS II, only 17 contributed to the actual SAPS II score, including: age, type of admission (planned surgical, unplanned surgical,

medical), underlying disease variables (acquired immunodeficiency syndrome, haematologic malignancy, metastatic cancer), heart rate, systolic blood pressure, temperature, $Pa0_2/Fi0_2$ ratio in ventilated patients, urinary output, serum urea or serum urea nitrogen, white blood cell count, serum potassium, serum sodium, serum bicarbonate, bilirubin level, and unsedated GCS score. A primary diagnosis was not required in SAPS II. In all cases the worst physiologic variable over the first 24 hours of ICU admission contributed to SAPS II.[19] Albumin was considered for inclusion but did not qualify for inclusion in the final model.

Model performance was evaluated using a total database of 13,152 patients, of which 65% were randomly selected for use as the developmental dataset and 35% for use as the validation dataset. Patients admitted with burns, for coronary care or cardiac surgery or who were younger than 18 years were excluded. In the developmental dataset, the aROC was 0.88 (95% CI 0.87 to 0.90) and the Hosmer Lemeshow GOF calibration statistic demonstrated good fit (P = 0.883). In the validation dataset, discrimination using the aROC was 0.86 (95% CI 0.84 to 0.88) and calibration as measured by the Hosmer Lemeshow GOF statistic was good (P=0.104).

Expanded SAPS II mortality prediction model

In 2005 Le Gall *et al.*[20] developed an expanded version of the SAPS II mortality prediction model incorporating variables that were routinely available at ICU admission and deemed by the authors as easy to collect. The following variables were included in the final extended model: age (<40 years, 40-59 years, 60-69 years, 70-79 years and >79 years), gender, clinical category (medical patient or other), patient location prior to ICU admission (emergency room, ward in same hospital, other hospital), hospital length of stay before ICU admission (<24 hours, one day, 2 days, 3-9 days and >9 days), and intoxication (yes, no).

One hundred and six French ICU's encompassing 77,490 admissions were randomly separated into development and validation datasets. When using the model development dataset, the aROC was 0.880 and the Hosmer Lemeshow GOF statistic was P = 0.275. Using their validation dataset, the expanded SAPS II mortality prediction model had good discrimination as measured by an aROC of 0.879 and good discrimination was measured by a Hosmer Lemeshow GOF test statistic of P = 0.812.

8.2.9 SAPS III

In 2005, an overall SAPS III model was developed to predict hospital mortality using data available at ICU admission.[21;22] Unlike other prediction models and scoring systems, both the newly developed SAPS III score and model were based on data prospectively collected from a multinational cohort of ICUs including Australasia, Central and South America, Eastern Europe, Central and Western Europe and North America. To account for possible differences between ICUs the authors updated their statistical modelling techniques to control for clustering of patients within ICUs, instead of assuming independence of observations. Customised SAPS III prediction equations were also developed for each of the geographical regions represented in the study.

Data collected to compute the SAPS III admission score falls into three categories: 1) patient characteristics prior to ICU admission; 2) reasons for ICU admission; and 3) evidence of physiologic derangement at or within an hour either side of ICU admission. Variables collected prior to ICU admission included: age; co-morbidities; length of stay prior to ICU admission; intra-hospital location prior to ICU admission and; use of vasoactive drugs prior to ICU admission. Reasons for ICU admission were categorised as: planned or unplanned medical admission; planned or emergency surgery; anatomical site of surgery; and acute infection at ICU admission. Variables collected after admission included: GCS score; highest

bilirubin; highest temperature; highest creatinine; highest heart rate; highest leukocyte count; lowest arterial pH; lowest platelet count; lowest systolic blood pressure; and measures of oxygenation. Any values found to be missing at time of collection were imputed as 'normal' at time of outcome prediction.[22]

The performance of SAPS III was evaluated in 16,784 patients from 309 ICU's across 35 countries. The model was developed in 80% of the database, with the remaining 20% forming the validation dataset. Performance statistics for the final SAPS III admission score revealed a final discrimination of aROC 0.848 and a Hosmer Lemeshow GOF statistic of P = 0.39.[22]

8.3 ICU outcome prediction: inclusion of measures of nutrition status

Currently none of the versions of the APACHE, SAPS and MPM models or scores incorporate any elements of nutrition assessment. Whilst serum albumin was formally assessed for inclusion in the early versions of APACHE and SAPS severity of illness scores, it did not meet the formal assessment criteria to warrant inclusion in the final predictive models. Albumin is included in the most recent APACHE IV model; however albumin is no longer accepted to measure nutrition status in critical illness.[23]

With widely held beliefs that metabolic reserve at admission to the ICU may be an important determinant of outcome,[24] the lack of any elements of an admission nutrition assessment in current severity of illness scoring systems has led to calls for them to be considered for inclusion in future versions of severity scores and outcome prediction models.[25]

8.4 Definition of Nutrition Assessment

A *nutrition assessment* has been defined by the American Society of Parenteral and Enteral Nutrition board of directors and standards committee as "a comprehensive approach to defining *nutrition status* that uses medical, nutrition and medication histories; physical examination; anthropometric measurements; and laboratory data".[26] This definition recognises the inextricable relationship between severity of illness, nutrition status and outcome, indicating that a *nutrition assessment* is comprehensive.[26]

8.5 Standardised Nutrition Assessment Tools

The Dietitians Association of Australia recommend the use of a *standardised nutrition assessment tool*, appropriate to the population in which it is to be applied, to define *nutrition status* in the acute care setting.[27] In December 2011, the New South Wales Ministry of Health supported these recommendations, releasing a policy mandating patients undergo nutrition assessment within two working days of referral to a dietitian.[28]

The only *standardised nutrition assessment tools* that have been recommended for use in Australia by the Dietitians Association of Australia[28] and have been evaluated for use in ICU patients include the Subjective Global Assessment (SGA)[29;30] tool and the Mini Nutrition Assessment (MNA)[31] tool.

8.5.1 The Subjective Global Assessment Tool

Use of the SGA tool to conduct a standardised nutrition assessment of hospitalised acutely ill patients has been endorsed by the Dietitians Association of Australia and the American Society of Parenteral and Enteral Nutrition.[32] It is a clinical technique designed to assess nutrition status based on patient medical history and physical examination, and was first described by Baker and Detsky in 1982.[33]

The refined SGA tool and detailed instructions for use were published in 1987[34] and consisted of five variables that focused on patient history and four variables that focused on patient physical examination.

The patient history components included: **1)** The amount of weight lost over the previous six months, which was recorded and compared with recent weight loss in the past two weeks. Patients who had been losing weight but in the two weeks prior to assessment had started to regain weight were regarded as better nourished than patients who had continued to lose weight throughout the six months prior to assessment. Total weight loss <5% was defined as a small loss, 5-10% as a potentially significant loss, and >10% as a definitely significant loss; **2)** The degree and duration of change in dietary intake compared to usual dietary intake; **3)** The presence of persistent gastrointestinal symptoms that had been present (nausea, vomiting, diarrhoea, and anorexia) on almost a daily basis for greater than two weeks; **4)** The patients' current functional capacity, with the assessor documenting the duration and degree of incapacity and; **5)** The underlying metabolic demands of the patients' disease.

The second domain of the SGA tool, physical assessment addressed: **1)** Evidence of loss of subcutaneous fat stores at the mid axillary line at the level of the lower ribs and the triceps region; **2)** Evidence of muscle wasting at the deltoids and quadriceps; **3)** Evidence of oedema at the ankles and sacral region and; **4)** Evidence of ascites. The patient was categorised as either normal, mild, moderate or severe for each physical assessment item. Where there was documentation of disease that would influence the physical appearance of the patient (Ex. ankle oedema due to heart failure), the clinician was told to place less emphasis on that physical finding.

On completing both the patient history and physical assessment, the SGA assigned an overall rating to indicate current nutrition status: A=well nourished; B=moderately malnourished; and C=severely malnourished.

The reliability of the SGA has been formally assessed in a study conducted on a population of 202 acutely ill patients. Whilst components of the physical assessment scales were found to have good reliability between assessors (subcutaneous Fat Loss Kendall's tau 0.82, Muscle Wasting Kendall's tau 0.78) the reliability of the history components were found to be poor (weight loss history Kendall's tau 0.56, ascites Kendall's tau 0.20, gastrointestinal symptoms Kendall's tau 0.28, oedema Kendall's tau 0.35, functional capacity Kendall's tau 0.42 and changes in dietary intake Kendall's tau 0.54).

Furthermore, using logistic regression, two different models were developed to investigate which of the individual components was significantly associated with the presence of malnutrition. Only subcutaneous Fat Loss ($P < 0.001$) and Muscle Wasting ($P < 0.05$) were found to be predictive of the presence of severe malnutrition.[34]

Use of the SGA tool, non-ICU patients

The SGA assessment tool has been accepted to assess nutrition status in a diverse range of populations including patients with ovarian cancer,[35] colorectal cancer,[36] digestive diseases,[37] HIV,[38] heart disease,[39] in patients undergoing liver transplantation[40] and in those undergoing dialysis.[41]

In a series of publications conducted in elective[30;42] and planned major gastrointestinal surgery patients,[34] Baker and Detsky showed the SGA tool to be valid when compared with objective measures such as total body potassium (See Page 37 for detailed description of the use of Total Body Potassium), with the SGA tool having a high level of inter-observer reliability.[29;30;30;34;42] Furthermore, SGA assessment categories significantly correlated with

morbidity outcomes such as the incidence of nutrition-related complications, infection, use of antibiotics and hospital length of stay,[30] and were found to be both sensitive and specific when diagnosing infection.[42]

8.5.2 The Mini Nutrition Assessment

The Mini Nutrition Assessment (MNA)[31] tool was developed in order to provide a standardised nutrition assessment specific to patients aged 65 years and older located in nursing homes, hospitals and home care programmes.[43] It is recommended for use in elderly populations by the European Society for Clinical Nutrition and Metabolism.[43]

The MNA tool has four assessment domains: **1)** dietary assessment; **2)** anthropometric assessment; **3)** general assessment and **4)** patient self assessment. The dietary domain consisted of six questions assessing number of meals consumed per day, daily protein intake per day, daily fruits and vegetables intake, daily fluid intake, whether food intake has declined over the previous three months, and level of feeding assistance required. The anthropometric domain consists of four questions and requires measurement of mid upper arm circumference, calf circumference, and Body Mass Index (BMI), and assessment of weight loss history over the past three months. The general assessment domain consists of six questions assessing independence in living, number of daily medications consumed, current mobility, presence of pressure sores, presence of neuropsychological problems, and whether the patient has suffered psychological stress or acute disease over the past three months. The last domain is assessed by the patient and consists of two questions. The first question asks whether the patient believes they have a nutrition problem, and the second asks for them to compare their current health status with others of the same age.

The assessment is scored, with a total of 30 points available. If the patient scores less than 17 points they are considered malnourished. If they score 17 to 23.5 points they are at

risk of malnutrition. Greater than or equal to 24 points the patient is considered to be well nourished.

The tool was developed using a French database of 155 hospitalised and community living elderly participants with a mean age of 79 years.[44] The database also included results of complete dietary history, detailed anthropometric assessments, mini-mental state assessments, and Katz activities of daily living.

The MNA has been used in many elderly populations, both in the community and general hospitalised settings.[45-48] Malnutrition as defined using the MNA tool has been associated with increased mortality,[45] increased length of ICU and hospital stay and increased postoperative complications.[47;48]

8.5.3 Performance of the SGA tool compared to the MNA tool

There has been one study that has directly compared the use of the SGA tool to the MNA tool in the ICU population.[49] The study enrolled 331patients from a mixed medical and surgical ICU. These patients were enrolled after 24 hours in the ICU. All patients were over the age of 65 years with an overall hospital mortality of 6.2% (16/260). Seventy-one percent (238/331) of patients were *not* mechanically ventilated at time of enrolment.[49] Dietitians administered the MNA and SGA tools concurrently.

To obtain the weight and dietary history elements of each tool, dietitians communicated directly with the patient whenever possible. If the patient was not able to communicate, dietitians made three separate attempts to interview a family member or proxy carer. It is not stated as to the number of patients that had family or proxies provide their nutrition histories. Despite at least three attempts to contact family or proxies, history items remained incomplete in 21% (71/331) of patients. Both the SGA tool and the MNA tool are only able to classify patients if the assessment is complete.

Of the 331 medical and surgical patients enrolled, results of the MNA were complete and reported for 75.5% (250/331) of patients and results of the SGA assessment were complete and reported for 74.0% (245/331). Using the MNA tool, 66% (164/250) of reported patients were defined as being normally nourished, 24% (61/250) at risk of malnutrition and 10% (25/245) were malnourished. The SGA tool defined 77% (188/245) of reported patients as normally nourished, 21% (53/245) as moderately malnourished and 2% (4/245) as severely malnourished.

Agreement between the MNA tool and the SGA tool was considered good (Pearson correlation 0.78).

8.6 Nutrition assessment in ICU patients: missing weight loss and dietary history

A number of studies have highlighted the problems associated with obtaining weight loss history and dietary history information early during ICU stay.[49-52]

Sheean *et al*. reported on a single centre study conducted in 57 mechanically ventilated medical ICU patients who remained in the ICU for more than 48 hours.[50] Despite extensive use of alternative methods to obtain historical information, the authors reported that weight loss histories were missing in 30% (17/57) of patients. Because all enrolled patients were mechanically ventilated and unable to communicate with assessors, Sheean *et al*. consulted food service and medical electronic hospital records and interviewed family to obtain complete SGA histories. Hospital records were searched for key words such as “unintentional weight loss”, “diarrhoea” and “nausea”, “wasted extremities”, “obese abdomen”. Documentation of functional capacity, gastrointestinal symptoms and body weight was sought. Nursing admission notes were reviewed for information on swallowing and

chewing difficulties, and other specific references to weight loss and gastrointestinal dysfunction.

Average length of stay in the hospital *prior to* ICU admission was 6.3 days (Standard Deviation (SD) 11.3 days) in the Sheean *et al*. study which should have increased the amount of historical data available from the electronic medical and food service records compared with patient populations who have little or no hospital stay prior to ICU admission.[50]

Heyland *et al*. attempted to prospectively collect a weight loss history and dietary history in 597 patients admitted to three mixed medical and surgical ICUs who were expected to stay in the ICU for more than 24 hours. Patients had a mean age of 63.9 years and a mean baseline APACHE II score of 21.0. The authors were able to obtain weight loss and dietary history in only 28.6% (171/597) of all patients in this large, multicentre project.[51] Furthermore, when a nutrition history was available, neither diet history (P = 0.10) nor weight loss history (P=0.06) were found to be significantly associated with 28-day mortality.

Huang *et al*. attempted to use family to determine weight loss histories in 49 mechanically ventilated ICU patients. However, the authors reported that they were unable to obtain usual body weight in the preceding six months in 100% (49/49) of patients as "many patients' relatives could not remember their usual body weight".[53]

Difficulties associated with obtaining a complete weight loss history and dietary history is not limited to ICU patients. Atalay *et al*.[52] retrospectively reviewed the charts of 119 hospitalised patients who were referred to the nutrition support team for assessment. Due to missing individual components, only 46% (55/119) of patients had the results of a complete nutrition assessment reported in their charts.

A comprehensive census of all 182 ICUs in Australia and New Zealand demonstrates obtaining a complete nutrition history early during ICU stay is not routine clinical practice in these two countries. Ferrie and Allman-Farinelli undertook extensive pilot testing to develop

and validate a comprehensive tool to determine nutrition assessment practices in the ICU.[54] They contacted and received responses from all 182 ICUs in Australia and New Zealand, describing nutrition assessment in critically ill patients in detail in their results publication.[55] The fact the investigators did not ask one single question about the collection of weight loss and dietary nutrition history information emphasises they are not viewed as viable clinical tools in ICU patients.

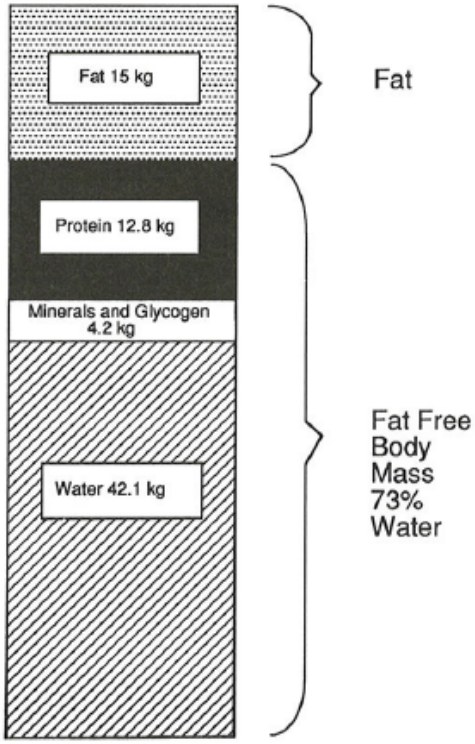
8.7 Measures of Body Composition

This section reviews the accepted criterion methods for measurement of body composition in adults and the proxy techniques used when criterion measurement is not undertaken.

Body composition: the physical components of body mass

The landmark publication by Beddoe *et al*.[56] is accepted to illustrate the breakdown of the physical components of body mass in a healthy 40 year old adult male (Figure 8.1). Based on mass, the healthy normal adult body is accepted to contain approximately 17% protein and 20% fat, with the remainder composed of water (57%), and a small amount of minerals and glycogen.

Figure 8.1: Physical components of body mass in a healthy 40 year old adult male.



From Hill *et al.*[57] Page 7.

8.7.1 Measurement of fat free mass, lean body mass and skeletal muscle mass

Fat free mass is composed of total body protein, total body water, glycogen and minerals. The protein component, also referred to as *lean body mass*, is the second largest component of fat free mass.[57]

Skeletal muscle mass contains about one third to one half of the body's lean body mass stores, and is the greatest reserve of total body protein. Approximately 73-75% of skeletal muscle mass is located in the appendages of the body.[58]

A variety of techniques are available to measure or estimate the protein component of the body and includes: Total Body Potassium; Total Body Nitrogen; Dual Energy X-ray Absorptiometry; Bioelectrical Impedance Analysis; abdominal Computed Tomography scans;

Ultrasound; Mid Arm Muscle Circumference measurement and; physical assessment of skeletal Muscle Wasting.

8.7.1.1 Total Body Potassium (TBK)

Lean body mass can be estimated through externally counting K^{40}, the naturally occurring radioisotope of potassium.[59] The technique was first described in 1961,[60] and is accepted to have a 5% error rate.[61]

Two known underlying assumptions allow measurement of TBK to estimate lean body mass: **1)** potassium is an intracellular cation which is not present in fat and; 2) K^{40} emits a characteristic gamma ray at 1.46 MeV and is known to be present in the other body compartments at a constant ratio of 0.012%. However, measurement of K^{40} requires specialised facilities.[62] Two TBK counting measurement methods are available: 1) using a specialised shadow shield counter in a purpose-built shielded room or chamber to measure the gamma spectrum emitted from K^{40} whilst reducing the background radiation during measurement and; 2) to measure the background radiation in the measurement room and subtract it from the total patient measurement. The second method does not require the patient to be shielded.[63]

Once the patient is in the correct position, measurement takes approximately 20 minutes. Measurement of TBK has been undertaken in a variety of different groups including people with chronic renal failure,[64] cancer,[65] and obesity.[66]

Estimation of TBK in the critically ill patient has been undertaken by Hill *et al.*[67] Measurements were made possible using a purpose built body composition laboratory situated in the study hospital, on the same floor as the ICU. TBK was measured by analysing the gamma spectrum emitted from naturally occurring K^{40} using a specialised shadow shield counter.

Thirteen patients with severe intra-abdominal sepsis, or major trauma who survived the 21-day study period were presented. It is unclear as to how many patients commenced measurements but did not complete the 21-day study period. Over the 21 day study period there was a significant reduction in TBK (from 3810 millimoles to 2990 millimoles, $P<0.001$). The first TBK measurement was taken a median of three days after ICU admission, when patients were deemed haemodynamically stable and able to be transferred out of the ICU for body composition measurement.

In a later study conducted by the same group of authors, Plank *et al.*[68] studied body composition change in 12 patients with peritonitis and 18 patients with major blunt trauma. Despite receiving nutrition support, TBK levels also reduced significantly from study day 0 to study day 21, reflecting a loss in lean body mass. On average, trauma patients lost 18.2 ± 2.7% of TBK and sepsis patients lost 16.7 ± 4.9% of TBK. It is unclear what ICU day the first measurement was taken (study day 0), although the authors stated that patients had to be haemodynamically stable prior to TBK measurement.

8.7.1.2 Total Body Nitrogen (TBN)

Lean body mass can be calculated from TBN measurement.

TBN is first measured using prompt gamma in vivo neutron capture analysis in which whole body nitrogen is measured independent of total body hydrogen, using a specialised laboratory.[69-71] The patient is bombarded with fast neutrons emitted from a neutron source such as ^{241}Americium-Beryllium, and detectors such as sodium iodide are used to measure the gamma rays emitted. The radiation is equal to the amount of radiation received during a standard chest X-ray and measurement takes approximately 20 minutes. Lean body mass is then calculated as 6.25 times the measured TBN.

TBN measurement was first described by Vartsky *et al*. in 1979.[72] Accuracy and precision of repeated TBN measurements using prompt gamma in vivo neutron capture analysis has been shown to be approximately 2-3% in healthy populations.[73]

TBN has been used to measure lean body mass in patients with anorexia nervosa,[74] chronic renal failure requiring dialysis,[75] and in patients with acquired immune deficiency syndrome[76] for example.

In the intensive care population, TBN has been measured using prompt gamma in vivo neutron activation in 13 intubated and ventilated patients, eight with severe sepsis and five patients with trauma.[67] Patients were first assessed a median of three days after ICU admission, using a purpose built facility. Patients lost an average of 11.48kg of lean body mass (from 61.29kg to 49.81kg, $P < 0.001$), and had a significant reduction in TBN (from 1.742kg to 1.496kg, $P<0.001$) over the 21 day study period.

8.7.1.2 Dual Energy X-ray Absorptiometry (DEXA)

DEXA scanning passes two (dual) low dose radiation X-ray beams, operating at different energy levels, throughout the tissues of the body.[77] As soft tissues and bone (bone ash, calcium hydroxyapatite) have different unique densities and therefore different levels of absorption, DEXA is able to differentiate different components of the body.

DEXA scans have most commonly been used to measure bone mineral density.[78] However, in some hospitalised settings they are also used to measure lean body mass, estimate skeletal muscle mass and estimate total fat mass.

DEXA is first used to measure bone mass. The bone mass is then subtracted from the patients total body weight to calculate fat free mass. Fat mass is then estimated by subtracting the bones of the limbs from the measured fat free mass.[58;68] Lastly, skeletal muscle mass is estimated using the Heymsfield equation, validated in healthy subjects.[58]

DEXA and densitometry measurement of total fat mass and soft tissues have been reported to be good when comparing the results of 18 healthy volunteers aged between 23-58 years ($r = 0.90$).[79]

DEXA has been used in a variety of patient types including the morbidly obese undergoing gastric banding,[80] patients with spinal muscular atrophy[81] and in adults with Prader Willi syndrome.[82]

Whilst DEXA scans can be undertaken in around 15 minutes few studies report the use of DEXA in critically ill ICU based patients.[67] Hill *et al.* report the results of DEXA scans in a study of 13 intubated and ventilated ICU patients, eight with severe sepsis and five patients with trauma, using a purpose built facility.[67] Patients were evaluated a median of three days into ICU stay.

Over the 21 day period, DEXA indicated ICU patients lost a significant amount of fat free mass (from 61.29kg to 49.81kg, $P < 0.001$), and skeletal muscle mass (from 24.41kg to 19.15kg, $P < 0.001$).

8.7.1.3 Bioelectrical Impedance Analysis (BIA)

BIA uses an electrical current to assess body composition by quantifying fat free mass and total body water through measuring tissue conductivity and using population specific BIA equations and established procedures.[83] Measurement is regarded as non-invasive, can be conducted at the bedside, and does not require active patient participation.[62] There are multiple methods available to measure BIA such as using single frequency, multi-frequency and bioelectrical spectroscopy. However, the accuracy and/or precision of the various BIA measurement methods are heavily dependent on a stable hydration state.[62;68;78]

BIA has been used in a wide variety of patients including patients with rheumatoid arthritis, acquired immune disease syndrome, chronic renal disease and chronic obstructive pulmonary disease.[83;84]

In the critically ill, Faisy *et al*.[85] undertook a study of 338 chronic obstructive pulmonary disease patients who required admission to the ICU. Two-frequency BIA was used within five days of ICU admission, and the results were compared to other anthropometric assessment techniques. However, only 15.1% (51/338) of patients assessed within five days of ICU admission had complete data and were reported. No overall measures of agreement between the techniques were stated and skeletal muscle loss over time was not quantified.

Robert *et al*.[86] also used BIA to assess lean body mass in 33 medical and surgical ICU patients with a mean age of 56.2 years. Single frequency BIA measurements were taken every other day until discharge or death. The authors report no significant differences between lean body mass measurements taken within 48 hours of ICU admission and at ICU discharge or death ($P > 0.05$).

8.7.1.4 Abdominal Computed Tomography (CT) scans

The cross-sectional skeletal muscle area, measured using single-slice abdominal CT scans at the third lumbar vertebral landmark, is accepted to be linearly related to fat free mass.[87] Compared to DEXA measurement in 50 cancer patients, its performance is accepted to be good at diagnosing sarcopenia.[87] In 2014, Weijs *et al*. applied this technique to critically ill patients.[88]

In an 8-year retrospective audit of 12,507 ventilated ICU patients who remained in a medical and surgical ICU for at least 4 days, 2.3% (293/12,507) of patients were found to have had an abdominal CT within four days of admission. However, 18% (53/293) of abdominal CT scans were unusable due to the presence of artefacts.

In the patients who did have usable CT scans, Weijs *et al*. reported that lower skeletal muscle area was significantly associated with higher hospital mortality compared with normal muscle area (38.2% versus 12.5% mortality, $P < 0.001$). Furthermore, using backwards stepwise logistic regression to control for APACHE II score and gender, CT muscle area remained a significantly associated with hospital mortality (odds ratio (OR) 4.3, 95% CI 2.0 to 9.0, $P < 0.001$).

Moisey *et al*.[89] reported a retrospective review of 149 elderly trauma patients admitted to an ICU who had abdominal CT scans taken on the day of admission. Skeletal muscle and adipose tissue cross sectional areas were calculated using single-slice CT scans at the third lumbar vertebra, and using specialised SliceOmatic version 3 image analysis software (TomoVision, Montreal, QC, Canada). Muscle index was further calculated by dividing muscle cross sectional area by height in meters squared, and then used to categorise patients as sarcopenic or not sarcopenic. Sarcopenia was defined as a muscle index less than $38.9 cm^2/m^2$ for females and less than $55.4 cm^2/m^2$ for males.

Seventy one percent (106/149) of enrolled patients were diagnosed as sarcopenic. In multiple logistic regression, increased muscle index was significantly associated with decreased mortality (OR per unit muscle index = 0.93, 95% CI 0.875 to 0.997, $P = 0.002$) after controlling for injury severity, age and gender.

Sheean *et al*.[90] have investigated the use of abdominal and pelvic CT scans in 301 ICU patients with acute lung injury. Sarcopenia was defined being present when the third lumbar vertebra skeletal muscle index was ≤ 38.5 centimetres/m^2 for women and ≤ 52.4 centimetres/m^2 for men. Sarcopenic obesity was considered present in all patients with a BMI of $\geq 30 kg/m^2$, meeting the above skeletal muscle indexes. Of the 301 patients screened for inclusion over 12 months, 18.6% (56/301) were included in the final study. The remaining 78.4% (236/301) did not have CT imaging, or had CT images that did not include the third lumbar region.

Sarcopenic obesity was diagnosed in 24% (8/34) of the patients with an appropriate CT image.

8.7.1.5 Ultrasound

Ultrasound using a 4[91;92] or 5[93] MHz transducer to produce a B-mode display can be used to quantify muscle layer thickness by measuring cross sectional area at the *M. quadriceps femoris* muscle. The earliest description of the technique being used is 1968.[94] More recently, Walton *et al*. showed there was no significant differences in ultrasound measurement compared with magnetic resonance imaging in a study of ten healthy volunteers.[93] Additionally, Tillquist *et al.*[95] showed intra-rater and inter-rater reliability to be excellent in healthy volunteers.

In the ICU patient, Gruther *et al.*[96] reported on two studies measuring muscle layer thickness in medical and surgical patients. The first study measured 17 patients on the second day of ICU admission and 28 days later. The second study measured 101 patients on one random occasion during ICU stay. They reported a 50% reduction in muscle layer thickness over the first 20 days of ICU stay (no P-value reported).

In an earlier ICU based study, Campbell *et al.*[97] reported on a study of nine patients with multiple organ failure who had serial measurements of muscle thickness taken at three sites (mid-biceps, anterior forearm and anterior thigh). All patients had a minimum of five repeat measurements taken throughout ICU stay, with the first measurement taken within five days of ICU admission. Muscle thickness decreased with time, with average rates of decrease as a percentage of the first measurement ranging from 2.0 to 9.2% per day in the nine patients.

8.7.1.6 Mid Arm Muscle Circumference

The measurement of Mid Arm Muscle Circumference provides an estimate of lean body mass.[62;98] Mid Arm Muscle Circumference is calculated from mid upper arm circumference and Triceps Skinfold Thickness measurements using the formula from Heymsfield.[99] Mid upper arm circumference is measured at the midpoint between the acromion process and the radial head using a non stretch tape measure. The Triceps Skinfold Thickness is measured at the same level as the mid upper arm circumference on the posterior surface of the arm using skinfold calipers.

When calculating Mid Arm Muscle Circumference from either standing or supine measured Triceps Skinfold Thickness and mid upper arm circumference, results have been found to be highly correlated (r=0.97).[100]

In a study of 124 medical and surgical ICU patients and using the SGA tool as a criterion method, Sungurtekin *et al.*[101] found Mid Arm Muscle Circumference admission measurements to be lower in malnourished groups compared with well nourished groups (17.2 ±1.9cm (severely malnourished), 18.8 ±2.1cm (moderately malnourished), and 21.3 ±2.6cm (well nourished), $P < 0.05$. Mortality was also found to negatively correlate with Mid Arm Muscle Circumference measurements (correlation coefficient -0.578, $P < 0.001$).

Ravasco *et al.*[102] calculated Mid Arm Muscle Circumference in 44 medical ICU patients with an ICU stay of greater than 48 hours. Mid Arm Muscle Circumference measurement was found to be significantly associated with clinical evaluation of muscle mass, palpated at the biceps and triceps areas ($P = 0.020$).[103] Patients who were ventilated had significantly lower Mid Arm Muscle Circumference measurements ($P = 0.005$), and more severe clinically evident muscle depletion ($P = 0.050$).

8.7.1.7 Physical assessment of Muscle Wasting

Physical assessment of Muscle Wasting is one of four physical assessment variables that form part of the standardised SGA tool.

Ravasco *et al.*[102] prospectively evaluated physical evidence of Muscle Wasting in 44 ventilated respiratory ICU patients. On personal communication with Professor Ravasco[103] she stated that the deltoid, biceps and triceps areas were palpated to determine physical evidence of Muscle Wasting within 48 hours of ICU admission. Using physical examination, moderate (55%, 24/44) and severe (38%, 17/44) Muscle Wasting was evident within 48 hours of ICU admission, and depletion was significantly more prevalent in patients over the age of 65 years ($P < 0.001$). Furthermore, physical evidence of Muscle Wasting was significantly associated with mid upper arm circumference and Mid Arm Muscle Circumference ($P = 0.05$ for both).

8.7.2 Measurement of body fat

Approximately 80% of body fat is regarded as storage fat. Storage fat is situated in subcutaneous, inter-muscular, intra-abdominal and intra-thoracic areas, and is a readily available metabolic energy reserve. The remaining 20% of storage fat is located in the bone marrow, the central nervous system and other organs; and is considered to be essential fat.[57]

A variety of techniques are available to measure or estimate body fat and include: Underwater weighing; nuclear techniques; Bioelectrical Impedance Analysis; saggital abdominal diameter measurement; abdominal CT scans; Skinfold Thickness measurement and; physical assessment of subcutaneous Fat Loss.

8.7.2.1 Underwater weighing

When measuring body fat the criterion method is considered to be hydrodensitometry or underwater weighing, with the technique first described during the 1960's by Goldman and Buskirk, and Akers and Buskirk.[62;104] During weighing, the patient is completely immersed in water, and must exhale and hold the breath while immersed. Specialised staff and equipment are required during measurement.

Whilst the technique is sensitive to temperature variations that may occur during measurement, it has been shown to be an accurate and reliable tool with a precision of within 1% body fat in the groups studied.[104;105] Underwater weighing has not been used in the ICU setting.

8.7.2.2 Nuclear techniques for measuring body fat

The three most common nuclear techniques used to measure body fat are TBN, TBK and DEXA. Body fat is estimated using these techniques after first directly measuring lean body mass.[57;68]

In the critically ill patient, DEXA measurement has been used to measure body fat an average of two days into ICU stay, and then 21 days later. Twelve patients with severe sepsis and 18 patients with trauma were studied. Body fat measurement significantly decreased from 13.79 ± 1.81 kilograms to 13.27 ± 1.81 kilograms in patients with trauma (P=0.047) and non-significantly from 17.17 ± 2.23 kilograms to 16.80 ± 2.00 kilograms in patients with severe sepsis (P=0.63).

8.7.2.3 Bioelectrical Impedance Analysis

When measuring body fat using BIA, fat free mass and total body water are first directly measured using the BIA machine. Body fat is then estimated as the difference between total body weight and the BIA-measured fat free mass.[62]

In non ICU patients, BIA estimated body fat has been shown to correlate with hydrodensitometry, the criterion method for measuring body fat.[106] Brodie and Eston found good correlation between single and multi frequency BIA and hydrodensitometry techniques when studying a variety of community based groups including obese women, athletic students, and healthy women and children. The lowest correlation coefficient was reported in 67 healthy women of normal adiposity using single frequency BIA (correlation coefficient 0.64) and the highest correlation coefficient in 25 obese women using multi frequency BIA (correlation coefficient 0.95).[106]

In the ICU population, Faisy *et al*. reported one study of 338 ICU patients with chronic obstructive pulmonary disease.[85] Low frequency (5kHz) and high frequency (1 MHz) BIA was used within five days of admission. Of the 15.1% (51/338) of patients with complete data, there was no association found between BIA measured body fat and ICU mortality (P >0.05). Average fat loss over time was not reported.

8.7.2.4 Saggital Abdominal Diameter measurement

Saggital abdominal diameter, which is described as the anteroposterior diameter of the abdomen in the saggital plane,[107] can be measured in supine positioned patients using an abdominal caliper. The caliper is placed at the level of the iliac crests and the upper arm of the caliper is gently brought down to touch the abdomen without compression.[108] In community based adult cohorts, saggital abdominal diameter measurement has been shown to be strongly correlated with overall abdominal fat,[109] overall mortality[110] and sudden death.[107]

Paolini *et al.*[108] conducted a prospective observational study in two general ICU's, measuring saggital abdominal diameter at admission in patients with a stay of 48 hours or longer. Saggital abdominal diameter was measured using a Holtain abdominal caliper. Patients with oedema, cirrhosis, pregnancy or amputation, and patients who were to or had undergone abdominal surgery were excluded from the study.

Of the 503 patients admitted to the ICU, 80% (403/503) were included in the study and 27% (109/403) were determined to be abdominally obese (abdominal diameter ≥26 centimetres). Abdominally obese patients were at increased risk of death measured at day 60 after controlling for age, SAPS II, and McCabe score (adjusted OR 2.12, 95% CI 1.25-3.60).

8.7.2.5 Abdominal CT scans

As well as measuring skeletal muscle area, single-slice abdominal CT scans can be used to measure adipose tissue cross-sectional area. Measured at the third lumbar vertebral landmark, adipose tissue cross-sectional area is accepted to be linearly related to whole-body fat mass.[87;111;112]

In 2013, Moisey *et al.*[89] studied 149 patients admitted to a single trauma centre who were over the age of 65 years. All patients had undergone a single-slice abdominal CT scan taken at the third lumbar vertebra on the day of ICU admission. SliceOmatic software version 4.3 (TomoVision Montreal QC Canada) was later used to determine total fat mass. Muscle index was used to define presence of sarcopenia and was identified as being present in females with less than 38.9cm^2/m^2 and in males with less than 55.4cm^2/m^2.

Patients with CT-defined sarcopenia had significantly lower total fat mass (P = 0.016) compared with patients who did not have sarcopenia. However there was no difference in visceral fat mass between sarcopenic and non-sarcopenic groups. After controlling for injury

severity, age and gender, total fat mass measured on admission was not associated with mortality (P = 0.110), ventilator-free days (P = 0.710) and ICU-free days (P = 0.820).

In 2014, Braunschweig *et al*.[113] reported on 33 respiratory ICU patients with a mean APACHE II score of 26 (SD 7) who had at least two CT scans during hospitalisation and received some form of nutrition support between the first and second CT scan. The first CT scan was done anytime during ICU stay, with the two scans separated by an average of 10 days. Results indicated that visceral fat deposits did not significantly decrease over time (females P = 0.810, males P = 0.870) and intermuscular fat deposits did not significantly change (females P = 0.630, males P = 0.900). Subcutaneous fat measurements could not be accurately assessed due to the scope of the CT scans.

8.7.2.6 Skinfold Thickness measurements

Skinfold thickness measurement can be used to calculate percentage total body fat and to provide a relatively accurate and direct measure of subcutaneous fat stores through measuring skin thickness and underlying adipose tissue. In 1981, Lohman reported the error in estimating body composition from skinfolds was approximately 5% depending on the population-specific prediction equations used.[114] Correlation coefficients of 0.80 and higher have also been reported between skinfold thickness measurements and ultrasound measurement.[115-117]

Skinfolds thickness measurements have been used to measure percentage total body fat in professional athletes, healthy communities, and in hospitalised populations.[62] They are non-invasive, regarded as safe, relatively inexpensive and time efficient, practical, and easily conducted at the patient bedside. Triceps Skinfold Thickness measurement remains the most commonly measured skinfold thickness in ventilated critically ill patients.[53;101;118]

Measurement of Triceps Skinfold Thickness has been shown to be highly reproducible for both within (intra-class correlation coefficient for intra-observer error 0.98) and between (intra-class correlation coefficient for inter-observer error 0.97) person variations using trained staff. Furthermore, reliability has been found to be almost identical whether measurements are taken in sitting or supine positions[118] (correlation coefficient 0.99).[100]

Measurement of Triceps Skinfold Thickness has been undertaken in a number of ICU based studies.[53;85;101;102;119] For example, Sungurtekin *et al*.[101] measured Triceps Skinfold Thickness in 124 medical and surgical patients at ICU admission. Lower Triceps Skinfold Thickness values were significantly associated with the presence of severe and moderate malnutrition (22.7 ±3.7 millimetre (mm) severely malnourished; 25.1 ±3.6mm moderately malnourished; and 29.2 ±5.0mm well nourished; $P < 0.05$). Triceps Skinfold Thickness measurements were not significantly correlated with mortality (-0.046, $P = 0.615$).

Huang *et al.*[53] measured Triceps Skinfold Thickness in 49 medical and surgical ICU patients and failed to find a significant association between Triceps Skinfold Thickness and ICU or hospital length of stay ($P>0.05$).

Ravasco *et al.* measured Triceps Skinfold Thickness in 44 medical ICU patients, 82% (36/44) of which were ventilated.[102] During measurement the patient was positioned on their back with their arm fully relaxed and lifted before the Triceps Skinfold Thickness measurement was taken. Triceps Skinfold Thickness measurement was not associated with mortality ($P >0.05$).

Skinfold Thickness measurements: assumptions

Percentage (total) body fat is estimated from one of four external surface measurements using over 100 different body density regression equations.[120] The onus is on the user to choose an equation that has been developed on a similar population to the one

under study, as well as ensuring the same anatomical landmarks and brand of skinfold caliper are used.[121;122]

Different regression equations have been published for use in various Australian populations: for example, two have been developed for use in high level athletes,[123;124] with a third developed for use in young females with a mean age of 22.3 years (range 17.4-35.2 years).[125] Other well known regression equations such as Durnin and Womersley were developed in Scotland and involved community based males and female volunteers from 16 to 72 years of age.[120] Katch and McArdle[126] developed their regression equation on volunteer female and male American college students with a mean age of approximately 20 years. No regression equations have been published for use in intensive care patients, either in Australia or overseas, with ICU researchers calling for the development of normative tables for use in critically ill patients.[53]

Other assumptions which may introduce errors when determining body density and hence percentage body fat include: the assumption that skin thickness is uniform throughout the measurement population, when it has been shown to be thicker in males and to decrease with age; that skin compressibility is constant, when in fact cadaveric analysis has shown it can vary by up to 200%; and that the relationship between external subcutaneous fat mass and total fat mass is linear, when cadaveric analysis has indicated that body fat deposition is influenced by such factors as age, gender, measurement technique and degree of fatness. Additionally, there is no individualisation of fat distribution patterns, with the assumption that after measuring a few skinfold sites that this accurately represents overall subcutaneous fat mass.[121]

8.7.2.7 Physical assessment of Subcutaneous Fat Loss

Physical assessment of subcutaneous fat loss is one of four physical assessment components of the standardised SGA tool.

In a study of all hospital patients, which included ICU patients, Nursal *et al*.[127] investigated the use of physical assessment of subcutaneous Fat Loss and compared it with results of the entire SGA tool. Physical evidence of subcutaneous Fat Loss predicted malnutrition in 91.9% of cases when compared with diagnosis using the SGA tool (OR 57.14, 95% CI 39.75 to 82.15, P <0.001). During logistic regression, physical evidence of subcutaneous Fat Loss had the most significant weighted effect on the final SGA diagnosis of malnutrition (P = <0.001).

8.7.3 Measurement of Total Body Water

Total body water is the largest component of fat free mass, and includes both intracellular and extracellular water. In healthy adults, total body water levels are reported to remain relatively stable and are mostly affected by age, gender, race, height and weight. Normative values for the healthy individual were published in 2007.[128]

Critically ill patients often receive large volumes of resuscitation fluids to maintain haemodynamic stability due to the continuous depletion of plasma volume. The expansion of the interstitial fluid space is caused in part by changes in the interstitial matrix and cell membranes as well as an increase in capillary permeability. The interstitial fluid space accounts for approximately 80% of the extracellular fluid volume and is regarded as a dynamic compartment which allows protein, electrolytes and water to continually pass between plasma and cells.

Total body water is well known to be altered under certain disease conditions; therefore normative reference values may be inappropriate for critically ill patients due to the

fact that some patients may have expanded total body water, particularly the extracellular component; and others may not. Septic critically ill patients and patients who receive large amounts of fluid management are particularly prone to increased total body water.[53;68;129;130]

Total body water can be measured by such techniques as: Isotope Dilution; BIA; and physical assessment of Oedema.

8.7.3.1 Isotope Dilution

The criterion method used to measure total body water in humans is the isotope dilution technique. Measurement using isotope dilution technique has been undertaken using tritium oxide, oxygen-18, hydrogen and deuterium oxide for example. Once ingested or injected, the isotopes are then detected in body fluids such as saliva, plasma and/or urine at a later date, using appropriate analytic techniques. However, isotope measurement requires specialised equipment, is time-consuming and labour intensive, and use of oxygen-18 is comparatively expensive. Also, tritium oxide cannot be used in pregnant women and children due to its radioactive nature.

Studies using isotope dilution technique in the ICU setting are discussed in the following BIA section. Precision depends on variables such as the isotope given, the route used to deliver the isotope, the population under study, and hydration status of the population.

8.7.3.2 Bioelectrical Impedance Analysis

The use and acceptance of BIA in the ICU as a clinical tool to measure total body water and its components have been highly debated.[84] This is because the BIA method assumes that stable hydration conditions are met, which may not be accurate in all ICU patients. As such, some researchers have declared that BIA is not a useful or accurate tool.[131]

BIA is however cheaper than isotope dilution and doesn't involve the use of a radioactive tracer.

Patel *et al.* compared the use of single (5 kHz) and multi frequency (5 to 1000kHz) BIA machines with isotope dilution in eight male patients six hours after coronary artery bypass graft surgery.[132] All patients were admitted to the cardiothoracic ICU and had a mean APACHE II score of 14.8 (SD 2.7). Compared with deuterium oxide, multi frequency BIA significantly underestimated total body water by an average of 5.6 litres (P = 0.02). There was no significant difference between measurements made with single frequency BIA and deuterium oxide. There were also no significant differences between single and multi frequency BIA when measuring extracellular water compared with the criterion method of bromide dilution.

Plank *et al.*[133] measured extracellular water volume using multi-frequency (5-500kHz) bioimpedance spectroscopy, and compared it with bromide dilution as the criterion measure. Thirty seven patients with a median age of 40 years, admitted due to major trauma (n=18) or serious sepsis (n=19) were included in the study. Measurements were undertaken when patients were haemodynamically stable (time point not specified) and ten days later. Using bromide dilution, on study day 0 the mean extracellular water measurement was 26.02 ± 6.56 litres and at study day 10 it was 21.58 ± 6.49 litres (10-day loss 4.43 ± 4.84 litres, P<0.001) for all 37 patients. On both measurement days, bioelectrical impedance spectroscopy significantly underestimated extracellular water measurement as determined by bromide dilution (P = 0.015).

In a later publication, Plank *et al.* studied 12 patients with peritonitis and 18 with blunt trauma.[68] Total body water was measured using tritiated water dilution as the criterion method, and extracellular water was estimated using sodium bromide dilution as the criterion method. Results were compared to bioelectrical impedance spectroscopy (5-500kHz). The

median time from ICU admission to the first body composition assessment was stated as two to three days, and the last measurement was taken 21 days later.

On average, extracellular water measurement decreased in the peritonitis group from 28.16 ± 2.11 litres at study day 0 to 20.35 ± 2.03 litres at study day 21 ($P > 0.05$), and decreased from 22.75 ± 0.78 litres at study day 0 to 18.11 ± 0.82 litres at study day 21 ($P < 0.05$) in the blunt trauma group. Measurement of extracellular water in the blunt trauma group was comparable using bromide dilution and bioelectrical impedance spectroscopy (figures not provided); however, bioelectrical impedance spectroscopy underestimated extracellular water measurement using bromide dilution by four litres at study day 0 and two litres at study day 21 in patients with peritonitis. The authors suggest this may have been due to retention of fluid in the abdominal cavity which was not fully measured by the impedance method.[68]

Measurement of total body water using bioelectrical impedance spectroscopy and tritiated water dilution were in good agreement for both trauma and peritonitis patients (figures not provided).

8.7.3.3 Physical assessment of Oedema

The most commonly used bedside nutrition assessment technique to identify the presence of oedema in hospitalised populations comes from the physical assessment component of the SGA tool.[134] Whilst two ICU based studies[102;119] have assessed the prevalence of oedema it is unclear as to whether they used the SGA tool to do so. Both studies appear to have deviated from the original tool in terms of body sites assessed[102;119] and oedema categories used.[102]

8.7.4 Measures of overall Body Size

8.7.4.1 Body Mass Index (BMI)

Body mass index is defined as weight in kilograms divided by the square of the height in meters.[135] Organisations such as the WHO taskforce,[136] the National Institutes of Health (NIH)[137] and the National Health and Medical Research Council[138] categorise 'body fatness'[136] or body size[138] using BMI. The WHO categories are widely adopted as they allow different groups to compare relative risks of mortality and morbidity at the population level. The WHO defines a BMI of less than 18.50kg/m^2 as underweight, between 18.50 kg/m^2 and 24.99 kg/m^2 as normal weight, between 25.00 kg/m^2 to 29.99 kg/m^2 overweight, 30.00 kg/m^2 to 39.99 kg/m^2 obese Class 1 and ≥40.00 kg/m^2 obese Class 2.[136;139]

In 2015, the European Society for Clinical Nutrition and Metabolism released a consensus statement defining presence of malnutrition based on BMI alone (BMI <18.5kg/m^2).[140]

BMI is regarded as a crude measure of body composition as it does not discriminate between fat mass and lean body (muscle) mass. In healthy non hospitalised patients, the association between high BMI and increased all-cause mortality has been well documented.[139]

BMI and outcome in critically ill patients

Physicians' caring for obese patients report the prediction of higher mortality and/or poorer functional recovery compared with non-obese patients. O'Brien *et al.* administered a mail based survey to 289 American Thoracic Society members who cared for septic patients. A series of case studies involving a patient with identical APACHE II scores, septic shock and multi-organ failure was presented. The case studies varied by BMI (BMI 22kg/m^2 or BMI 40kg/m^2). Physicians predicted a higher percent point increase in predicted mortality in patients with a BMI of 40kg/m^2 compared with a BMI of 22kg/m^2 (4.3 points, 95% CI 2.5 to

6.2, P<0.001). They also predicted a higher percentage point change in predicted problems with self care at six months in patients who survived and had a BMI of 40kg/m^2 compared with 22kg/m^2 (5.3 point change, 95% CI 3.2 to 7.4, P<0.001).[141]

Retrospective and prospective studies have shown BMI at time of admission to the ICU to be related to outcome.[25;141-147] For example, Pickkers *et al.*[142] conducted a study in 62 medical and surgical ICU's across The Netherlands, enrolling 154,308 patients from the Dutch National Intensive Care Evaluation registry. BMI was analysed using the WHO categories with the 'normal' BMI category used as the referent. All analyses were adjusted for SAPS II score, gender and neoplasm. They reported that compared to Normal BMI, a BMI of less than 18.5kg/m^2 was significantly associated with a higher hospital mortality (OR 1.62, 95% CI 1.52 to 1.72), whereas patients with a BMI of 30.0kg/m^2 to 34.9kg/m^2 (OR 0.86, 95% CI 0.84 to 0.89) and 35.0kg/m^2 to 39.9kg/m^2 (OR 0.86, 95% CI 0.83 to 0.90) were associated with a lower hospital mortality.

Marik *et al*. reported results obtained from a database collected at 101 American medical and surgical ICU's from 84 hospitals.[145] BMI was analysed using the National Heart, Lung and Blood Institute (NIH) categories[137] with Normal BMI (BMI 18kg/m^2 to 24.9kg/m^2) used as the referent category.

Multivariable logistic regression controlled for severity of illness (SAPS II score), presence of sepsis, and medical or surgical admission. Compared to Normal BMI, being underweight (BMI <18.5kg/m^2) was associated with a significant increase in hospital mortality (OR 1.26, 95% CI 1.14 to 1.40) whereas being overweight (OR 0.86, 95% CI 0.80 to 0.92) or having a BMI of 30 to 34.9kg/m^2 (OR 0.85, 95% CI 0.78 to 0.93) or BMI 35 to 39.9kg/m^2 (OR 0.76, 95% CI 0.66 to 0.87) was associated with significantly lower hospital mortality.

Using the same initial database as Marik *et al.*, O'Brien *et al.*[143] investigated the association between admission BMI and hospital mortality in a subgroup of 1,488 patients with acute lung injury. BMI was analysed as a continuous variable and then categorised using the NIH categories[137] with the Normal BMI category being used as the referent.

Using univariate logistic regression, BMI was significantly associated with hospital mortality analysed as a continuous ($P < 0.001$) and as a categorical variable ($P = 0.006$). When BMI was adjusted for age, gender, race, SAPS II probability of survival, diagnosis of renal or genitourinary disease and acquired renal or genitourinary complications, compared to Normal BMI, the odds of hospital mortality were found to be significantly higher at BMI's $<18.5 kg/m^2$ (adjusted OR 1.94, 95% CI 1.05 to 3.60, $P = 0.035$) and significantly lower at BMI of 30-39.9kg/m^2 (adjusted OR 0.67, 95% CI 0.46 to 0.97, $P = 0.033$). Other categories did not reach significance. The continuous BMI variable also remained significantly associated with hospital mortality in multivariable ($P<0.001$) regression although the covariates adjusted for were not explicitly stated.

In a subsequent publication, O'Brien *et al.* investigated the relationship between BMI and hospital mortality whilst controlling for processes of care as potential confounders.[141] Five hundred and eighty mechanically ventilated patients were enrolled from three ICU's in the United States of America. BMI was categorised as $<25 kg/m^2$, 25 to 30kg/m^2 and $\geq 30 kg/m^2$; with $<25 kg/m^2$ used as the referent category.

Controlling for obstructive sleep apnoea, SAPS II score, highest tidal volume per ideal body weight, use of benzodiazepines and opioids on study day 1, compared to Normal, patients with a BMI of 25 to 30kg/m^2 had a significantly lower risk of death (hazard ratio 0.68, 95% CI 0.47 to 0.99, $P = 0.044$) during hospital stay.

Peake *et al.*[146] evaluated the association between BMI and 30 day and 12 month mortality in 493 medical and surgical ICU patients enrolled in a single Australian ICU. BMI

was analysed using three different methods; as a continuous variable, categorised according to the WHO[136] or dichotomised (<35kg/m^2 or ≥35.0kg/m^2). Sixty patients (12.2%) did not have a measured or premorbid weights recorded due to medical instability and were excluded from the study.

Analysed as a continuous variable, BMI was not found to be associated with mortality (time ratio 1.02, 95% CI 0.995-1.044, P = 0.120). However, when categorised according to the WHO criteria, with Normal BMI as the referent category, BMI ≥35.0kg/m^2 was found to be associated with a survival benefit (time ratio 2.06, 95% CI 1.088-3.909, P = 0.030). When dichotomised, BMI ≥35.0kg/m^2 also was found to be associated with increased survival at 30 days (time ratio 1.853, 95% CI 1.053-3.260, P = 0.032) and 12-months (time ratio 1.034, 95% CI 1.005-1.063, P = 0.019).

Aldawood *et al*.[147] also investigated the association between BMI and mortality at hospital discharge in 1,835 medical and surgical ICU patients enrolled from a single ICU in Saudi Arabia. BMI was categorised as per the NIH,[137] with Normal BMI used as the referent category.

In multivariable analysis, when compared to Normal BMI, BMI >40kg/m^2 was associated with a significant reduction in hospital mortality (OR 0.51, 95% CI 0.28-0.92, P = 0.025) after controlling for respiratory illness, gender, age, medical and trauma admission.

In France, Garrouste-Orgeas *et al*.[25] investigated the relationship between BMI and hospital mortality across six mixed medical and surgical ICU's enrolling 1,698 patients. BMI was categorised according to the WHO categories,[136;148] with Normal BMI assessed as the referent category. As the final database contained 23 patients (0.01%) with a BMI ≥40 kg/m^2, the authors collapsed the 30-39.9 kg/m^2 and the ≥40 kg/m^2 categories. On univariate analysis, compared to Normal BMI, having a BMI <18.5 kg/m^2 was significantly associated with a higher hospital mortality (OR 1.63, 95% CI 1.1-2.39, P = 0.010), whilst being overweight was

associated with a lower mortality (OR 0.60, 95% CI 0.40-0.88, P = 0.010). However, removing patients with AIDS and metastatic cancer from the analysis, the underweight category (BMI < 18.5) was no longer significantly associated with mortality (OR 1.49, 95% CI 0.98-2.26, P = 0.060*).*

In contrast to the previous studies demonstrating significant relationships between BMI and outcome, many other adequately powered studies have failed to duplicate these results. For example in a single centre study conducted in a medical ICU enrolling 2,148 patients, Ray *et al.*[149] investigated the relationship between BMI categorised according to the NIH[137] and hospital mortality. Univariate logistic regression failed to find a significant relationship between BMI and ICU or hospital mortality ($\chi^2 = 2.82$, P-value = 0.588; $\chi^2 = 3.56$, P-value = 0.469 respectively).

Pieracci *et al.*[150] conducted a single centre study of 1,298 surgical ICU patients. BMI was analysed as a five-group categorical variable according to the NIH criteria[137] with Normal body weight used as the referent category. BMI was also dichotomised (BMI ≥40kg/m^2 vs BMI <40kg/m^2). In univariate analysis, neither categorised BMI (P = 0.090) nor dichotomised BMI (P = 0.270) was significantly associated with mortality. In addition, after conducting multivariable logistic regression controlling for age, APACHE III score, gender, pre-existing diabetes, and insulin infusion neither categorised BMI (P = >0.05) nor dichotomised BMI (P = 0.100) were significantly associated with mortality.

Similarly, Sakr *et al.* conducted a study enrolling 2,878 patients from 198 ICU's across 24 European countries.[151] BMI was categorised according to the NIH and WHO criteria, with Normal BMI category (18.5 to 24.9kg/m^2) used as the referent group for analysis. After adjusting for SAPS II, BMI was not found to be significantly associated with hospital mortality (OR 1.27, 95% Cl 0.75 to 2.14, P = 0.371).

8.7.4.2 Mid Upper Arm Circumference: a surrogate measure of BMI

Mid upper arm circumference is measured at the midpoint between the acromion process and the radial head using a non stretch tape measure. In the hospitalised patient, mid upper arm circumference, a composite measure of muscle and fat stores, was proposed as a surrogate for BMI where patients are unable to have their heights or weights easily measured.[152] Measurement of mid upper arm circumference has been shown to be highly reproducible for both within (intra-class correlation coefficient for intra-observer error 0.99) and between (intra-class correlation coefficient for inter-observer error 0.98) person variation.[118] Reliability has been found to be almost identical whether measurements are taken in standing or supine positions (r = 0.98).[100]

Sungurtekin *et al*.[101] measured mid upper arm circumference at admission in 124 medical and surgical ICU patients. Using the SGA tool as the criterion method to diagnose malnutrition, mid upper arm circumference measurements were significantly lower in malnourished patients compared with well nourished patients (24.3 ±2.8 centimetre (cm) severely malnourished; 26.7 ±2.8cm moderately malnourished; and 30.5 ±3.8cm well nourished; $P < 0.05$).

Ravasco *et al*. measured mid upper arm circumference within 48 hours of medical ICU admission in 44 patients with a mean APACHE II score of 23.8.[102] Patients who had a mid upper arm circumference less than the 15th percentile of the healthy population had a significantly higher mortality rate in multivariable analysis ($P = 0.030$) when controlling for sepsis and multiple organ dysfunction syndrome.

In a study of 116 ventilated patients over the age of 70 years, Dardaine *et al*.[153] reported mid upper arm circumference measurements under the 10th percentile for the older healthy French population to be a significant predictor of six month mortality when controlling for SAPS II score, and high daily omega score.

8.8 Other components of a comprehensive nutrition assessment

8.8.1 Medical History

Nutrition and intensive care societies are supportive of including elements of the medical history in the nutrition assessment. For example, the American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine[154] recommend incorporating comorbidities, primary medical diagnosis and severity of disease as *key features* of the nutrition assessment[32] as does the European Society for Clinical Nutrition and Metabolism.

APACHE, MPM, and SAPS have each undertaken extensive research to establish which elements of a Medical History best predict outcome from critical illness. For example, the various APACHE predictive equations include the medical history elements of age, chronic health states, source of admission, surgical and non-surgical admission status, primary reason for admission and; in the APACHE IV predictive equation it also includes the patients length of hospital stay prior to admission.

8.8.2 Time spent in hospital prior to ICU admission

The number of days a patient has spent in hospital prior to ICU admission has been recommended as a surrogate measure for increasing risk of developing hospital malnutrition.[50;119;155] Time spent in hospital is now included in the APACHE IV severity of illness scoring system.[14]

In 57 ventilated medical ICU patients, Sheean *et al*.[50] reported that patients defined as moderately or severely malnourished using the SGA tool spent a mean of 14.0 days (SD 15.6 days) in the hospital prior to ICU admission, significantly longer than patients defined as normally nourished using the SGA tool (6.4 days, SD 4.8 days, $P < 0.001$).

Similarly, Fontes *et al*. reported an association between hospital stay prior to ICU admission and malnutrition in 185 medical and surgical ICU patients, 69.7% (129/185) of

whom were unventilated.[119] Patients who had a hospital stay greater than 48 hours were more likely to be moderately or severely malnourished defined using the SGA tool (70.3% malnourished) compared with patients admitted directly to the ICU or having spent less than or equal to 48 hours in hospital prior to ICU admission (45.5% malnourished, $P < 0.05$). However, time spent in hospital prior to ICU admission was not associated with hospital mortality in univariate analyses ($P>0.05$).[119]

In a study of 93 ICU patients admitted to a respiratory ICU with a mean APACHE II score of 14.3, Singh *et al.*[155] also reported an association between hospital stay prior to respiratory ICU admission and hospital mortality. However this was only apparent in univariate analysis (OR 1.12, 95% CI 1.03 to 1.22, $P = 0.005$), and not multivariable analysis (OR 1.05, 95% CI 0.95 to 1.16, $P = 0.330$) after controlling for admission SOFA score and mean calorie delivery less than 50% at time of enrolment.

9.0 SUMMARY OF THE PROBLEM

At admission to the ICU, a limited amount of data is collected to objectively determine severity of illness and subsequent risk of poor outcome, which is used to support structured quality assurance projects and clinical research. However, none of the commonly used severity of illness scores or models incorporates *any* elements of a patient's nutrition status.

Many elements of a comprehensive nutrition assessment require patient or family interviews to obtain the historical information (history of weight change, dietary history etcetera) as much of this information is not available early in ICU stay when patients are ventilated. Physical assessment and anthropometric measures of body composition do not require patient participation and can be undertaken at the bedside early in ICU stay.

10. METHODS

10.1 Purpose

The purpose of this multi-centre analytic observational study is to determine whether specific measures of nutrition status can add additional information to a widely used method of outcome prediction for critically ill patients.

The measures of nutrition status to be evaluated in this project include: BMI; Triceps Skinfold Thickness; Mid Arm Muscle Circumference; and the physical assessment components of the SGA tool measuring Muscle Wasting and subcutaneous Fat Loss.

Each of these measures is an element of a comprehensive nutrition assessment and is accepted to assess a specific domain of nutrition status, body composition, either by physical examination or direct anthropometric measurement.

10.2 Aims

Aim 1:

To assess the predictive ability and clinical utility of each specific measure of body composition for predicting mortality prior to hospital discharge, univariate analysis was conducted.

Aim 2:

To assess whether each specific measure of body composition remained a significant *independent* predictor of mortality before hospital discharge, multivariable analysis was conducted to control for the effects of severity of illness and other traditional risk factors.

Aim 3:

To assess whether each specific measure of body composition remained a significant *independent* predictor of mortality before hospital discharge in the presence of BMI,

multivariable analysis was conducted to control for the effects of BMI, severity of illness and other traditional risk factors.

Aim 4:

To determine the best combination of all available measures of body composition, multivariable analysis was conducted to control for the effects of all measures of body composition, severity of illness, and other traditional risk factors.

10.3 Data Sources and Ethics

Data used in this analytic observational study were collected as an approved add-on study within a National Health and Medical Research Council funded multicentre randomised controlled trial conducted at 31 hospitals throughout Australia and New Zealand (The Early Parenteral Nutrition Trial, Australian and New Zealand Clinical Trials Registry, Number: ACTRN012605000704695). The Early Parenteral Nutrition Trial was conducted by the University of Sydney's Northern Clinical School Intensive Care Research Unit and was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group. Complete methods and results of the Early Parenteral Nutrition Trial are reported elsewhere.[156;157] As the study intervention in the Early Parenteral Nutrition Trial had no effect on hospital mortality, standard care and study intervention patients were pooled *as one patient cohort* in this observational study.

Ethics approval was obtained from each participating site's Human Research Ethics Committee and from the University of Sydney's Human Research Ethics Committee. Written consent was documented in accordance with local and national laws. The study was conducted in accordance with The International Conference on Harmonisation Good Clinical Practice Guidelines. All appropriate national and local laws and regulations were obeyed. See Appendix E for a copy of the Sydney University ethics letter.

10.4 Summary of Data Collected

The following severity of illness and traditional risk factors were collected within 24 h of admission to a study ICU: Age, Gender, length of hospital stay prior to study ICU admission, APACHE II score, APACHE III source of ICU admission, APACHE III surgical or non-surgical admission status, APACHE II chronic health states and APACHE III ICU admission diagnosis.

Complete details of each severity of illness and traditional risk factor collected are reported starting on Page 69.

The following specific physical assessment and anthropometric measures of body composition (specific measures of body composition) were collected within 24 h of admission to a study ICU: Triceps Skinfold Thickness;[102] mid upper arm circumference; physical evidence of subcutaneous Fat Loss as defined using the SGA tool[23;30] (SGA Fat Loss) and; physical evidence of Muscle Wasting as defined using the SGA tool[23;30] (SGA Muscle Wasting). Mid Arm Muscle Circumference was later calculated from Triceps Skinfold Thickness and mid upper arm circumference,[99] and BMI was calculated from Height and Weight.[136;152]

Complete details of the collection and calculation of all specific bedside measures of body composition are presented starting on Page 75.

The primary outcome was mortality prior to discharge from hospital, collected from the study hospitals clinical record keeping system.

10.5 Summary of Analytic Plan

Complete details of the analytic plan are presented starting on Page 84.

Aim 1*:* Univariate analysis of measures of body composition

A statistically significant relationship with outcome is accepted to be the most basic and necessary condition required of any risk prediction marker.[158] P-value <0.05 from an appropriate statistical test was accepted to identify variables with *statistically significant univariate predictive ability*.

Clinical utility, which can be defined as the ability to discriminate between patients who will eventually develop the event of interest from those who will not, was assessed using the area under the receiver operating characteristic curve (aROC).[158] *Statistically significant clinical utility* was defined by a 95% confidence interval (CI) around the aROC whereby the lower 95% confidence limit exceeded the value of 0.5. The guidelines by Hosmer and Lemeshow were used to define the *degree* of clinical utility.[159]

Aim 2: Multivariable analysis of each specific measure of body composition

For *each* specific measure of body composition, a backwards stepwise elimination multivariable model was constructed to control for the effects of severity of illness and traditional risk factors. A specific measure of body composition was declared a *significant independent predictor of outcome* if it remained in the final multivariable model *and* had a P-value of <0.05 obtained from a likelihood ratio (LR) test.[159]

Aim 3: Multivariable analysis comparing each specific measure of body composition to BMI.

For *each* specific measure of body composition, a backwards stepwise elimination multivariable model was constructed to control for the effects of BMI, severity of illness *and*

traditional risk factors. A specific measure of body composition was declared to be a *better independent predictor of mortality* than BMI if it remained in the final multivariable model with a P-value smaller than the P-value of BMI, where each P-value is obtained from a LR test.[159]

Aim 4: Multivariable analysis to identify the best combination of available measures of body composition.

A backwards stepwise elimination multivariable model was constructed containing *all* eligible measures of body composition, measures of severity of illness *and* traditional risk factors. A specific measure of body composition was declared to be the *best independent predictor* if it remained in the final multivariable model with a LR P-value smaller than each of the other specific measures of body composition.[159]

10.6 Patient Population

Adult critically ill patients were eligible for inclusion in the study if they met the following criteria: 1) Documented to be over the age of 18 years at the time of ICU admission; 2) Were screened and enrolled into the study within 24 hours of ICU admission, 3) Were not expected to be discharged from the study ICU for at least two additional calendar days after enrolment, 4) Were currently critically ill enough to require monitoring or treatment delivered through a central venous access line which was in-situ at the time of study enrolment and; 5) At the time of screening were not being fed enterally, parenterally or orally, nor expected to be fed for at least one calendar day after enrolment.

Complete details of the Early Parenteral Nutrition Trial exclusion criteria are presented in Appendix F.

10.7 Detailed Methods of Data Collection

10.7.1 Collection of severity of illness and other traditional risk factors

Age

Date of birth was collected from the patients' medical records and addressograph details, and speaking with family and friends as required. Patient age was calculated in years from the patient's date of birth at the time of study entry.

Gender

Legal gender at the time of study admission was recorded.

APACHE II score variables

APACHE II score was calculated using standard methodology[7] from three scoring domains: acute physiology score (APS), age points and chronic health points.

Acute Physiology Variables

The APS variables collected were: temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, pH, serum sodium, serum potassium, serum creatinine, acute renal failure, haematocrit, haemoglobin, total white blood cell count, GCS score, and serum bicarbonate.

The most abnormal (worst) value recorded 24-hours prior to study entry was documented according to the methods of Knaus and colleagues[7]. The APS abnormal value guide was reproduced on the study data collection forms, and is provided for completeness in Appendix G. Actual values were documented.

Temperature

Temperature was recorded in degrees Celsius (^{0}C). A central temperature was preferred (i.e. rectal, tympanic, oesophageal, or temperature from a central venous catheter). Where a central temperature was not available, 0.5^{0}C was added to the oral or axillary temperature.

Mean arterial pressure

Mean arterial pressure (MAP) was recorded in millimetres of mercury (mmHg). Where the intensive care unit individually recorded systolic blood pressure and diastolic blood pressure the following equation was used to calculate the MAP:

$$MAP = \frac{2}{3} diastolic\ pressure\ + \frac{1}{3} systolic\ pressure$$

Heart Rate

Heart rate was recorded in ventricular beats per minute. Where the patient had any form of cardiac dysrhythmia only the ventricular beats were recorded.

Respiratory rate

Respiratory rate was recorded in total breaths per minute. Total breaths included the sum of ventilated breaths and spontaneous breaths.

Alveolar-arterial (A-a) oxygenation gradient

Oxygenation was recorded as the Alveolar-arterial (A-a) gradient when the fraction of inspired oxygen ($Fi0_2$) was greater than or equal to 0.5.

Partial pressure of arterial oxygen

Oxygenation was recorded as the partial pressure of arterial oxygen ($Pa0_2$) when the $Fi0_2$ was less than 0.5. Partial pressure of arterial oxygen was recorded in mmHg.

Both the A-a gradient and $Pa0_2$ was calculated if the $Fi0_2$ changed over the 24 hours prior to study entry.

The Alveolar-arterial oxygenation gradient was calculated using the following formula:

$$A - a\ gradient = (713 \times Fi02) - (1.25 \times PaCo2) - Pa02$$

Arterial pH

Arterial pH was collected independent of oxygenation and therefore did not have to be derived from the same arterial blood gas as that used for the oxygenation variables.

Serum sodium

Serum sodium was recorded in millimoles per litre (mmol/L).

Serum potassium

Serum potassium was recorded in mmol/L.

Serum creatinine

Serum creatinine was recorded in micromoles per litre (μmol/L).

Rapid creatinine rise

APACHE II defines rapid rise in creatinine as at least a 20% increase, to a value of 120μmol/L or more compared with the last known creatinine, combined with evidence of a clinical condition or risk factor know to predispose to acute renal failure.

Risk factors were: acute heart failure, hypotension, vasodilation, low cardiac output, multiple organ dysfunction syndrome, sepsis, toxins, amino glycosides, penicillins, non steroidal anti-inflammatory agents, dyes, urinary obstruction or myoglobin.

Patients who were receiving chronic dialysis and those whose most deranged serum creatinine was <120μmol/L were not considered to have rapid creatinine rise.

Haematocrit

Haematocrit was recorded and expressed as a percentage (%). If haematocrit was *not* available then haemoglobin values were documented.

Haemoglobin

Haemoglobin was recorded in grams per litre (g/L).

Total White Blood Cell Count

Total white blood cell count was recorded. The units used were $x10^9$ per litre ($x10^9$).

Glasgow Coma Scale Score

The lowest GCS score was recorded as per the methods of Teasdale[160] except in sedated non-head injured patients where pre-sedated scores were sought. Patients who were

admitted to the ICU due to drug overdose were considered to be non-sedated unless they were actively receiving added sedation.

Serum bicarbonate

Serum or venous bicarbonate was recorded when no *arterial* blood gas measurements had been taken. The units used were mmol/L.

APACHE III Source of admission to the study ICU

The location of the patient *immediately* prior to ICU admission was categorised as per Knaus et al.[8] Only *one* location was selected from the following list of locations:

Accident and Emergency Department

The patient was admitted to the study ICU directly from the accident and emergency ward.

Operating Theatre/Recovery Room

The patient was admitted directly to the study ICU from surgery or the recovery room.

Hospital Floor/ward

The patient was admitted directly to the study ICU from any other ward, floor or treatment unit. This excluded accident and emergency, surgery and/or transfer from another ICU, which were categorised separately.

Transfer from other intensive care unit

The patient was admitted directly from another ICU within the study hospital or from another ICU from another hospital. An ICU was defined as any high dependency area that was able to routinely provide invasive mechanical ventilation for greater than 24 hours.

Readmission to this intensive care unit

The patient had previously been admitted to the ICU during the *current* period of hospitalisation, had been discharged, and then later readmitted to the study ICU. This category took precedence over all other readmission status or location categories.

Transfer from other hospital

The patient was admitted directly to the study ICU due to being transferred from any area in *another* hospital, excluding another ICU.

APACHE III Surgical or non-surgical patients

Admissions to the study ICU were categorised as *either* surgical or non-surgical admissions.

Postoperative surgical patients who were admitted directly from the operating theatre or recovery room to the study ICU were further categorised into emergent or elective surgery.

Emergent surgery was defined as surgery required immediately, correcting a life threatening situation.[1]

APACHE II Chronic Health States

Chronic Health States included immuno-compromised chronic health state, chronic hepatic cirrhosis, chronic cardiovascular disease, chronic respiratory disease, and/or chronic dialysis. They were obtained from the past medical history section of the patient medical record. To be recorded as present, they had to be evident *prior* to the current hospital admission, and meet the original definitions as described by Knaus and colleagues.[7] Patients were able to have multiple chronic health states recorded.

The presence of chronic diabetes requiring insulin for treatment was also recorded.[14] The need for insulin to control the patients' diabetes had to be present *prior* to the current hospital admission. Full descriptions are provided in table 10.1.

Table 10.1: Definition of Chronic Health States as collected in the analytic observational study.

Chronic health state	**Definition**
Hepatic cirrhosis	Biopsy proven cirrhosis and documented portal hypertension; episodes of upper gastrointestinal bleeding due to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma
Chronic dialysis	Receiving chronic dialysis
Cardiovascular disease	New York Heart Association Class IV
Respiratory disease	Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (unable to climb stairs, perform household duties) or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mm Hg) or respiratory dependency.
Immuno-compromised	Therapy that suppresses resistance to infection (immune-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids) or disease sufficiently advanced to suppress resistance to infection (e.g. leukaemia, lymphoma, AIDS)
Insulin treated diabetes	Insulin dependent diabetes (Type I or Type II)

AIDS: Acquired Immune Deficiency Syndrome.

APACHE III Principal Diagnostic Categories leading to ICU Admission

APACHE III ICU admission diagnosis categories were collected at time of admission to the study. These categories were then mapped back to the original APACHE II ICU admission diagnosis categories as previously undertaken by Stow and colleagues[1] for the Adult Patient Database group of the Australian and New Zealand Intensive Care Society. A complete listing of the APACHE III admission diagnostic categories available for selection is presented in Appendix H.

Length of hospital stay prior to study ICU admission

Hospital admission date and study enrolment date were recorded at study entry. The number of days the patient spent in the study hospital prior to their enrolment to the study was calculated.

10.7.1.1 Training

Research coordinators who collected the data at each of the 31 ICU's were trained in the collection of the above severity of illness and traditional risk factor data at one of eight small group two-day study start–up meetings. These meetings were held between September 2006 and January 2009 and conducted by the author and others in the research team. Training was supported by a detailed data dictionary, which provided the definitions reported above.

10.7.2 Collection of measures of body composition

The following physical assessment and anthropometric measures of body composition were collected within 24 hours of study ICU admission at the patients' bedside: BMI;[136;152] Triceps Skinfold Thickness;[102] Mid Arm Muscle Circumference;[99] SGA Fat Loss[23;30] and; SGA Muscle Wasting.[23;30]

The below details are a summary of the methodology used to undertake each physical assessment and anthropometric measure of body composition. *Full* details are provided in the hard copy photographic Anthropometric Procedures Manual[161] developed and published (DOI:10.4451) by the author. A copy is provided in Appendix B.

For the measurement of Triceps Skinfold Thickness, mid upper arm circumference and demi-armspan (demispan), lateralised anthropometric measurements were preferentially taken from the *right* side of the body as per the International Standards for Anthropometric Assessment (ISAK).[162] If there was evidence of abnormality or injury to the right arm, the left

arm was used for *all* measurements. For all measurements, the patient was measured by the trained research coordinator in the supine position, as flat as possible, within 24 hours of ICU admission.

Height

Height was used to calculate BMI.

Unless an accurate recent height measurement was documented in the patient's medical chart, height was estimated from demispan measurement. If the patient's arm could not be manipulated to obtain an accurate demispan measurement, a height measurement was obtained in the supine position, or a visual estimate was recorded.

Demispan, defined as the distance between the mid-point of the sternal notch and the finger web root of the patients' hand,[163] was measured to the nearest 0.5 of a cm with a non-stretch but flexible steel tape measure (Lufkin, Coopertools, Apex, NC, USA). The patient's arm was supported by the attending bedside nurse throughout the measurement to ensure it was horizontally abducted in neutral flexion and wrist in neutral rotation.[163]

The following gender specific calculations were used to calculate height in meters from measured demispan in centimetres:[163]

$$Female\ height, m = [1.35 \times demispan, cm + 60.1]/100$$

$$Male\ height, m\ = [1.4 \times demispan, cm + 57.8]/100$$

Where demispan could not be measured (e.g. injury to both arms), height was measured or estimated in the supine position.

Supine height measurement was directly measured in meters or estimated by trained research coordinators. When measuring height in the supine position, a clipboard or similar

flat surface was used to extend the perpendicular lines from the top of the head to the lowest extremity of the patient. A non-stretch but flexible steel tape measure (Lufkin, Coopertools, Apex, NC, USA) was then used to measure between the two clipboards or similar flat surfaces.

When estimating height, direct observation by the trained research coordinator rather than reports from family members was preferred.

Height in meters was recorded to the nearest 0.5 of a centimetre.

Weight

The patient's current weight was measured using calibrated scientific scales such as bed scales or sling scales. Where patients' were not weighed on admission, the trained research coordinator obtained an *estimate* from direct observation in preference to family members.

Weight was recorded in kilograms, to the nearest 0.1 of a kilogram (kg).

Weight was used to calculate BMI.

BMI

Weight and height were measured or estimated as above, and then used to calculate BMI. BMI was calculated by dividing weight in kilograms by the square of height in meters as per Keys:[135]

$$BMI = \frac{Weight(kg)}{Height\ (m)2}$$

The units of BMI were kilograms per meter squared (kg/m^2).

Triceps Skinfold Thickness

Triceps Skinfold Thickness was measured using Slim Guide skinfold calipers (Mentone Educational, Moorabbin, Victoria Australia). Calipers were applied to the posterior surface of a fully relaxed and lifted arm, at the same level as the midpoint between the acromion process of the scapula and radial head, determined with a non-stretch but flexible

metal tape measure (Lufkin, Coopertools, Apex, NC, USA). A fold of fat and skin was lifted away from the underlying muscle and held in place while the triceps skinfold was measured, with the caliper placed on the skin just below the fingers lifting up the fat fold. The measurement was taken three seconds after the caliper was applied to the skinfold.[164] The ISAK standards were used to guide measurement,[162] and have been adapted for use in critically ill bed-bound patients by Ravasco *et al.*[102]

Measurement was recorded to the nearest millimetre.

Mid Upper Arm Circumference

Mid Upper Arm Circumference was measured to calculate Mid Arm Muscle Circumference. Measurement was undertaken at the midpoint between the acromion process and the radial head using a non stretch but flexible steel tape measure (Lufkin, Coopertools, Apex, NC, USA). The arm was fully relaxed when the measurement was taken. The ISAK standards were used to guide the measurement,[162] and have been adapted for use in critically ill bed-bound patients by Ravasco et al.[102]

Measurement was recorded to the nearest 0.1of a centimetre.

Mid Arm Muscle Circumference

Mid Arm Muscle Circumference was calculated from mid upper arm circumference and Triceps Skinfold Thickness, using the formula from Heymsfield:[99]

$$Mid\ Arm\ Muscle\ Circumference\ (cm) = mid\ upper\ arm\ circumference - (\pi * triceps\ skinfold\ thickness)$$

SGA Muscle Wasting and SGA Fat Loss.

At the time of admission to the study ICU, trained research coordinators graded each patient for evidence of Muscle Wasting and evidence of Fat Loss using the physical assessment component of the SGA tool.[29;30] Physical evidence of SGA Fat Loss was graded at

the Triceps Skinfold area and under the fat pads of the eye. Physical evidence of SGA Muscle Wasting was graded at the clavicle and deltoids area. The trained research coordinator categorised the patient using one of the four SGA categories (normal, mild, moderate, or severe).[29;30]

10.7.2.1 Training

Initial training

Research coordinators at each of the 31 ICU's were trained in the collection of the measures of body composition at one of eight small group two-day study start–up meetings.[165;166] These meetings were held between September 2006 and January 2009 and conducted by the author and others in the research team. Training was supported by a detailed Anthropometric Procedures Manual,[161] a small group interactive workshop, a training video, and follow-up one-on-one education.

At each of the eight start-up meetings, a two-hour, small group interactive workshop was held to practice anthropometric techniques used in this project.

The workshops were led by two experienced and formally trained anthropometrists (the author and a colleague). First, the anatomical landmarks used in each of the measures of body composition were described and demonstrated using two different volunteer adult models lying in the supine position. The research coordinators were then invited to practice taking Triceps Skinfold Thickness, mid-upper arm circumference and demispan measurements on the supine models and on at least two other volunteers. Trained anthropometrists supervised and assisted with the measurements. Both male and female adult models were used.

A standardised SGA training video (Baxter Renal Division 1993, Baxter Healthcare Corporation, Illinois, United States of America)[167] was used in each of the eight small group

interactive workshops to teach the research coordinators how to identify and categorise SGA Muscle Wasting and SGA Fat Loss as described by Detsky *et al.*[29] Participants then practiced on volunteer models guided by photographic examples contained in the hard copy Anthropometric Procedures Manual,[161] with support and supervision from the two trained anthropometrists.

Ongoing training

The author followed-up initial training with at least two site visits to all 31 participating sites: One visit was conducted before the study commenced recruiting and *at least* one other visit mid-recruitment. At each visit, initial training was reinforced by the author in a one-on-one training session. Only research coordinators that had undergone full anthropometry and SGA physical assessment training were allowed to undertake body composition measurements. If a new research coordinator was appointed during the study, on site education was arranged and undertaken by the author. If there were no trained research coordinators available at the time of scheduled baseline patient measurement, no measurements were taken, and the measurement was recorded as missing.

More than 80 on-site training visits were conducted by the author during the study in addition to the eight interactive workshops held during the two-day study start-up meetings.

Anthropometric Procedures Manual

A detailed hard copy coloured photographic procedures manual was developed[161] and published (http://dx.doi.org/10.4451/EarlyPN_APM) by the author. It was used to support the face-to-face interactive workshop and on-site one-on-one training. Copies of the Anthropometric Procedures Manual are available on the study web site: http://www.EvidenceBased.net/EarlyPN. A copy is provided in Appendix B.

Anthropometry and physical assessment kit

To standardise data collection each research coordinator at each of the 31 ICU's was provided with an anthropometry and physical assessment kit. The kit included Slim Guide Calipers (Mentone Educational, Moorabbin, Victoria Australia), a Lufkin tape measure (Lufkin, Coopertools, Apex, NC, USA), a hard copy of the authors' published (http://dx.doi.org/10.4451/EarlyPN_APM) Anthropometric Procedures Manual,[161] a ball of non-stretch string, a soft makeup pencil for marking anthropometric landmarks on patients, and a copy of the SGA training video by Baxter (Baxter Renal Division 1993, Baxter Healthcare Corporation, Illinois, United States of America).[167]

10.7.3 Study outcome: hospital discharge mortality

Mortality at hospital discharge was the primary outcome of this analytic observational study. It was determined from hospital records.

10.8 Statistics

10.8.1 Database cleaning and range restrictions

Prior to the conduct of any analysis, the database underwent extensive validity checks. A frequency distribution was constructed for all continuous variables to identify outlying values. When any value was identified that was outside plausible ranges[7] a data query was sent to the study site and the value was checked against source documents. Where any database value disagreed with source documents, the database was edited.

Acute Physiology Variables and APACHE II score

Complete information on all APS variables was required to be able to calculate an APACHE II score for each patient. Therefore, any missing APS variables were imputed using the mean or median values calculated from all other non-missing data.[168]

The number of missing APS variables that were imputed are reported in the thesis.

Age, Gender, Height and Weight

All patients required an Age, Gender, Weight, and Height at study enrolment to determine patient trial eligibility.

Severity of illness and traditional risk factors

During data cleaning, if patients did not have an ICU admission diagnosis, surgical or non-surgical admission status, source of admission, or outcome at hospital discharge, this was queried with the site based research coordinators, and the database edited accordingly.

Missing measures of body composition

Measures of body composition collected within 24 hours of ICU admission were *not* imputed with average values calculated from non-missing values. Instead the missing value was assumed to be Missing at Random and the patient was excluded from further analysis.

The number of missing values for each specific measure of body composition is declared in the thesis.

10.8.2 Assessment of normality for continuous variables

Frequency plots were created in SAS (Version 9.2) for all continuous variables to assess the assumptions of normality. The Shapiro-Wilk test was used.[169]

Where variables were found to be normally distributed, data were described using mean and standard deviation. Where data was not normally distributed, data were described using median and range. See Appendix I for details.

10.8.3 Categorical variables

A contingency table was constructed for all categorical variables to identify categories with less than ten total observations per category.[170] To avoid instability, categories with less than 10 total observations collapsed into the next most similar category.[171]

All analysis of categorical variables was undertaken using dummy variables, coded against a stable referent group.

The following severity of illness and traditional risk factors were analysed using dummy variables: Gender, APACHE III source of admission, APACHE III surgical or non surgical admission status, APACHE II chronic health state and APACHE III ICU admission diagnosis.

The following measures of body composition were analysed as dummy variables: SGA Muscle Wasting, and SGA Fat Loss.

BMI

BMI is reported as both a *categorised*[136;172] ($BMI_{categorical}$) and a *continuous*[173] ($BMI_{continuous}$) variable in the literature. Therefore it was analysed using both presentations.

BMI was categorised using the World Health Organisation (WHO)[136;139] criteria[172] into the following ranges: BMI of <18.50 kg/m^2; a BMI of 18.50 kg/m^2 to 24.99 kg/m^2; 25.0 kg/m^2 to 29.99kg/m^2; 30.0 kg/m^2 to 39.99kg/m^2 and; BMI of ≥40.0 kg/m^2.[136;139]

10.8.4 Continuous variables

Severity of illness and traditional risk factors

Age, APACHE II score, and length of hospital stay prior to ICU admission were analysed as continuous variables.

Other measures of body composition

BMI, Triceps Skinfold Thickness and Mid Arm Muscle Circumference variables were analysed as continuous variables.[156]

10.8.5 Statistical significance and Confidence Intervals

Statistical significance was defined as a two-sided P-value less than 0.05. All reported P-values were obtained from LR chi-square (χ^2) tests.[171]

All CI in this thesis were reported using the 95% level.

10.8.6 Analysis Software

All statistical analyses were undertaken using PC SAS Version 9.2 TS Level 1M3 running on Windows XP_Pro platform, Windows Version 5.1.2600, using Windows 7 on a Pentium computer.

10.8.7 Logistic regression model development: Detailed Analytic Plan

All logistic regression modelling was undertaken in PC SAS version 9.2 using the PROC LOGISTIC function.

Aim 1

To assess the univariate predictive ability and clinical utility of each specific measure of body composition for predicting mortality prior to hospital discharge. *Acceptable* univariate predictive ability was defined as a statistically significant LR P-value <0.05 obtained from univariate logistic regression.

If the *lower limit* of the 95% CI around the aROC was greater than 0.5, a statistically significant *potential* for clinical utility was declared.[159] The following guide by Hosmer and

Lemeshow was used to classify the aROC to assess the *strength* of clinical utility: between 0.7 to 0.8, acceptable strength; 0.8 to 0.9, excellent strength; and greater than 0.9, outstanding strength.[159;174]

The specific measures of body composition considered in Aim 1 included Triceps Skinfold Thickness, Mid Arm Muscle Circumference, $BMI_{continuous}$, $BMI_{categorical}$, SGA Muscle Wasting and SGA Fat Loss.

Aim 2

To assess whether each specific measure of body composition remained a significant independent predictor of mortality before hospital discharge, multivariable analysis was conducted to control for the effects of severity of illness and other traditional risk factors.

Univariate logistic regression was undertaken to determine which severity of illness and other traditional risk factors would be included in the *maximum* model.

All severity of illness and other traditional risk factors with a univariate LR P-value <0.25 were included in the *maximum* model.[171] The *maximum* model was assessed for multicollinearity using Eigenanalysis. A condition index of ≥30 was accepted to indicate the presence of excessive multicollinearity within the model.[175] Where excessive multicollinearity was detected, highly correlated variables were identified by inspecting the proportion of variation. If two variables were highly correlated, the variable with the highest proportion of variation was removed from the model and the condition index was re-calculated. This process was repeated until Eigenanalysis indicated there was no further evidence of excessive multicollinearity. The initial multivariable model found to be free of excessive multicollinearity is referred to as the *stable* maximum model.

After identification of the stable maximum model, each eligible measure of body composition with a univariate LR P-value <0.25 was added to the stable maximum model for

evaluation, one variable at a time. Each new model was again assessed for multicollinearity, and where present (condition index ≥30), highly correlated variables were removed until excessive multicollinearity was no longer present (condition index <30).

Once multicollinearity was addressed, backwards stepwise elimination was commenced.

During backwards stepwise elimination, a LR P-value was calculated for each variable in the model, and at each step, the variable with the highest LR P-value was eliminated from the model and all LR P-values were re-calculated. This process was continued until all remaining LR P-values were less than 0.1.[170]

A measure of body composition was declared to be *significant independent predictor of outcome* if it remained in the final multivariable model *and* had a LR P-value of <0.05.[159]

The adequacy of fit of the final model was assessed using the Hosmer Lemeshow Ĉ GOF statistic with eight degrees of freedom.[159;176]

The specific measures of body composition considered in Aim 2 included Triceps Skinfold Thickness, Mid Arm Muscle Circumference, $BMI_{continuous}$, $BMI_{categorical}$, SGA Muscle Wasting and SGA Fat Loss.

Aim 3

To assess whether each specific measure of body composition remained a significant independent predictor of mortality before hospital discharge in the presence of BMI, multivariable analysis was conducted to control for the effects of BMI, severity of illness and other traditional risk factors.

First, $BMI_{continuous}$ was compared to $BMI_{categorical}$ with regards to predictive ability. The BMI model with the smallest LR P-value was deemed to be the best predictor.

Second, *both* BMI and each eligible measure of body composition with a univariate LR P-value <0.25 was added to the same *stable* maximum model. This process was repeated for each specific measure of body composition.

For each model, an assessment of multicollinearity was made, and where present (condition index ≥30), highly correlated variables were removed one variable at a time, until excessive multicollinearity was no longer evident (condition index <30).

Once excessive multicollinearity was removed, backwards stepwise elimination was commenced.

During backwards stepwise elimination, each variable in the model had its LR P-value calculated, and at each step, the variable with the highest LR P-value was permanently removed from the model. All LR P-values were then recalculated for the new model.[170]

The backwards stepwise process continued until all remaining LR P-values were less than 0.1.

For each model, the '*best*' measure of body composition was identified based on the *smallest* LR P-value performed on the final model.

The adequacy of fit of the final model was assessed using the Hosmer Lemeshow $\hat{C}$ GOF statistic with eight degrees of freedom.[159;176]

The specific measures of body composition considered in Aim 3 included Triceps Skinfold Thickness, Mid Arm Muscle Circumference, SGA Muscle Wasting and SGA Fat Loss.

Aim 4

To determine the best combination of all available measures of body composition, multivariable analysis was conducted to control for the effects of *all* measures of body composition, severity of illness, and other traditional risk factors.

All measures of body composition with a univariate LR P-value <0.25 in univariate logistic regression were added to the same stable maximum model. An assessment of multicollinearity was made, and where a condition index of ≥30 indicated excessive multicollinearity, highly correlated variables were removed one variable at a time until a condition index <30 indicated excessive multicollinearity was no longer evident in the model.

Backwards stepwise elimination was then performed. Each variable had its LR P-value calculated at each step, with the variable with the highest LR P-value removed from the model.[170] All LR P-values were then recalculated for the new model.

The backwards stepwise modelling process continued until all remaining LR P-values were less than 0.1.

The '*best*' combination of all available measures of body composition was identified based on the *smallest* LR P-value obtained from the final model.

The adequacy of fit of the final model was assessed using the Hosmer Lemeshow $\hat{C}$ GOF statistic with eight degrees of freedom.[159;176]

The specific measures of body composition considered in Aim 4 included Triceps Skinfold Thickness, Mid Arm Muscle Circumference, $BMI_{continuous}$, $BMI_{categorical}$, SGA Muscle Wasting and SGA Fat Loss.

11. RESULTS

11.1 Participating centres

Thirty-one adult ICU's from 31 hospitals across Australia and New Zealand contributed patients to the study database. The number of beds in each ICU ranged from five to 24, with a median of 13 beds. All 31 ICUs treated both medical and surgical patients. Twenty seven of the participating hospitals were public hospitals and four were private hospitals. All ICUs were classified as Level two or Level three ICUs, and 100% (31/31) were closed unit ICUs being staffed by full time intensive care practitioners.

The complete list of participating sites is listed in Appendix D.

Patients were enrolled into the trial from the 19th October 2006 to the 30th June 2011.

11.2 Consent withdrawal

1,372 patients were enrolled into the trial within 24 h of ICU admission. After enrolment, 0.7% (9/1,372) patients withdrew consent to continue participating in the study.

The final patient database eligible for analysis in this observational study contained 1,363 unique patient records.

11.3 Missing database values.

The primary outcome, hospital discharge mortality, was available in 100% (1,363/1,363) of patients eligible for analysis. Similarly, Age, Gender, Height and Weight were reported in 100% of eligible patients.

A single element of the APACHE II score was found to be missing in 4.2% (57/1,363) of patients. As per standard procedures, missing elements of the APACHE II score were

imputed[177] with the mean value obtained from patients enrolled into the study with non-missing values, resulting in 0/1,363 missing APACHE score elements.

Source of admission to the ICU, surgical or non-surgical admission, principal diagnostic categories leading to ICU admission, and number of days in the study hospital prior to ICU admission was available in 100% (1,363/1,363) of eligible patients.

Triceps Skinfold Thickness measurement was missing in 4.8% (66/1,363) of patients and mid upper arm circumference was missing in 4.5% (62/1,363) of patients; calculated Mid Arm Muscle Circumference measurement was missing in 5.0% (68/1,363) of eligible patients. SGA Muscle Wasting (32/1,363) and SGA Fat Loss (32/1,363) measurement was missing in 2.3% of patients.

Measures of body composition collected within 24 hours of ICU admission were *not* imputed with average values calculated from non-missing values. Instead the missing value was assumed to be Missing at Random and the patient was excluded from further analysis.

11.4 Patient Characteristics

The median age of the 1,363 enrolled patients was 71.3 years, with range from 18.3 years to 96.3 years. Sixty percent of the patients were male (60.2%, 820/1,363). The median APACHE II score was 20.0, with a range from 5 to 51.

Patients spent a median of 1.0 day in the study hospital prior to being admitted to the study ICU, with a range of 0-63 days. Seventeen percent (232/1,363) of patients did not stay in the hospital prior to ICU admission, and 51.5% (695/1,363) of patients had a stay of 1.0 day.

After study enrolment, patients remained in the ICU for a median of 6.0 days, with a range from one to 112 days. Median hospital stay was 16.0 days (SD 25.49) with a range from one to 277 days. Overall hospital discharge mortality was 21.4% (291/1,363).

A complete list of traditional risk factors for hospital mortality are reported in Table 11.1.

Frequency plots for continuous variables are provided in Appendix I.

11.4.1 APACHE III source of admission to the study intensive care unit

Admission to the study ICU was directly via the operating theatres in 65.6% (894/1,363) of cases, followed by transfer from another hospital (11.8%, 161/1,363) and admission from the emergency department (11.6%, 158/1,363). Patients were admitted directly from the hospital floor/ward in 10.3% (140/1,363) of cases. *No* patients were readmitted to the study ICU from the same ICU as this was a primary study exclusion criterion. See Table 11.1 for complete details.

Table 11.1: Frequency Table: Traditional risk factors, in descending order by variable.

Variable	n/N	%
APACHE III Source of ICU admission		
Operating theatres/recovery room	894/1,363	65.6
Transfer from other hospital	161/1,363	11.8
Emergency department	158/1,363	11.6
Hospital ward/floor	140/1,363	10.3
Transfer from other ICU	10/1,363	0.7
ICU readmission	0/1,363	0
APACHE III Type of Surgery		
Elective Surgery admission	625/1,363	45.9
Not Surgical admission	469/1,363	34.4
Emergency Surgery admission	269/1,363	19.7
APACHE II Chronic health states[a]		
Insulin treated diabetes	107/1,363	7.9
Immuno-compromised	63/1,363	4.6
Respiratory disease	61/1,363	4.5
Cardiovascular disease	48/1,363	3.5
Hepatic cirrhosis	16/1,363	1.2
Chronic dialysis	15/1,363	1.1
APACHE II ICU admission diagnosis		
Gastrointestinal	821/1,363	60.2
Cardiovascular/vascular	271/1,363	19.9
Sepsis	97/1,363	7.1
Respiratory	78/1,363	5.7
Trauma	40/1,363	2.9
Other	18/1,363	1.3
Neurological	17/1,363	1.3
Renal	9/1,363	0.7
Metabolic	7/1,363	0.5
Gynaecological	2/1,363	0.2
Haematological	2/1,363	0.2
Orthopaedic surgery	1/1,363	0.01

N=1,363.
APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive care unit.
[a]Patient's could have had more than one chronic health state.

11.4.2 APACHE III surgical and non –surgical patients

Patients were admitted to *either* the overall surgical or non-surgical category. Non-surgical admissions totalled 34.4% (469/1,363) of the overall study database, and surgical

admissions totalled 65.6% (894/1,363). All study database patients had either a non-surgical or surgical admission recorded. See Table 11.1.

Of the 894 surgical patients, 69.9% (625/894) required emergency surgery, and 30.1% (269/894) required elective surgery.

11.4.3 APACHE II Chronic Health States

One or more chronic health states as defined by Knaus *et al.*[7] was evident in 14.9% (203/1,363) of the study database.

Insulin treated diabetes was also recorded. While not being an original APACHE II chronic health state as defined by Knaus *et al.*[7] if the number of insulin treated diabetics are included in the chronic health figures a total of 310/1,363 or 22.7% of the overall population could be considered to have had one or more chronic health states at study admission.

Insulin treated diabetes (Type 1 or II) was the most commonly recorded condition at 7.9% of the overall database (107/1,363), followed by chronic immuno-compromised health state (4.6%, 63/1,363) and chronic respiratory disease (4.5%, 61/1,363). A complete list of chronic health states, which also includes hepatic cirrhosis, chronic dialysis and cardiovascular/vascular disease, is given in Table 11.1.

11.4.4 Principal Diagnostic Categories leading to ICU admission

According to APACHE III methodology, each patient had *one* of the 81 possible post-operative *or* non-operative ICU admission diagnosis categories recorded at time of admission to the study database. Patients admitted directly from surgery had an operative ICU admission diagnosis recorded. There were no patients with missing ICU admission diagnoses.

Sixty six of the 81 possible ICU admission diagnosis categories were recorded in the study database.

Each of the 66 APACHE III ICU admission diagnosis categories listed was then mapped back to one of the 12 original APACHE *II* ICU admission diagnosis groups as undertaken by the Adult Patient Database group of the Australian and New Zealand Intensive Care Society.[1]

The most common APACHE II ICU admission diagnosis category was gastrointestinal (60.2%, 821/1,363), followed by cardiovascular/vascular (19.5%, 271/1,363) and respiratory (5.7%, 78/1,363). For further details on the nine remaining ICU admission diagnosis categories, see Table 11.1.

11.5 Measures of Body Composition

11.5.1 Weight, Height and BMI

All patients had Height, Weight and BMI recorded. The median weight of the study population was 80.0 kilograms, with a range from 35.0 kilograms to 235.0 kilograms. A direct measurement of weight (e.g. using bed scales) was available in 21.2% (289/1,363) of patients, whilst weight was estimated in 78.8% (1074/1,363) of patients.

The median height of the population was 168.4 centimetres with a range from 140.0 to 203.4 centimetres. Height was estimated from demispan in 90% (1228/1,363) of patients; with 5.4% (74/1,363) of patients having their heights measured by a direct technique, and 4.5% (61/1,363) of patients having their height estimated.

Calculated from height and weight, the median BMI was 27.3 kg/m^2, with a range from 14.6 kg/m^2, to 70.6 kg/m^2.

Frequency plots for height, weight and BMI analysed as a continuous variable are provided in Appendix I.

In categorising BMI according to WHO categories, 36.9% (503/1,363) of all patients were classified as overweight with a BMI of 25.0 to 29.99kg/m^2, 24.7% (337/1,363) were

classified as obese with a BMI of 30.0 to 39.99kg/m^2 and 29.3% (400/1,363) of all patients were classified as of normal weight with a BMI of 18.5 to 24.99kg/m^2. See Table 11.2 for further details regarding BMI categories.

Table 11.2: Frequency Table: BMI categorised by World Health Organisation criteria.

Variable	**n/N**	**Percent**
BMI, WHO[a] categories, kilograms/m^2		
<18.5	46/1,363	3.4
18.5 to 24.99	400/1,363	29.3
25.0 to 29.99	503/1,363	36.9
30.0 to 39.99	337/1,363	24.7
≥40	77/1,363	5.7

N= 1,363.
BMI: Body Mass Index.
[a]categorised according to the World Health Organisation.[136;139]

11.5.2 Triceps Skinfold Thickness

There were 66 patients who had no admission Triceps Skinfold Thickness measurement recorded (4.8%, 66/1,363). Missing measurements were *not* imputed.

The median Triceps Skinfold Thickness measurement for the remaining 1,297 patients was 13.0 millimetres, with range from 4.0 millimetres to 50.0 millimetres.

A frequency plot is provided in Appendix I.

11.5.3 Mid Upper Arm Circumference

There were 62 patients who had no admission mid upper arm circumference measurement recorded (4.5%, 62/1,363). Missing measurements were *not* imputed.

The median mid upper arm circumference measurement for the 1301 patients who had a measurement recorded was 31.0 centimetres, with a range from 16.0 centimetres to 58.0 centimetres. A frequency plot is provided in Appendix I.

11.5.4 Mid Arm Muscle Circumference

Mid Arm Muscle Circumference was calculated using the equation from Heymsfield and McManus.[99] As both Triceps Skinfold Thickness and mid upper arm circumference patient values were required to calculate Mid Arm Muscle Circumference, it was unable to be calculated on a total of 68 patients (68/1,363, 5.0%).

In the 1,295 patients with recorded Mid Arm Muscle Circumference measurements, the median Mid Arm Muscle Circumference was 26.7 centimetres, with a range from 3.4 to 48.1 centimetres.

A frequency plot is provided in Appendix I.

11.5.5 Evidence of SGA Muscle Wasting and SGA Fat Loss

SGA Muscle Wasting

There were 32 patients (2.3%, 32/1,363) who had missing baseline enrolment values for SGA Muscle Wasting. These values were not imputed.

In the 1331 patients with SGA Muscle Wasting measurements, 73.6% (980/1,331) of all patients had no evidence of Muscle Wasting at admission to the study database. Mild Muscle Wasting was evident in 17.2% (229/1,331) of patients, moderate Muscle Wasting in 7.2% (96/1,331) of patients, and severe Muscle Wasting in 2.0% (26/1,331) of patients. See Table 11.3.

Table 11.3: Frequency Table: SGA Muscle Wasting.

SGA Muscle Wasting category	n/N	%
No obvious wasting	980/1,331	73.6
Mild wasting	229/1,331	17.2
Moderate wasting	96/1,331	7.2
Severe wasting	26/1,331	2.0

N=1,331.
SGA: Subjective Global Assessment.

SGA Fat Loss

There were 32 patients (2.3%, 32/1,363) who had missing baseline enrolment values for SGA Fat Loss. These values were not imputed.

Seventy two percent of patients had no obvious Fat Loss on admission (72.2% or 961/1,331). Mild Fat Loss was evident in 18.8% (250/1,331) of patients, moderate Fat Loss was evident in 7.1% (95/1,331) of patients, and severe Fat Loss was evident in 1.9% (25/1,331) of all patients. See Table 11.4.

Table 11.4: Frequency Table: SGA Fat Loss.

SGA Fat Loss category	n/N	%
No obvious loss	961/1,331	72.2
Mild fat loss	250/1,331	18.8
Moderate fat loss	95/1,331	7.1
Severe fat loss	25/1,331	1.9

N=1,331.
SGA: Subjective Global Assessment.

11.6 Aim 1: Univariate Analysis

Aim 1:

To assess the predictive ability and clinical utility of each specific measure of body composition for predicting mortality prior to hospital discharge, univariate analysis was conducted.

11.6.1 Measures of Body Composition

11.6.1.1 BMI analysed as a continuous variable

$BMI_{continuous}$ was found to be significantly associated with survival at hospital discharge during univariate analysis, (OR 0.98, 95% CI 0.96 to 0.99, LR P-value = 0.028) with an aROC of 0.54 (95% CI 0.51-0.58). See Table 11.6.

11.6.1.2 BMI assessed according to WHO categories

$BMI_{categorical}$ was not significantly associated with hospital mortality (LR χ^2_{4df} = 8.13, LR P-value = 0.087), with an aROC of 0.55 (95% CI 0.51-0.58). See Table 11.5 for complete details.

Table 11.5: Univariate analysis of categorised BMI on hospital mortality.

Variable	**Parameter estimate**	**SE parameter estimate**	**Odds ratio**	**95% Cl**	**LR χ^2, P-value**[a]	**aROC** *(95% Cl)*
BMI, WHO[b] category, kg/m^2						
<18.5	0.52	0.33	1.69	0.88 to 3.23	$_{4df}$ = 8.13, 0.087	0.55 *(0.51 to 0.58)*
18.5 to 24.99			Referent			
25.0 to 29.99	- 0.23	0.16	0.80	0.58 to 1.09		
30.0 to 39.99	- 0.30	0.18	0.74	0.52 to 1.06		
≥40	- 0.35	0.32	0.70	0.38 to 1.31		

aROC: area under the receiver operating characteristic curve; BMI: Body Mass Index; CI: confidence interval; SE: standard error; WHO: World Health Organisation.
[a]P-values were obtained from the LR tests for the entire dummy variable.
[b]18.5 to 24.99 kg/m^2 was the referent category.

11.6.1.3 Triceps Skinfold Thickness

Triceps Skinfold Thickness was not significantly associated with survival at hospital discharge during univariate analyses (OR 1.01, 95% CI 0.99 to 1.02, LR P-value = 0.324). The aROC was 0.52 (95% CI 0.48-0.56). See Table 11.6.

11.6.1.4 Mid Arm Muscle Circumference

Mid Arm Muscle Circumference was significantly associated with survival at hospital discharge (OR 0.95, 95% CI 0.93 to 0.98, LR P-value = <0.001), with an aROC of 0.56 (95% CI 0.52-0.60). See Table 11.6.

Table 11.6: Univariate analysis of continuous variables: BMI, Triceps Skinfold Thickness, and Mid Arm Muscle Circumference, on hospital mortality.

Variable	**Parameter estimate**	**SE parameter estimate**	**Odds Ratio**	**95% CI**	**LR χ^2, $_{1df}$ =**	**P-value**[a]	**aROC,** *(95% CI)*
BMI	-0.02	0.01	0.98	0.96 to 0.99	4.86	0.03	0.54 *(0.51 to 0.58)*
Triceps Skinfold Thickness	0.01	0.01	1.01	0.99 to 1.02	0.97	0.32	0.52 *(0.48 to 0.56)*
MAMC	-0.05	0.01	0.95	0.93 to 0.98	11.69	<0.001	0.56 *(0.52 to 0.60)*

aROC: area under the receiver operating characteristic curve; BMI: Body Mass Index; CI: confidence interval; MAMC: Mid Arm Muscle Circumference; SE: standard error.
[a]P-values were obtained from LR tests.

11.6.1.5 SGA Muscle Wasting.

SGA Muscle Wasting was significantly associated with survival at hospital discharge (LR χ^2_{3df} = 15.98, LR P-value = 0.001) and had aROC of 0.56 (95% CI 0.53 to 0.59). See Table 11.7.

11.6.1.6 SGA Fat Loss.

SGA Fat Loss was significantly associated with survival at hospital discharge, (LR χ^2_{3df} = 18.37, LR P-value = <0.001) and an aROC of 0.57 (95% CI 0.54 to 0.60). See Table 11.7.

Table 11.7: Univariate analysis of SGA Muscle Wasting and SGA Fat Loss categories on hospital mortality.

Variable	**Parameter estimate**	**SE parameter estimate**	**Odds ratio**	**95% Cl**	**LR χ^2, P-value**[a]	**aROC** *(95% Cl)*
SGA Muscle Wasting						
No obvious wasting[b]			Referent			
Mild wasting	0.64	0.17	1.89	1.36 to 2.62	$_{3df}$ = 15.98, 0.001	0.56 *(0.53 to 0.59)*
Moderate wasting	0.34	0.25	1.40	0.86 to 2.32		
Severe wasting	0.69	0.43	1.99	0.85 to 4.65		
SGA Fat Loss						
No obvious fat loss[c]			Referent			
Mild fat loss	0.61	0.16	1.84	1.34 to 2.54	$_{3df}$ = 18.37, <0.001	0.56 *(0.53 to 0.59)*
Moderate fat loss	0.49	0.25	1.64	1.00 to 2.64		
Severe fat loss	0.94	0.43	2.56	1.11 to 5.89		

aROC: area under the receiver operating characteristic curve; CI: confidence interval; SE: standard error; SGA: Subjective Global Assessment.
[a]P-values were obtained from LR tests for the entire dummy variable.
[b]No obvious Muscle Wasting was referent category.
[c]No obvious Fat Loss was referent category.

Aim 2:

To assess whether each specific measure of body composition was a significant independent predictor of mortality before hospital discharge, multivariable analysis was conducted to control for the effects of severity of illness and other traditional risk factors.

11.6.2 Severity of illness and traditional risk factors

Univariate analysis was conducted with each severity of illness and traditional risk factor being regressed against the primary outcome of hospital mortality. As per the analysis plan, only those severity of illness and traditional risk factors with a P-value <0.25 were considered for entry into the *maximum* model.

11.6.2.1 Age, APACHE II score, and Gender

Based on univariate analysis, Age was found to be significantly associated with hospital mortality (OR 1.04, 95% CI 1.02 to 1.05, LR P-value <0.001), as was APACHE II score (OR 1.08, 95% CI 1.06 to 1.10, LR P-value <0.001). Both were therefore included in the maximum model.

Gender, using female as the referent category, was not significantly associated with hospital mortality. However, as gender met the criteria for inclusion in the maximum model (LR P-value <0.25) it was retained for later use (OR 0.79, 95% CI 0.68 to 1.03; LR P-value 0.079).

For complete details regarding the univariate analysis of Age, Gender and APACHE II score on hospital mortality, see Table 11.8.

Table 11.8: Univariate analysis of age, APACHE II score and gender on hospital mortality.

Variable	**Parameter estimate**	**SE parameter estimate**	**Odds Ratio**	**95% CI**	**LR χ^2_{1df} =**	**P-value[a]**
Age	0.03	0.005	1.04	1.02 to 1.05	46.09	<0.001
APACHE II score	0.08	0.008	1.08	1.06 to 1.10	78.90	<0.001
Male gender	-0.24	0.13	0.79	0.68 to 1.03	3.09	0.079

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; SE: standard error.

[a]*P* values were obtained from LR tests.

11.6.2.2 APACHE III Source of admission to the ICU

Source of admission was found to be significantly associated with hospital mortality during univariate analyses (LR χ^2_{4df} = 17.93, LR P-value = 0.001), and was therefore included in the maximum model. Hospital ward/floor was used as the referent category in the model.

For complete details regarding the univariate analysis of the source of admission variable, see Table 11.9.

Table 11.9: Univariate analysis of APACHE III Source of admission on hospital mortality.

Variable	Parameter estimate	SE parameter estimate	Odds ratio	95% Cl	LR χ^2, P-value[a]
APACHE III Source of ICU admission					
Hospital Ward[b]			Referent		$_{4df}$ = 17.93, 0.001
Other Hospital	-1.13	0.26	0.88	0.53 to 1.45	
Emergency Dept.	-0.14	0.26	0.87	0.53 to 1.44	
Transfer from ICU	0.59	0.79	1.80	0.39 to 8.41	
Operating theatres	-0.64	0.20	0.53	0.36 to 0.79	

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; Dept: Department; SE: standard error.
[a]P-values were obtained from LR tests.
[b]Hospital ward/floor was the referent category.

11.6.2.3 APACHE III Surgical and Non-surgical patients

Patients were able to be classified as *either* a non-surgical or surgical admission to the study ICU. Surgical admissions were further classified into emergency or elective surgery admissions. In the univariate model, non-surgical admission was used as the referent category.

Non-surgical versus surgical admission status was found to be significantly associated with hospital mortality during univariate analyses (LR χ^2_{2df} = 20.13, LR P-value = <0.001). It was retained and included in the *maximum* model.

For complete details regarding the univariate analysis of non-surgical or surgical admission status, see Table 11.10.

Table 11.10: Univariate analysis of APACHE III surgical and non-surgical admission status on hospital mortality.

Admission	Parameter estimate	SE parameter estimate	Odds ratio	95% CI	LR χ^2, P-value[a]
APACHE III surgical and non surgical admission					
Not surgical[b]			Referent		
Elective Surgery	-0.82	0.20	0.44	0.30 to 0.66	$_{2df}$ = 20.13, <0.001
Emergency Surgery	-0.46	0.14	0.63	0.48 to 0.84	

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; SE: standard error.
[a]P-values were obtained from LR tests.
[b]Non-surgical admission was the referent category.

11.6.2.4 Pre-existing Chronic Health States

As patients may have had more than one pre-existing chronic health state at entry to the study, univariate analyses were conducted *individually*.

Having chronic hepatic cirrhosis was found to be significantly associated with hospital mortality during univariate analyses (OR 4.86, 95% CI 1.79 to 13.15, LR P-value = 0.002), as was having a prior history of a respiratory disease (OR 3.35, 95% CI 1.99 to 5.65, LR P-value <0.001), and requiring insulin to treat diabetes (OR 1.73, 95% CI 1.12 to 2.66, LR P-value = 0.017). All were therefore included in the maximum model.

Being chronically immuno-compromised, while not significantly associated with hospital mortality, nevertheless met the threshold for inclusion in the maximum model (OR 1.51, 95% CI 0.86 to 2.64, LR P-value = 0.166).

Cardiovascular/vascular disease and chronic dialysis did not meet the threshold for inclusion in the maximum confounder model and were excluded from further consideration.

For complete details regarding the univariate analysis of each pre-existing chronic health variable on hospital mortality see Table 11.11.

Table 11.11: Univariate analysis of pre-existing chronic health states on hospital mortality.

Chronic health state	**Parameter estimate**	**SE parameter estimate**	**Odds Ratio**	**95% Cl**	**LR χ^2, $_{1df}$ =**	**P-value[a]**
Cardiovascular disease	0.21	0.34	1.24	0.64 to 2.41	0.38	0.537
Chronic dialysis	0.62	0.55	1.86	0.63 to 5.48	1.16	0.281
Hepatic cirrhosis	1.58	0.51	4.86	1.79 to 13.15	9.36	0.002
Immuno-compromised	0.41	0.29	1.51	0.86 to 2.64	1.92	0.166
Insulin treated diabetes	0.55	0.22	1.73	1.12 to 2.66	5.74	0.017
Respiratory disease	1.21	0.27	3.35	1.99 to 5.65	19.21	<0.001

CI: confidence interval; SE: standard error.
[a]P-values were obtained from LR tests.

11.6.2.5 APACHE II ICU admission diagnosis.

Prior to univariate analysis, the twelve major APACHE II ICU admission diagnoses categories[1] were entered into a frequency table to identify categories with zero mortality, and categories with less than ten observations.

Table 11.12: Frequency Table: APACHE II ICU admission diagnosis.

APACHE II ICU admission diagnosis	**Alive**	**Dead**	**n/N**	**% Mortality**
Gastrointestinal	668	153	821/1,363	18.6
Gynaecological	2	0	2/1,363	0
Haematological	2	0	2/1,363	0
Metabolic	5	2	7/1,363	28.6
Neurological	13	4	17/1,363	23.6
Orthopaedic surgery	1	0	1/1,363	0
Other	17	1	18/1,363	5.6
Renal	7	2	9/1,363	22.2
Respiratory	59	19	78/1,363	24.4
Sepsis	63	34	97/1,363	35.1
Trauma	32	8	40/1,363	20.0
Vascular/cardiovascular	203	68	271/1,363	25.1

N = 1,363.

As can be seen from Table 11.12, three ICU admission diagnosis categories had zero mortality (gynaecological, orthopaedic surgery and haematological). A further two ICU admission diagnosis categories had less than ten total observations (metabolic and renal ICU admission diagnosis). Prior to undertaking univariate analysis, all APACHE II ICU admission diagnosis categories with zero mortality and categories with less than ten total observations were collapsed into the 'other' APACHE II ICU admission diagnosis category to improve statistical stability.[170] Table 11.13 shows the newly collapsed categories.

Table 11.13: Frequency Table: Collapsed APACHE II ICU admission diagnosis categories.

ICU admission diagnosis	**n/N**	**%**
Gastrointestinal	821/1,363	60.2
Vascular/cardiovascular	271/1,363	19.9
Sepsis	97/1,363	7.1
Respiratory	78/1,363	5.7
Trauma	40/1,363	2.9
Other	39/1,363	2.9
Neurological	17/1,363	1.3

ICU: Intensive Care Unit.
[a]Other category includes gynaecological, haematological, metabolic, renal and orthopaedic surgery.

Univariate analysis was then conducted on the (collapsed) APACHE II ICU admission diagnosis categories using sepsis as the referent category. ICU admission diagnosis category was found to be significantly associated with hospital mortality during univariate analyses (LR χ^2_{6df} = 17.89, LR P-value = 0.007). It was retained and included in the maximum model.

For complete details regarding the univariate analysis of the (collapsed) ICU admission diagnosis category, see Table 11.14.

Table 11.14: Univariate analysis of APACHE II ICU admission diagnosis category on hospital mortality.

Variable	Parameter estimate	SE parameter estimate	Odds ratio	95% Cl	P-value[a]
APACHE II ICU admission diagnosis					
Sepsis[b]			Referent		
Cardiovascular/vascular	- 0.48	0.26	0.62	0.38 to 1.02	$_{6df}$ =
Gastrointestinal	- 0.86	0.23	0.42	0.27 to 0.67	17.89,
Neurological	- 0.56	0.61	0.57	0.17 to 1.89	0.007
Other[c]	- 1.30	0.52	0.27	0.10 to 0.76	
Respiratory	- 0.52	0.34	0.60	0.31 to 1.16	
Trauma	- 0.77	0.45	0.46	0.19 to 1.12	

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; SE: standard error.
[a]P-values were obtained from LR tests for the entire dummy variable.
[b]Sepsis was the referent category.
[c]Other category includes gynaecological, haematological, metabolic, renal and orthopaedic surgery.

11.6.2.6 Number of days in study hospital prior to ICU admission

Number of days in study hospital prior to ICU admission was *not* significantly associated with hospital mortality during univariate analyses (OR 1.01, 95% CI 0.98 to 1.04, LR P-value = 0.465). It was therefore not considered for inclusion in the maximum model.

11.7 Aim 2: Maximum model and Stable Maximum Model

The maximum model included the following variables which demonstrated a univariate LR P-value < 0.25: Age, APACHE II score, chronic respiratory disease, APACHE III surgical/non surgical admission status, chronic hepatic cirrhosis, APACHE II ICU admission diagnosis, APACHE III source of admission, chronic insulin treated diabetes, Gender, and immuno-compromised chronic health state.

11.7.1 Assessment of multicollinearity

Multicollinearity within the maximum model was assessed using Eigenanalysis. SAS (Version 9.2) reported that the APACHE III source of admission variable (admission to the ICU from the operating room) and its sub-categories (admission after elective surgery and admission after emergency surgery) were "exact linear combinations" of each other. Furthermore, elective surgery had a condition index of 2,564,140. As the sub-categories provide more information to the reader, they were retained in the model, and the source of admission variable (admission to the ICU from the operating room) was permanently removed from candidacy.

This methodology has previously been used in other statistical analysis plans of randomised controlled trials conducted in critically ill patient populations.[178] Further details are provided in Table 11.15.

Table 11.15: Eigenanalysis and condition index for maximum model and adjusted condition index for *stable* maximum model.

Eliminated variable	**Eigenvalue for eliminated variable**	**Proportion of variation (eliminated variable)**	**Model CI pre-removal**[a]	**Model CI post-removal**[b]
APACHE III Admission to ICU from operating theatres	$1E^{12}$	1.0000	2564140	21.73817

APACHE: Acute Physiology and Chronic Health Evaluation; CI: condition index.
[a] Maximum model
[b] Stable maximum model

The remaining variables in the *maximum* model were once again assessed using Eigenanalysis. All other variables had a condition index of less than 30 and an Eigenvalue of greater than zero, and were therefore retained in the model. This model, hereafter known as

the *stable maximum model*, was therefore used as a starting point for *all* further backwards elimination calculations.

Backwards elimination assessment of *each* measure of body composition was therefore commenced using the following model of severity of illness and traditional risk factors: Age, APACHE II score, Gender, chronic hepatic cirrhosis, chronic respiratory disease, insulin treated diabetes, immuno-compromised chronic health state, APACHE III source of admission, APACHE II ICU major disease category, and APACHE III surgical and non-surgical admission status.

The model aROC was 0.73, indicating the model had acceptable discrimination as per the definitions of Hosmer and Lemeshow.[159] The Hosmer Lemeshow GOF statistic was LR χ^2_{8df} = 6.97, LR P-value = 0.540, indicating it had *good* calibration. See Table 11.16 for the *stable maximum* model.

Table 11.16: Stable maximum model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
Age, years	1.04	1.03 to 1.05	$_{1df}$ = 41.78	<0.001
Gender (Male)	0.78	0.59 to 1.04	$_{1df}$ = 2.77	0.096
APACHE II score	1.05	1.03 to 1.08	$_{1df}$ = 41.78	<0.001
APACHE III Source of ICU admission				
Hospital Ward[b]		Referent	$_{3df}$ = 3.70	0.30
Other hospital	1.02	0.59 to 1.75		
Emergency Department	0.79	0.46 to 1.37		
Transfer from ICU	3.92	0.73 to 20.96		
APACHE III Type of Surgery				
Not surgical[c]		Referent	$_{2df}$ = 3.72	0.156
Elective Surgery	0.58	0.33 to 1.03		
Emergency Surgery	0.66	0.41 to 1.07		
Chronic health states				
Insulin treated diabetes	1.53	0.95 to 2.46	$_{1df}$ = 2.95	0.086
Immuno-compromised	1.50	0.81 to 2.78	$_{1df}$ = 1.57	0.210
Respiratory disease	2.37	1.35 to 4.19	$_{1df}$ = 8.62	0.003
Hepatic cirrhosis	7.14	2.46 to 20.72	$_{1df}$ = 12.60	<0.001
APACHE II ICU admission diagnosis				
Sepsis[d]		Referent		
Cardiovascular / vascular	1.08	0.60 to 1.95		
Gastrointestinal	0.70	0.41 to 1.21	$_{6df}$ = 9.63	0.141
Respiratory	0.62	0.30 to 1.28		
Trauma	1.35	0.49 to 3.70		
Neurological	1.07	0.29 to 3.93		
Other[e]	0.49	0.17 to 1.47		

APACHE: Acute Physiology and Chronic Health Evaluation; CI: Confidence Interval; ICU: Intensive Care Unit.

[a]P-values were obtained from LR tests.

[b]Hospital ward/floor was referent category.

[c]Not surgical admission was referent category.

[d]Sepsis was referent category.

[e]Other category includes renal, metabolic, haematological, gynaecological and orthopaedic surgery.

Candidate measures of body composition

The following measures of body composition met the prespecified univariate LR threshold (P<0.25) for consideration in multivariable analysis: $BMI_{continuous}$, $BMI_{categorical}$, SGA Muscle Wasting, SGA Fat Loss and Mid Arm Muscle Circumference.

Triceps Skinfold Thickness (P = 0.324) did *not* meet the pre-specified univariate threshold for consideration in multivariable analysis and was therefore excluded from further consideration.

11.7.2 Final model: BMI analysed as a continuous variable

$BMI_{continuous}$ was added to the *stable* maximum model and inspected for multicollinearity using Eigenanalysis. As all condition indexes were less than 30 (highest was 27.23), backwards logistic regression was commenced.

The following variables were removed, in presented order: immuno-compromised chronic health state (LR χ^2_{1df} = 1.42, LR P = 0.234), APACHE III source of admission (LR χ^2_{3df} = 3.52, LR P = 0.318), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 9.19, LR P = 0.163) and Gender (LR χ^2_{1df} = 2.45, LR P = 0.118).

$BMI_{continuous}$ remained a *significant independent predictor* of outcome (LR χ^2_{1df} = 4.36, LR P = 0.037) controlling for the following traditional risk factors: Age (P < 0.001), APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = 0.001), chronic respiratory disease (P = 0.006), APACHE III surgical and non surgical admission status (P = 0.025) and chronic insulin treated diabetes (P = 0.065).

The model aROC was 0.72, indicating the model had *acceptable* discrimination as per the definitions of Hosmer and Lemeshow.

The Hosmer Lemeshow GOF statistic was LR χ^2_{8df} = 15.21, LR P-value = 0.055 indicating *acceptable* calibration. See Table 11.17 for complete details.

Table 11.17: $BMI_{continuous}$ - Final Model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
BMI continuous, kg/m^2	0.98	0.96 to 1.00	$_{1df}$ = 4.36	0.037
Age, years	1.03	1.02 to 1.05	$_{1df}$ = 34.44	<0.001
APACHE II score	1.06	1.04 to 1.08	$_{1df}$ = 36.92	<0.001
APACHE III Type of Surgery				
Not surgical[b]		Referent	$_{2df}$ = 7.37	0.025
Elective Surgery	0.63	0.41 to 0.97		
Emergency Surgery	0.68	0.50 to 0.93		
Chronic health states				
Insulin treated diabetes	1.59	0.99 to 2.55	$_{1df}$ = 3.59	0.053
Respiratory disease	2.18	1.25 to 3.78	$_{1df}$ = 7.38	0.006
Hepatic cirrhosis	5.53	1.94 to 15.76	$_{1df}$ = 10.04	0.001

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body Mass Index; CI: confidence interval.
[a]P-values were obtained from LR tests.
[b]Not surgical admission was the referent category.

11.7.3 Final model: BMI assessed according to WHO categories

BMI was categorised according to the WHO,[136;139] and then added to the *stable* maximum model using normal body weight (BMI 18.50 kg/m^2 to 24.99 kg/m^2) as the referent category. Eigenanalysis revealed no evidence of moderate to severe multicollinearity in the new model (the highest condition index was 27.33), hence backwards logistic regression was commenced.

The following variables were removed from the model: APACHE II ICU admission diagnosis (LR χ^2_{6df} = 9.80, LR P = 0.133), APACHE III source of admission (LR χ^2_{3df} = 3.57, LR P = 0.312), immuno-compromised chronic health state (LR χ^2_{1df} = 0.69, LR P = 0.406) and Gender (LR χ^2_{1df} = 1.78, LR P = 0.182). All remaining variables had a LR P-value of <0.1, and were therefore retained.

$BMI_{categorical}$ was *not* a *significant independent predictor* of hospital mortality in the final model (LR χ^2_{4df} = 8.68, P = 0.070). The final model controlled for the effects of Age (P < 0.001), APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = 0.001), chronic

respiratory disease (P = 0.006), APACHE III surgical and non surgical admission status (P = 0.033) and insulin treated diabetes (P = 0.065).

The aROC for the final model was 0.73, indicating *acceptable* discrimination. The Hosmer Lemeshow GOF Test statistic was LR χ^2_{8df} = 13.71, P-value = 0.090 indicating *acceptabl*e calibration. See Table 11.18 for complete details.

Table 11.18: $BMI_{categorical}$ – final model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
BMI, WHO categories, kg/m^2				
<18.5	1.53	0.76 to 3.08		
18.5 – 24.99[b]		Referent	$_{4df}$ = 8.68	0.070
25.0 – 29.99	0.75	0.54 to 1.05		
30.0 – 39.99	0.66	0.45 to 0.97		
≥40	0.67	0.34 to 1.33		
Age, years	1.03	1.02 to 1.05	$_{1df}$ = 35.31	<0.001
APACHE II score	1.06	1.04 to 1.08	$_{1df}$ = 37.11	<0.001
APACHE III Type of Surgery				
Not surgical[c]		Referent	$_{2df}$ = 6.85	0.033
Elective Surgery	0.64	0.41 to 0.98		
Emergency Surgery	0.69	0.50 to 0.94		
Chronic health states				
Insulin treated diabetes	1.56	0.97 to 2.51	$_{1df}$ = 3.29	0.065
Respiratory disease	2.17	1.25 to 3.78	$_{1df}$ = 7.24	0.006
Hepatic cirrhosis	5.69	1.99 to 16.27	$_{1df}$ = 10.24	0.001

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body Mass Index; CI: confidence interval.
[a]P-values were obtained from LR tests.
[b]BMI 18.50 kg/m^2 to 24.99kg/m^2 was the referent category.
[c]Not surgical admission was the referent category.

11.7.4 Final model: Mid Arm Muscle Circumference

Mid Arm Muscle Circumference was added to the stable maximum model and inspected for multicollinearity using Eigenanalysis. As the highest condition index was less than 30 (28.12), backwards elimination was commenced.

The following variables were sequentially removed from the model in presented order: APACHE III source of admission (LR χ^2_{3df} = 1.84, LR P = 0.606), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 9.04, LR P = 0.171), Gender (LR χ^2_{1df} = 0.31, LR P = 0.576) and immuno-compromised chronic health state (LR χ^2_{1df} = 2.15, LR P = 0.142).

All other remaining variables were had a LR P-value of <0.1, and were therefore retained in the final model.

Mid Arm Muscle Circumference *was a significant independent predictor of hospital mortality* (LR χ^2_{1df} = 5.77, LR P = 0.016). Other strong predictors, APACHE II score (P < 0.0001), Age (P < 0.0001), chronic hepatic cirrhosis (P = <0.001), insulin treated diabetes (P = 0.023), APACHE III surgical and non surgical admission status (P = 0.024), and chronic respiratory disease (P = 0.037) also remained in the final model.

The aROC for the final model was 0.72, indicating the model had *acceptable* discrimination. The Hosmer Lemeshow GOF statistic was LR χ^2_{8df} = 7.41, P-value = 0.493, indicating *good* calibration. See Table 11.19 for details.

Table 11.19: Mid Arm Muscle Circumference – final model.

Variable	**Odds Ratio**	**95% CI**	**LR χ^2**	**P-value**[a]
MAMC	0.97	0.94 to 0.99	$_{1df}$ = 5.77	0.016
Age, years	1.04	1.02 to 1.05	$_{1df}$ = 34.45	<0.001
APACHE II score	1.06	1.03 to 1.08	$_{1df}$ = 28.28	<0.001
APACHE III Type of Surgery				
Not surgical[b]		Referent	$_{2df}$ = 7.44	0.024
Elective Surgery	0.61	0.39 to 0.96		
Emergency Surgery	0.67	0.49 to 0.93		
Chronic health states				
Insulin treated diabetes	1.72	1.05 to 2.81	$_{1df}$ = 4.49	0.023
Respiratory disease	1.86	1.04 to 3.32	$_{1df}$ = 4.22	0.037
Hepatic cirrhosis	7.19	2.37 to 21.86	$_{1df}$ = 12.13	<0.001

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; MAMC: Mid Arm Muscle Circumference.
[a]P-values were obtained from LR tests.
[b]Not surgical admission was referent category.

11.7.5 Final model: SGA Muscle Wasting

Evidence of SGA Muscle Wasting was added to the stable maximum model as a categorised variable using the four SGA categories. No obvious muscle loss was used as the referent category.

As there was no evidence of moderate to severe multicollinearity in the model (highest condition index 22.26), backwards logistic regression was commenced.

The following variables were sequentially removed from the model: APACHE III source of admission (LR χ^2_{3df} = 1.86, LR P = 0.602), and immuno-compromised chronic health state (LR χ^2_{1df} = 2.39, LR P = 0.122). All other variables had a LR P-value of <0.1, and thus were retained in the final model.

SGA Muscle Wasting (LR χ^2_{3df} = 10.52, LR P = 0.015), *was* a *significant independent predictor of hospital mortality*, controlling for other severity of illness and traditional risk factors: Age (P < 0.001), APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = <0.001), chronic respiratory disease (P = 0.006), insulin treated diabetes (P = 0.014), APACHE III surgical and non surgical admission status (P = 0.035), Gender (P = 0.042) and APACHE II ICU admission diagnosis (P = 0.078).

The aROC for the multivariable model containing SGA Muscle Wasting was 0.74, showing the model had *acceptable* discrimination. The Hosmer Lemeshow GOF statistic was LR χ^2_{8df} = 7.56, P-value = 0.478 indicating the model had *good* calibration. See Table 11.20 for details.

Table 11.20: SGA Muscle Wasting - Final model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
SGA Muscle Wasting				
No obvious wasting[b]		Referent		
Mild wasting	1.79	1.25 to 2.57	$_{3df}$ = 10.52	0.015
Moderate wasting	1.29	0.76 to 2.21		
Severe wasting	1.68	0.68 to 4.20		
Age, years	1.03	1.02 to 1.05	$_{1df}$ = 31.05	<0.001
Gender (Male)	0.74	0.55 to 0.99	$_{1df}$ = 4.12	0.042
APACHE II score	1.05	1.03 to 1.08	$_{1df}$ = 25.73	<0.001
APACHE III Type of Surgery				
Not surgical[c]		Referent	$_{2df}$ = 6.73	0.035
Elective Surgery	0.56	0.35 to 0.91		
Emergency Surgery	0.67	0.46 to 0.96		
Chronic health states				
Insulin treated diabetes	1.84	1.13 to 2.98	$_{1df}$ = 5.78	0.014
Respiratory disease	2.29	1.27 to 4.15	$_{1df}$ = 7.23	0.006
Hepatic cirrhosis	6.50	2.20 to 19.19	$_{1df}$ = 11.21	<0.001
APACHE II ICU admission diagnosis				
Sepsis[d]		Referent		
Cardiovascular / vascular	1.26	0.69 to 2.31		
Gastrointestinal	0.74	0.43 to 1.29	$_{6df}$ = 11.34	0.078
Respiratory	0.64	0.31 to 1.33		
Trauma	1.57	0.57 to 4.34		
Neurological	1.27	0.34 to 4.73		
Other[e]	0.63	0.21 to 1.88		

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; ICU: intensive care unit; SGA: Subjective Global Assessment.
[a]P-values were obtained from LR tests.
[b]No obvious Muscle Wasting was the referent category.
[c]Not surgical was the referent category.
[d]Sepsis was the referent category.
[e]Other category included renal, metabolic, haematological, gynaecological and orthopaedic surgery.

11.7.6 Final model: SGA Fat Loss

Evidence of SGA Fat Loss was added to the stable maximum model as a categorised variable using the four SGA categories. No obvious loss of fat was used as the referent category.

As there was no evidence of multicollinearity in the new model (highest condition index 22.25), backwards logistic regression was commenced.

The following variables were sequentially removed from the model: APACHE III source of admission (LR χ^2_{3df} = 1.62, LR P = 0.656) and immuno-compromised chronic health state (LR χ^2_{1df} = 2.24, LR P = 0.135).

SGA Fat Loss (LR χ^2_{3df} = 14.41, LR P = 0.002), remained a *significant independent predictor of outcome*. The final covariate adjusted model controlled for confounding due to Age (P < 0.001), APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = <0.001), chronic respiratory disease (P = 0.009), insulin treated diabetes (P = 0.017), Gender (P = 0.038), APACHE III surgical and non surgical admission status (P = 0.049), and APACHE II ICU admission diagnosis (P = 0.074).

The aROC for the covariate adjusted model containing SGA Fat Loss was 0.74, indicating the model had *acceptable* discrimination. The Hosmer Lemeshow GOF statistic was LR χ^2_{8df} = 6.71, LR P-value = 0.568 indicating the model also had *good* calibration. See Table 11.21 for complete details.

Table 11.21: SGA Fat Loss - Final model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
SGA Fat Loss				
No obvious loss[b]		Referent		
Mild loss	1.83	1.29 to 2.60	$_{3df}$ = 14.41	0.002
Moderate loss	1.65	0.98 to 2.79		
Severe loss	2.27	0.92 to 5.60		
Age, years	1.03	1.02 to 1.05	$_{1df}$ = 29.43	<0.001
Gender (Male)	0.73	0.55 to 0.98	$_{1df}$ = 4.31	0.038
APACHE II score	1.06	1.04 to 1.08	$_{1df}$ = 29.51	<0.001
APACHE III Type of Surgery				
Not surgical[c]		Referent	$_{2df}$ = 6.05	0.049
Elective Surgery	0.59	0.36 to 0.95		
Emergency Surgery	0.67	0.47 to 0.97		
Chronic health states				
Insulin treated diabetes	1.80	1.11 to 2.92	$_{1df}$ = 5.46	0.017
Respiratory disease	2.22	1.22 to 4.02	$_{1df}$ = 6.67	0.009
Hepatic cirrhosis	6.19	2.10 to 18.22	$_{1df}$ = 10.71	<0.001
APACHE II ICU admission diagnosis				
Sepsis[d]		Referent		
Cardiovascular / vascular	1.25	0.68 to 2.23		
Gastrointestinal	0.75	0.43 to 1.29	$_{6df}$ = 11.50	0.074
Respiratory	0.61	0.29 to 1.27		
Trauma	1.59	0.58 to 4.39		
Neurological	1.28	0.35 to 4.77		
Other[e]	0.61	0.20 to 1.82		

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; ICU: intensive care unit; SGA: Subjective Global Assessment.
[a]P-values were obtained from LR tests.
[b]No obvious loss was the referent category.
[c]Not surgical was the referent category.
[d]Sepsis was the referent category.
[e]Other category included renal, metabolic, haematological, gynaecological and orthopaedic surgery.

11.8 Aim 3: Specific measures of Body Composition, controlling for BMI

To assess whether each specific measure of body composition remained a significant independent predictor of mortality before hospital discharge in the presence of BMI, severity of illness, and other traditional risk factors.

A specific measure of body composition was declared to be a *better independent predictor of mortality* than BMI if it remained in the final multivariable model with a P-value smaller than the P-value of BMI, where each P-value is obtained from a LR test.[159]

Candidate measures of body composition

BMI was analysed as a continuous (OR 0.98, LR P-value = 0.028) variable throughout, as it was found to perform better than BMI categorical (LR χ^2_{4df} = 8.13, LR P-value = 0.087) on univariate analysis.

The following measures of body composition met the prespecified threshold (P<0.25) for consideration in multivariable analysis: $BMI_{continuous}$ (P = 0.028), SGA Muscle Wasting (P = 0.001), SGA Fat Loss (P < 0.001) and Mid Arm Muscle Circumference (P < 0.001).

11.8.1 Mid Arm Muscle Circumference controlling for BMI

Maximum Model

The *maximum* model included the following variables that met the pre-specified LR P-value <0.25 on survival at hospital discharge: Age (OR 1.04, LR P < 0.001), APACHE II score (OR 1.08, LR P < 0.001), chronic respiratory disease (OR 3.35, LR P = <0.001), APACHE III surgical/non surgical admission status (LR χ^2_{2df} = 20.13, LR P = <0.001), chronic hepatic cirrhosis (OR 4.86, LR P = 0.002), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 17.89, LR P = 0.006), APACHE III source of admission (LR χ^2_{4df} = 17.93, LR P = 0.013), chronic insulin treated diabetes (OR 1.73, LR P = 0.017), Gender (OR 1.27, LR P = 0.079), and immuno-compromised chronic health state (OR 1.51, LR P = 0.166).

Stable Maximum Model

$BMI_{continuous}$ and Mid Arm Muscle Circumference were added to the maximum model. A condition index of >30 (30.28) indicated the presence of moderate to severe multicollinearity. The proportion of variation within the model was inspected by variable. Age had the highest proportion of variation (proportion of variation 0.575) and was permanently removed from the model.

Eigenanalysis was repeated indicated there was no evidence of moderate to severe multicollinearity (condition index 24.39). Backwards elimination was therefore commenced with the stable maximum model.

Final model: Mid Arm Muscle Circumference controlling for BMI

The following variables were sequentially removed from the model during backwards elimination in presented order: APACHE III Source of admission (LR χ^2_{3df} = 1.12, LR P = 0.774), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 7.67, LR P = 0.263), chronic immuno-compromised health state (LR χ^2_{1df} = 1.00, LR P = 0.316), Gender (LR χ^2_{1df} = 1.17, LR P = 0.280), APACHE III surgical/non surgical admission status (LR χ^2_{2df} = 3.46, LR P = 0.177) and $BMI_{continuous}$ (χ^2_{1df} = 2.02, LR P = 0.155).

Mid Arm Muscle Circumference was found to remain a significant independent predictor of mortality in the final model (χ^2_{1df} = 10.65, LR P = 0.001). $BMI_{continuous}$ was eliminated from the model during the backwards stepwise elimination (χ^2_{1df} = 2.02, LR P = 0.155).

The final model controlled for the effects of APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = 0.006), insulin treated diabetes (P = 0.019) and chronic respiratory disease (P = 0.023).

The Hosmer Lemeshow GOF test was LR χ^2_{8df} = 5.34, P-value = 0.721 showing the model had *good* calibration. However, the model aROC was 0.68, indicating the model did *not* have acceptable discrimination. See Table 11.22.

Table 11.22: $BMI_{continuous}$ and Mid Arm Muscle Circumference - Final Model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
MAMC	0.96	0.93 to 0.98	$_{1df}$ = 10.65	0.001
APACHE II score	1.07	1.05 to 1.09	$_{1df}$ = 53.30	<0.001
Chronic health states				
Insulin treated diabetes	1.77	1.10 to 2.86	$_{1df}$ = 5.21	0.019
Respiratory disease	1.95	1.09 to 3.46	$_{1df}$ = 4.94	0.023
Hepatic cirrhosis	4.43	1.53 to 12.79	$_{1df}$ = 7.63	0.006

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; MAMC: Mid Arm Muscle Circumference.
[a]P-values were obtained from LR tests.

11.8.2 SGA Muscle Wasting controlling for BMI

Maximum model

The *maximum* model included the following variables that met the pre-specified LR P-value <0.25 on survival at hospital discharge: Age (OR 1.04, LR P < 0.001), APACHE II score (OR 1.08, LR P < 0.001), chronic respiratory disease (OR 3.35, LR P = <0.001), APACHE III surgical/non surgical admission status (LR χ^2_{2df} = 20.13, LR P = <0.001), chronic hepatic cirrhosis (OR 4.86, LR P = 0.002), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 17.89, LR P = 0.006), APACHE III source of admission (LR χ^2_{4df} = 17.93, LR P = 0.013), chronic insulin treated diabetes (OR 1.73, LR P = 0.017), Gender (OR 1.27, LR P = 0.079), and immuno-compromised chronic health state (OR 1.51, LR P = 0.166).

Stable Maximum model

$BMI_{continuous}$ and SGA Muscle Wasting were added to the maximum model. As there was no evidence of moderate to severe multicollinearity (condition index 28.19), backwards elimination was commenced.

Final model: SGA Muscle Wasting controlling for BMI

The following variables were sequentially removed from the stable maximum model using backwards elimination: APACHE III source of admission (LR χ^2_{3df} = 1.98, LR P = 0.577), chronic immuno-compromised health state (LR χ^2_{1df} = 2.27, LR P = 0.132) and $BMI_{continuous}$ (LR χ^2_{1df} = 1.71, LR P = 0.192).

SGA Muscle Wasting was found to remain a *strong independent predictor of mortality* in the final model (LR χ^2_{3df} = 10.52, LR P = 0.015). $BMI_{continuous}$ was *not* a strong independent predictor of mortality in the same model (LR χ^2_{1df} = 1.71, LR P = 0.192). Known severity of illness and traditional risk factors remaining in the final model were; Age (P < 0.001), APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = <0.001), chronic respiratory disease (P = 0.006), insulin treated diabetes (P = 0.014), APACHE III surgical/non surgical admission status (P = 0.035), Gender (P = 0.042), and APACHE III ICU admission diagnosis (P = 0.078).

The Hosmer Lemeshow GOF test was LR χ^2_{8df} = 7.56, P-value = 0.478, indicating the model had *good* calibration. The aROC was 0.74, indicating the model had *acceptable* discrimination. See Table 11.23.

Table 11.23: $BMI_{continuous}$ and SGA Muscle Wasting - Final Model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
SGA Muscle Wasting				
No obvious wasting[b]		Referent		
Mild wasting	1.79	1.25 to 2.57	$_{3df}$ = 10.52	0.015
Moderate wasting	1.29	0.76 to 2.21		
Severe wasting	1.68	0.68 to 4.20		
Age, years	1.03	1.02 to 1.05	$_{1df}$ = 31.05	<0.001
Gender (Male)	0.74	0.55 to 0.99	$_{1df}$ = 4.12	0.042
APACHE II score	1.05	1.03 to 1.08	$_{1df}$ = 25.73	<0.001
APACHE III Type of Surgery				
Not surgical[c]		Referent	$_{2df}$ = 6.73	0.035
Elective Surgery	0.56	0.35 to 0.91		
Emergency Surgery	0.67	0.46 to 0.96		
Chronic health states				
Insulin treated diabetes	1.84	1.13 to 2.98	$_{1df}$ = 5.79	0.014
Respiratory disease	2.29	1.27 to 4.15	$_{1df}$ = 7.23	0.006
Hepatic cirrhosis	6.50	2.20 to 19.19	$_{1df}$ = 11.21	<0.001
APACHE II ICU admission diagnosis				
Sepsis[d]		Referent		
Cardiovascular / vascular	1.26	0.69 to 2.31		
Gastrointestinal	0.74	0.43 to 1.29	$_{6df}$ = 11.34	0.078
Respiratory	0.64	0.31 to 1.33		
Trauma	1.57	0.57 to 4.34		
Neurological	1.27	0.34 to 4.73		
Other[e]	0.63	0.21 to 1.88		

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; ICU: intensive care unit; SGA: Subjective Global Assessment.
[a]P-values were obtained from LR tests for the entire dummy variable where appropriate.
[b]No obvious Muscle Wasting was the referent category.
[c]Not surgical admission was the referent category.
[d] Sepsis was the referent category.
[e]Other category included renal, metabolic, haematological, gynaecological and orthopaedic surgery.

11.8.3 SGA Fat Loss controlling for BMI

Maximum model

The *maximum* model included the following variables that met the pre-specified LR P-value <0.25 on survival at hospital discharge: Age (OR 1.04, LR P < 0.001), APACHE II

score (OR 1.08, LR P < 0.001), chronic respiratory disease (OR 3.35, LR P = <0.001), APACHE III surgical/non surgical admission status (LR χ^2_{2df} = 20.13, LR P = <0.001), chronic hepatic cirrhosis (OR 4.86, LR P = 0.002), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 17.89, LR P = 0.006), APACHE III source of admission (LR χ^2_{4df} = 17.93, LR P = 0.013), chronic insulin treated diabetes (OR 1.73, LR P = 0.017), Gender (OR 1.27, LR P = 0.079), and immuno-compromised chronic health state (OR 1.51, LR P = 0.166).

Stable Maximum model

$BMI_{continuous}$ and SGA Fat Loss were added to the maximum model. There was no evidence of moderate to severe multicollinearity (condition index 28.20), and backwards elimination was commenced.

Final model: SGA Fat Loss controlling for BMI.

The following variables were sequentially removed from the stable maximum model using backwards elimination: APACHE III source of admission (LR χ^2_{3df} = 1.70, LR P = 0.638), chronic immuno-compromised health state (LR χ^2_{1df} = 2.16, LR P = 0.142) and $BMI_{continuous}$ (LR χ^2_{1df} = 0.94, LR P = 0.332).

SGA Fat Loss remained a *strong independent predictor of mortality* in the final model (LR χ^2_{3df} = 14.41, LR P = 0.002). $BMI_{continuous}$ was *eliminated* from the model (LR χ^2_{1df} = 0.94, LR P = 0.332). The final model controlled for the effects of Age (P < 0.001), APACHE II score (P < 0.001), chronic hepatic cirrhosis (P = <0.001), chronic respiratory disease (P = 0.009), insulin treated diabetes (P = 0.017), Gender (P = 0.038), APACHE III surgical/non surgical admission status (P = 0.049), and APACHE II ICU admission diagnosis (P = 0.074).

The Hosmer Lemeshow GOF test was LR χ28df = 6.71, LR P-value = 0.568, indicating good calibration. The aROC was 0.74, indicating the model had good discrimination. See Table 11.24.

Table 11.24: $BMI_{continuous}$ and SGA Fat Loss - Final Model.

Variable	Odds Ratio	95% CI	LR χ^2	P-value[a]
SGA Fat Loss				
No obvious loss[b]		Referent		
Mild loss	1.83	1.29 to 2.60	$_{3df}$ = 14.41	0.002
Moderate loss	1.65	0.98 to 2.79		
Severe loss	2.27	0.92 to 5.60		
Age, years	1.03	1.02 to 1.05	$_{1df}$ = 29.43	<0.001
Gender (Male)	0.73	0.55 to 0.98	$_{1df}$ = 4.31	0.038
APACHE II score	1.06	1.04 to 1.08	$_{1df}$ = 29.51	<0.001
APACHE III Type of Surgery				
Not surgical[c]		Referent		
Elective Surgery	0.56	0.35 to 0.91	$_{2df}$ = 6.05	0.049
Emergency Surgery	0.67	0.46 to 0.96		
Chronic health states				
Insulin treated diabetes	1.80	1.11 to 2.92	$_{1df}$ = 5.46	0.017
Respiratory disease	2.22	1.22 to 4.02	$_{1df}$ = 6.67	0.009
Hepatic cirrhosis	6.19	2.10 to 18.22	$_{1df}$ = 10.72	<0.001
APACHE II ICU admission diagnosis				
Sepsis[d]		Referent		
Cardiovascular / vascular	1.25	0.68 to 2.28		
Gastrointestinal	0.75	0.43 to 1.29	$_{6df}$ = 11.50	0.074
Respiratory	0.61	0.29 to 1.27		
Trauma	1.59	0.58 to 4.39		
Neurological	1.28	0.35 to 4.77		
Other[e]	0.61	0.20 to 1.82		

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; ICU: intensive care unit; SGA: Subjective Global Assessment.
[a]P-values were obtained from LR tests for the entire dummy variable where appropriate.
[b]No obvious loss was the referent category.
[c]Not surgical admission was the referent category.
[d]Sepsis was the referent category.
[e]Other category included renal, metabolic, haematological, gynaecological and orthopaedic surgery.

11.9 Aim 4: Best combination of all measures of Body Composition

To determine the best combination of all available measures of body composition, multivariable analysis was conducted to control for the effects of all measures of body composition, severity of illness and other traditional risk factors.

Candidate measures of body composition:

BMI was analysed as a continuous (OR 0.98, LR P-value = 0.028) variable, as it was found to perform better than BMI categorical (LR χ^2_{4df} = 8.13, LR P-value = 0.087) on univariate analysis.

The remaining measures of body composition that met the pre-specified univariate threshold (P <0.25) were considered eligible for multivariable assessment: $BMI_{continuous}$ (P = 0.028), SGA Muscle Wasting (P = 0.001), SGA Fat Loss (P < 0.001) and Mid Arm Muscle Circumference (P < 0.001). Triceps Skinfold Thickness was not eligible for model entry (P = 0.324).

Maximum model

The *maximum* model included the following variables that met the pre-specified LR P-value <0.25 on survival at hospital discharge: Age (OR 1.04, P < 0.001), APACHE II score (OR 1.08, P < 0.001), chronic respiratory disease (OR 3.35, P = <0.001), APACHE III surgical/non surgical admission status (LR χ^2_{2df} = 20.13, P = <0.001), chronic hepatic cirrhosis (OR 4.86, P = 0.002), APACHE II ICU admission diagnosis (LR χ^2_{6df} = 17.89, P = 0.006), APACHE III source of admission (LR χ^2_{4df} = 17.93, P = 0.013), chronic insulin treated diabetes (OR 1.73, P = 0.017), Gender (OR 1.27, P = 0.079), and immuno-compromised chronic health state (OR 1.51, P = 0.166).

Stable Maximum model

$BMI_{continuous}$, SGA Muscle Wasting, SGA Fat Loss and Mid Arm Muscle Circumference were added to the maximum model. A condition index of >30 indicated the presence of moderate to severe multicollinearity. The proportion of variation within the model was inspected by variable. Mid Arm Muscle Circumference had the highest proportion of variation (proportion of variation 0.746) and was permanently removed from the model. Eigenanalysis indicated there was no further evidence of moderate to severe multicollinearity (condition index 29.02). Backwards elimination was commenced with the *stable* maximum model.

Final model: best combination of all available measures of body composition.

During backwards elimination the following variables were sequentially removed from the model in presented order: APACHE II ICU admission diagnosis (LR χ^2_{6df} = 10.27, LR P = 0.114), APACHE III source of admission (LR χ^2_{3df} = 2.12, LR P = 0.548), Gender (LR χ^2_{1df} = 1.62, LR P = 0.203), immuno-compromised chronic health state (LR χ^2_{1df} = 1.89, LR P = 0.169), $BMI_{continuous}$ (LR χ^2_{1df} = 1.41, LR P = 0.235), and SGA Muscle Wasting (LR χ^2_{3df} = 3.40, LR P = 0.334). All other variables had a LR P-value of <0.1 and therefore remained in the final model.

SGA Fat Loss (LR χ^2_{3df} = 21.76, LR P = <0.001) remained a *significant independent predictor of hospital mortality* when controlling for the effects of Age (P = <0.001), APACHE II score (P = < 0.001), chronic hepatic cirrhosis (P = 0.001), APACHE III surgical/non surgical admission status (P = 0.017), insulin treated diabetes (P = 0.037), and chronic respiratory disease (P = 0.042).

No other measures of body composition were included in the final model. SGA Fat Loss was therefore deemed to be the *'best'* available measure of body composition in this observational study.

The aROC for the final model was 0.73, indicating the model had *acceptable* discrimination. The Hosmer Lemeshow GOF statistic for the final model was LR $\chi^2_{8df} = 5.28$, LR P-value = 0.727, showing the model had *good* calibration. See Table 11.25.

Table 11.25: The "best" measure of body composition - Final model.

Variable	**Odds Ratio**	**95% CI**	**LR χ^2**	**P-value**[a]
SGA Fat Loss				
No obvious loss[b]		Referent		
Mild loss	1.82	1.28 to 2.57	$_{3df} = 21.76$	<0.001
Moderate loss	1.64	0.97 to 2.78		
Severe loss	1.82	0.72 to 4.59		
Age, years	1.03	1.02 to 1.05	$_{1df} = 29.22$	<0.001
APACHE II score	1.06	1.04 to 1.08	$_{1df} = 30.22$	<0.001
APACHE III Type of Surgery				
Not surgical[c]		Referent	$_{2df} = 6.61$	0.017
Elective Surgery	0.62	0.40 to 0.98		
Emergency Surgery	0.69	0.50 to 0.95		
Chronic health states				
Insulin treated diabetes	1.71	1.05 to 2.78	$_{1df} = 4.36$	0.037
Respiratory disease	1.86	1.03 to 3.36	$_{1df} = 4.13$	0.042
Hepatic cirrhosis	7.02	2.29 to 21.55	$_{1df} = 11.61$	0.001

APACHE: Acute Physiology and Chronic Health Evaluation; CI: confidence interval; SGA: Subjective Global Assessment.
[a]P-values were obtained from LR tests.
[b]No obvious loss was the referent category.
[c]Not surgical was the referent category.

12. DISCUSSION

The purpose of this multi-centre analytic observational study was to determine whether key measures of nutrition status can add additional information to a widely used method of outcome prediction for critically ill patients. To address this question, severity of illness, other traditional risk factors and specific measures of body composition were prospectively collected on 1,363 critically ill patients admitted to the ICUs of 31 hospitals throughout Australia and New Zealand.

Using logistic regression to predict hospital discharge mortality, multivariable analysis controlling for severity of illness and other traditional risk factors revealed that specific measures of body composition *do* add additional information to outcome prediction. Better nutrition status was always related to better survival regardless of the measure of body composition used. Furthermore, multivariable analysis was undertaken to identify the *best combination* of measures of body composition: controlling for severity of illness, other traditional risk factors and all available measures of body composition, after backwards stepwise elimination, SGA Fat Loss was the only measure of body composition that remained a significant independent predictor of mortality.

12.1 Method of outcome prediction assessed

The method of outcome prediction used in this current study is based on the approach most commonly used in observational studies[4;179-181] and randomised controlled trials recruiting critically ill patient populations.[182-187] Each study selects one of the three main methods to assess severity of illness (APACHE, SAPS or MPM) and collects additional information on a focused set of other traditional risk factors. The most commonly collected traditional risk factors include: ICU admission diagnosis;[4;179;180;186] pre-existing chronic health states;[4;179;180;183] source of admission;[182;183;185;186] surgical or non-surgical admission

status;[4;179;180;182;185] gender;[4;179;180;182] and age.[4;179;180;182;183;185-187] The APACHE II score is the most commonly used measure to control for severity of illness at study baseline in Australia and New Zealand multicentre studies.[4;179;180;183;185-187] Unlike the APACHE III predictive equation, the APACHE II predictive equations have been published in the public domain, allowing for calculation of an individual patient's risk without paying any subscription fees.

None of the severity of illness scores or traditional risk factors used in critical care are accepted to have statistical interactions with other traditional risk factors, and polynomial relationships are not accepted to exist with mortality.[4;179;180;183;185-187] To maintain consistency with accepted approaches, interaction terms and the existence of polynomial relationships were not investigated in this present study.

12.2 Relevance

In Australia and New Zealand 60,000 patients require intensive care each year, with total costs to the public healthcare system reaching $AUD 1 billion annually.[1] Despite these allocated resources, approximately 15% of *all* ICU patients die prior to hospital discharge. In order to improve the efficiency and effectiveness of intensive care, the Australian and New Zealand Intensive Care Society's Centre for Outcome and Resource Evaluation (ANZICS CORE) collects ICU admission data on all patients admitted to each of the 140 intensive care units throughout Australia and New Zealand. This admission data, which includes a severity of illness score, ICU admission diagnosis, pre-existing chronic health states, source of admission, surgical or non-surgical admission status, gender and age, is used to standardise risk of mortality across each different ICU. The standardised risk of mortality generated by the ANZICS CORE supports quality assurance benchmarking projects conducted by each participating ICU. The results of this current analytic observational study suggests that

inclusion of a simple bedside measure of body composition could add additional information to the model used by ANZICS CORE, thus improving the relevance of each and every quality assurance benchmarking project and potentially leading to improved patient outcomes and reduced overall costs of care. Furthermore, an improved understanding of the relationship between admission nutrition status and death after onset of critical illness could lead to new and novel research directions and findings.

Experts in nutrition in critical illness recognise that "critically ill patients cannot communicate verbally to provide diet histories"[188] leaving measures of body composition as the only elements of a comprehensive nutrition assessment that can be routinely used to measure nutrition status at time of ICU admission. A recent review paper published in the New England Journal of Medicine highlights the failure of randomised controlled trials to provide insights into the identification of subgroups of critically ill patients most likely to benefit from enhanced nutrition support.[13] Whilst previous clinical trials have used BMI to assess nutrition status at ICU admission, the results of this current analytic observational study suggests measures of body composition that focus on either lean body (muscle) mass or fat mass provide more information than BMI.

BMI is a crude measure of 'body size' and does not distinguish between lean body mass or fat mass. It is possible that new insights could be gained by using focused measures of lean body mass and fat mass to identify ICU patient populations most likely to benefit from enhanced approaches to nutrition support evaluated in clinical trials. In addition, the finding that nutrition status at time of ICU admission is associated with hospital mortality begs the question of whether improving nutrition status *before* a patient requires ICU care can improve outcomes from ICU care.

In non-critically ill hospitalised patients where it is possible to conduct a comprehensive nutrition assessment, the onset of malnutrition is known to be associated with

increased length of stay, increased costs and increased risk of death.[189] Indeed, non-critically ill hospitalised patient populations who are at high risk of becoming malnourished are also at high risk of requiring ICU admission. For example, 100% of patients undergoing Bone Marrow Transplantation become malnourished,[190] with 24-40% of all Bone Marrow Transplant patients also requiring ICU care.[191-194] Bone Marrow Transplant patients have poor nutrition intake due to nausea and vomiting. If nutrition status can be maintained during the hospitalised portion of their transplantation, perhaps when ICU care is required, outcomes can be improved. Clinical trials using measures of nutrition status that are more sensitive to patient outcomes at time of ICU admission may provide insights into complex relationships between different patient populations and appropriate nutrition support. As the authors of the New England Journal of Medicine review article implore, measures of nutrition status that are more sensitive to patient outcomes from critical illness may help us better "identify patients who are able to effectively use macronutrients for recovery and thus are likely to benefit from more aggressive earlier nutrition". [195]

12.3 Specific findings

12.3.1 BMI assessed according to WHO categories

BMI assessed according to WHO categories did not achieve statistical significance with regards to univariate predictive ability (P = 0.087), however it did demonstrate statistically significant clinical utility (aROC 0.55, 95% CI 0.51-0.58). Furthermore, in multivariable analysis controlling for severity of illness and other traditional risk factors, BMI assessed according to WHO categories did not remain a significant independent predictor of outcome (P = 0.07). Because larger studies have found categorised BMI to be associated with mortality when controlling for severity of illness and other traditional risk factors, these

borderline significant results may reflect an inadequate sample size in this current observational study.

Pickkers *et al.*[142] conducted a study in 62 medical and surgical ICU's, enrolling 154,308 patients and demonstrated BMI analysed using WHO categories was significantly associated with hospital mortality. Similarly, Marik *et al.*[145] used a database collected from 101 American medical and surgical ICU's enrolling 48,176 patients and demonstrated BMI analysed using the NIH categories[137] was significantly associated with hospital mortality.

If the relationship between categorised BMI and mortality only becomes apparent in extremely large studies, it is possible that the current analytic observational study was too small to show positive significant results between categorised BMI and outcome. BMI may be appropriate for use in extremely large studies, but alternate measures of body composition may provide more information than categorised BMI when studies are not extremely large.

12.3.2 BMI analysed as a continuous variable

BMI analysed as a continuous variable was found to have acceptable univariate predictive ability (P = 0.028) and clinical utility (aROC 0.54, 95% CI 0.51-0.58). When considered with other traditional risk factors and severity of illness measures, BMI analysed as a continuous variable remained a significant independent predictor of outcome (P = 0.037). In addition, the higher the patients BMI, the *better* the overall survival (OR 0.98, 95% CI 0.96 to 1.00).

The primary statistical literature cautions[196] that grouping continuous variables into two or more categories, whilst simplifying the clinical interpretation of the results, and perhaps being inappropriately perceived as the recommended approach by many clinicians "may create rather than avoid problems, notably a considerable loss of power and residual confounding".[197] Furthermore, they suggest that "dichotomising continuous data is

unnecessary for statistical analysis and in particular should not be applied to explanatory variables in regression models".[197]

Hosmer and Lemeshow suggest categorisation of a continuous variable can be explored if the continuous variable does *not* have a linear relationship with outcome across the log-odds risk scale used by logistic regression.[198] Since other research conducted on moderately sized critically ill patient populations (474 patients) also reports a significant relationship between BMI analysed as a continuous variable and mortality using logistic regression,[199] it can be concluded that BMI *does* have a reasonably good linear relationship with outcome across the log-odds scale. To warrant grouping BMI into categories for analysis in moderately sized projects, instead of analysing BMI as a continuous variable, additional research is required to clearly demonstrate gains from categorisation. Given that both the WHO and NIH categories for BMI were developed to capture risk of adverse outcomes in healthy populations, future research could investigate novel categorisation thresholds that clearly capture risk in critically ill patients.

12.3.3 SGA Muscle Wasting

SGA Muscle Wasting had acceptable univariate predictive ability (P = 0.001) and clinical utility (aROC 0.56, 95% CI 0.53-0.59). SGA Muscle Wasting remained a significant independent predictor of outcome after controlling for severity of illness and other traditional risk factors (P = 0.015). Furthermore, the lower the SGA Muscle Wasting category, corresponding to better nutrition status, the *better* the overall survival (LR χ^2_{3df} = 10.52, LR P = 0.015).

SGA Muscle Wasting has been shown to be one of only two components of the SGA tool that was predictive of the onset of severe malnutrition in hospitalised patients.[29] In 2012, the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral

Nutrition published a Consensus Statement to standardise the clinical criteria used to identify and document malnutrition in hospitalised adults. This statement recognises SGA Muscle Wasting as an essential instrument for the clinical diagnosis of malnutrition.[23] Despite these findings, only one 44-patient single centre study has investigated the use of the SGA Muscle Wasting scale in critically ill patients, and did not find it to be associated with mortality.[102]

The finding that the SGA Muscle Wasting assessment scale is associated with mortality is consistent with recent ICU based research measuring skeletal muscle mass using abdominal CT imaging. In two separate studies published in 2013 and 2014, lower skeletal muscle area as measured by CT scan was found to be associated with increased mortality.[88;89] Future research should investigate the reliability of physical evidence of the SGA Muscle Wasting scale against CT measured skeletal muscle mass in critically ill patients.

12.3.4 SGA Fat Loss

SGA Fat Loss assessment had acceptable univariate predictive ability (P = <0.001) and clinical utility (aROC 0.57, 95% CI 0.54-0.60). SGA Fat Loss was also a significant independent predictor of outcome after controlling for severity of illness and other traditional risk factors (P=0.002). The lower the SGA Fat Loss category, corresponding to better nutrition status, the *better* the overall survival (LR χ^2_{3df} = 14.41, LR P = 0.002).

As with SGA Muscle Wasting, SGA Fat Loss has been shown to be one of only two components of the full SGA that was predictive of the onset of severe malnutrition in hospitalised patients.[29] The most recent consensus statement from the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition Consensus Statement to standardise the clinical criteria used to identify and document malnutrition in hospitalised adults recognises SGA Fat Loss as an essential instrument for the clinical diagnosis of malnutrition.[23] However, extensive literature searching failed to reveal other

studies conducted in critically ill patients investigating the performance of the SGA Fat Loss scale.

Our understanding of chronic disease progression has changed over time. It is now accepted that significant muscle mass may be lost before adipose tissue begins to be catabolised.[200] This understanding of disease progression provides insights as to why the SGA Fat Loss scale performed well. If fat stores represent the *last* body compartment to be lost as a chronic disease progresses, detection of significant fat loss may represent the most advanced state of chronic disease progression. This issue is addressed in more detail later in the Discussion in the context of the identification of the best combination of measures of body composition.

12.3.5 Triceps Skinfold Thickness

Univariate analysis failed to demonstrate a significant relationship between Triceps Skinfold Thickness and mortality (P = 0.324, aROC 0.52, 95% CI 0.48-0.56). These findings are consistent with the results of other small single centre ICU based studies.[53;85;101;102;119] It has been suggested that the presence of oedema, which is ubiquitous in critical illness,[133] interferes with the reliability of the measurement of Triceps Skinfold Thickness in ICU patients.[85] Daily patient fluid balance, or other measures of oedema, was not collected in this current observational study. Whilst the measurement of oedema could have been quantified using isotope dilution methods, funds were not available to conduct this assessment.

To minimise the effect of oedema on the Triceps Skinfold Thickness measurement, research coordinators were instructed to take the reading from the calipers *three seconds* after application of the caliper to the fat fold, allowing fluid to be 'squeezed out' of the skinfold prior to measurement.[164]

Future studies should collect fluid balance data to determine the effect of oedema on accuracy of triceps skinfold thickness measurements and explore the use of alternate measures of total body water to assess the impact of oedema on this measurement.

12.3.6 Mid Arm Muscle Circumference

The measurement of Mid Arm Muscle Circumference demonstrated statistically significant univariate predictive ability (P = <0.001) and clinical utility (aROC 0.56, 95% CI 0.52-0.60). In multivariable analysis, Mid Arm Muscle Circumference remained a significant independent predictor of outcome (P = 0.016) after controlling for severity of illness and other traditional risk factors. In addition, the higher the patient's Mid Arm Muscle Circumference, corresponding to better nutrition status, the *better* the overall survival (OR 0.97, 95% CI 0.94 to 0.99).

Previous ICU based studies that have measured Mid Arm Muscle Circumference at admission[101;102] have not investigated the association between Mid Arm Muscle Circumference measurement and mortality. The authors' results are the first to show that Mid Arm Muscle Circumference is a significant independent predictor of outcome in the ICU patient.

The finding that Mid Arm Muscle Circumference is a significant independent predictor of mortality is consistent with the authors finding that SGA Muscle Wasting is also a strong independent predictor of mortality; and is consistent with studies conducted in critically ill patient populations using abdominal CT scans to assess muscle mass.[88;89]

12.3.7 BMI compared to other specific measures of body composition

In *all* multivariable models, when controlling for severity of illness and other traditional risk factors, BMI analysed as a continuous variable did not remain a significant

independent predictor of outcome when modelled in the presence of each of the focused measures of body composition (Mid Arm Muscle Circumference, SGA Fat Loss, and SGA Muscle Wasting). Each focused measure of body composition was compared to BMI one measure at a time using a unique multivariable model developed for each comparison. Because BMI is the most commonly reported measure of body composition in research conducted in critically ill patient populations,[172;185;201;202] multivariable analysis controlling for each focused measure of body composition, one measure at a time, provides a useful comparison to an accepted reference.

BMI is regarded as a composite measure of *body size* and does not distinguish between fat mass, lean body (muscle) mass or fluid compartments. When patients with chronic disease present to ICU, especially if patients have received a significant amount of resuscitation fluid prior to ICU admission, a BMI categorised as normal (18.5 to 24.99kg/m^2), or even obese (> 30kg/m^2), may mask significant muscle loss.[133] *Focused* physical assessment and anthropometric measures of body composition may stage the progression of a pre-existing chronic disease state more accurately than a *crude* BMI assessment and thus each provides more predictive information that crude BMI. As BMI is the most commonly collected measure of body composition, the findings that other measures outperform BMI in a multivariable assessment are important and novel.

12.3.8 The best combination of all available measures of body composition

When modelled with *all other* measures of body composition, severity of illness and other traditional risk factors, SGA Fat Loss was the only measure of body composition to remain an independent significant predictor of mortality ($P < 0.001$). No other measure of body composition, specifically no measure of lean body mass or overall body size (BMI), remained a significant independent predictor of mortality when included in the same model as

SGA Fat Loss. SGA Fat Loss was regarded as the 'best' measure of body composition in this analytic observational study.

This finding is entirely consistent with the current understanding of chronic disease progression over time: in chronic states like cancer or chronic obstructive pulmonary disease, fat mass is the last body compartment to be consumed such that when fat begins to be lost, poor outcome is imminent.[200]

12.4 Fat Mass, Lean Body Mass and Survival

Several mechanistic theories have been proposed to explain why ample lean body (muscle) mass and fat mass reserves may be protective during critical illness.[143;203;204] These theories range in scope from the obvious advantages provided by enhanced metabolic energy reserves, to subtle physiological relationships that exist between lean body mass and fat mass stores during the general inflammatory response to critical illness and sepsis.

Both muscle and adipose tissue provide energy reserves during critical illness.[205] When nutritional intake is not adequate to meet caloric requirements, the first source of energy reserve utilised by the critically ill patient is glycogen, the storage form of glucose. It is estimated the average adult person has approximately 700 grams of glycogen stored primarily in the liver (200 grams) and muscle (500 grams).[57] At 4 Kilocalories of energy per gram of glycogen, these stores may last one to two days at most.

Once glycogen stores are depleted, if nutrition intake is not adequate to meet requirements, both lean body mass and adipose tissue stores are mobilised. Lean body mass stores are mobilised to release amino acids and adipose tissue stores are mobilised to release glycerol, both of which are used to generate new glucose molecules for energy via gluconeogenesis.[57] Whilst it is commonly accepted that starving or fasting a healthy person will eventually preserve existing muscle stores by using ketone bodies, in the critically ill

person, there is mounting evidence that muscle stores may continue to be mobilised even when glucose infusions are commenced.[206] For survivors of critical illness, muscle wasting and resultant muscle weakness is known to have profound effects on ventilator weaning, hospital stay and longer term physical function.[156;201;207] Skeletal muscle weakness and disability may persist for at least five years.[201]

During critical illness, it is accepted that patients require approximately 20 to 25 Kilocalories/kilogram per day to support their metabolic requirements.[208] Unfortunately, during the first 3 to 5 days of critical illness, patients rarely receive enough nutrition to support these needs.[209-211] This initial phase of critical illness, where caloric intake is much less than metabolic expenditure, has been referred to as a 'caloric debt'[209-211] and is associated with an increase in skin pressure sores,[210] infections,[211] total complication rates,[210] and mortality.[209] Adequate metabolic energy reserves in the form of lean body mass and fat mass stores may be particularly important to survival during the initial periods of critical illness because they provide an additional metabolic fuel source when critically ill patients are known to be highly catabolic and nutrition intake is inadequate to meet needs.[205;212-214]

Independent of lean body mass stores, adequate fat stores may confer benefits beyond those attributable to energy reserves. For example, individuals with higher levels of fat stores are known to have higher serum lipid and lipoprotein levels. Sepsis arising from gram-negative bacteria is a major problem during critical illness.[215] Lipids and lipoproteins such as cholesterol are able to bind endotoxins during septic insults, helping moderate the pro-inflammatory response leading to improved clinical outcomes from sepsis.[24]

Adipocytes or adipose tissue cells are also able to produce and secrete anti-inflammatory adipokines such as interleukin (IL)-10, and leptin. Both of these adipokines are elevated in the serum of patients with higher levels of fat stores, and may help to modulate the inflammatory processes common during general critical illness.[24] Interleukin-10 is able to

inhibit the release of pro-inflammatory cytokines including IL-6, IL-8 and tumour necrosis factor from macrophages. Higher plasma levels of IL-10 are associated with better outcomes in acute lung injury patients admitted to the ICU[24;216] and higher levels of leptin has been associated with increased survival from sepsis.[217]

Whilst physiologic reasons exist to explain why adequate fat stores at ICU admission may confer a survival advantage, differences in care process may also explain improved patient outcomes. Hogue *et al.*[214] proposed that compared with the non-obese patient, obese patients are more likely to be admitted to the ICU, and these admissions occur earlier during their hospital stay. More frequent and earlier admissions may be due to a heavier nursing workload on the wards outside of the ICU. Thus moving the patient to a part of the hospital that has a higher nurse to patient ratio, the ICU, also results in a transfer to a part of the hospital where the patient receives higher levels of all aspects of observation and care. This process knowingly or unknowingly results in differential treatment based on body weight.

12.5 Feasibility of collection of measures of body composition

Excessive missing values can invalidate clinical research.[168] Very few patients had missing body composition measurements in this observational study. Measurements were 100% complete for BMI, and missing in 2.3% (32/1,363) of cases when assessing both SGA Muscle Wasting and SGA Fat Loss. Triceps Skinfold Thickness had 4.8% (66/1,363) and Mid Arm Muscle Circumference had 5% (68/1,363) missing data. As a comparator, it is expected that approximately 5% of all critically ill patients enrolled into a major clinical trial will be found to be missing at least one element of the APACHE II score at study completion.[156] Small studies evaluating comprehensive nutrition assessments conducted in ICU patients have reported excessive missing values for variables such as diet history (21.5%)[49] and weight loss

history (100%).[53] In a larger multicentre study, Heyland *et al.*[51] discovered that diet and weight histories were missing in 70.8% of patients.

Based on informal observation, we estimate both SGA Muscle Wasting and SGA Fat Loss scales can be scored and recorded at the bedside in less than 3 minutes. The conduct of anthropometry to obtain Triceps Skinfold Thickness and Mid Arm Muscle Circumference may take 15 minutes to landmark, measure and calculate.

Considering estimated workload and the low amount of missing data, it can be concluded that collection of each of these measures is feasible in the busy clinical environment of the ICU.

12.6 Patient population studied

Although the inclusion criteria employed for this analytic observational study were broad and designed to enrol all patients' expected to remain in the study ICU at least two days, as with any study, unique aspects of the inclusion criteria may have resulted in a unique patient population. Although certain aspects of the patient population enrolled into this analytic observational study are similar to comparable multicentre studies, others aspects differ. The two multicenter clinical trials that employed inclusion criteria most similar to this study are the Australian and New Zealand Nutrition Guidelines study[218] and the CALORIES study[219] conducted in the United Kingdom.

In comparison to the Nutrition Guidelines study and the CALORIES study, patients enrolled into this analytic observational study were similar with regards to their overall severity of illness (APACHE II score), gender distribution, distribution of pre-existing chronic health states and the average ICU and hospital lengths of stay. However patients enrolled into this study tended to be eight to ten years older and were more likely to have had

surgery. Furthermore, hospital discharge mortality was lower in this analytic observational study compared to either of the other two studies.

Given the key similarities of the patient population enrolled into this study with the patient populations enrolled into other studies with similarly broad enrollment criteria, and in consideration that the primary findings of this study are consistent with the literature in this field, it is most likely the results will generalize to other specific critically ill patient populations.

Future research should attempt to repeat the results of this observational study in patient populations who may have been excluded from this current study. For example, burns patients, patients who received major organ transplants and ICU patients with a short expected length of stay.

12.7 Strengths and Weaknesses

Research coordinators who collected data for this study at each of the 31 participating ICUs received formal training in order to standardise techniques across sites. This training was provided in small group sessions, one-on-one and was supported by printed material. The printed material has been published in the public domain.[161] Researchers wishing to attempt replication can access this primary material and ensure data is collected using similar techniques in future studies. The importance of standardised methodology for anthropometric measurements has been well established.[62]

Much of the research addressing the association between measures of body composition and outcome in the ICU has failed to account for other elements of the patient's medical history that could adversely affected a patient's prognosis.[98] This observational study used comprehensive statistical analysis to control for the effects of severity of illness and other traditional risk factors. Furthermore, the analytic process used in this study accounted

for instability arising due to possible multiple correlations within the dataset (multicollinearity).[175]

A comprehensive nutrition assessment to determine nutrition status includes the consideration of medical history, food intake history, weight loss history, physical examination, anthropometric measurements, and laboratory data.[26] At the time of planning for the observational study, laboratory data such as albumin was no longer regarded as a measure of nutrition status.[23;220] Furthermore, whilst albumin was considered for inclusion in the APACHE II score by Knaus *et al.*[7] it was not found to increase its explanatory power and was therefore excluded from further consideration. Previous ICU based studies have shown that weight and dietary history information is missing early in ICU admission,[49;51;53;101;119] even after three attempts at completion,[49] leading one researcher to state that the degree of missing data "seriously limits the clinical utility of these measurements".[51]

Medical history information *was* collected and controlled for in multivariable analyses in this observational study. Elements of the medical history such as chronic health states, ICU admission diagnosis, insulin requiring diabetes and length of time in the hospital prior to ICU admission were all considered for inclusion in the maximum model.

In the non-ICU patient, the last component of a comprehensive nutrition assessment is often to conduct a functional assessment. Whilst functional assessment tests such grip strength[67;221-224] the six minute walk test[172;201;225-229] and the Physical Function Subscale of the Short-Form 36 health survey[201;230-240] have been applied to ICU patients, they are not applied at admission to ventilated and sedated patients. Functional estimates are more frequently made at time of ICU discharge, time of hospital discharge or later, when the critically ill *survivor* is able to actively participate in the assessment. Patients that die prior to having their functional assessments completed cannot be included in analyses. Functional assessments were therefore not included in this observational study.

Additional research is required to compare and contrast the performance of the specific bedside measures of body composition evaluated in this study to other measures of body composition such as abdominal CT scans or ultrasound determination of muscle layer thickness.[89;95]

The particular reasons why any data were missing were not collected. Missing measurements may have been due to absence of trained research coordinators at the time of patient enrolment (Ex. weekend, holidays etcetera), or because of some patient-specific reason. This information should be collected in future studies.

12.8 Conclusions

This analytic observational study collected data on 1,363 critically ill patients admitted to the ICUs of 31 hospitals throughout Australia and New Zealand. Standard analytic techniques were used to adjust for severity of illness and other traditional risk factors for mortality to determine whether nutrition status, assessed using key measures of body composition, can add additional information to a widely used method of outcome prediction from critical illness.

The results of this analytic observational study demonstrate that nutrition status, assessed using key measures of body composition, does contribute statistically significant information to the most commonly used method of outcome prediction from critical illness. With each eligible measure of body composition, improved nutrition status was associated with improved outcome. Furthermore, this project demonstrated that focused measures of lean body mass or fat mass contributed more information than BMI and identified SGA Fat Loss to be the 'best' independent predictor of outcome.

Given the key measures of body composition evaluated in this project were easy to collect and could be completed in more than 95% of patients enrolled, the author recommends

their collection and evaluation in quality assurance projects, observational studies and randomised controlled trials that need to adjust for potential differences in risk of mortality. An improved understanding of the relationship between treatment, care processes and the patient's current nutrition status could lead to important improvements in the efficiency of care provided to critically ill patients and may also lead to improved patient outcomes.

Given the ease of collection, completeness and predictive performance, we recommended the collection of SGA Fat Loss and SGA Muscle Wasting over the other measures evaluated in this project.

12.9 Further research

This analytic observational study demonstrated the existence of significant independent *associations* between a patient's nutrition status and outcome from critical illness. Future research should focus on determining whether this relationship is *causal*. For example, can improving nutrition status *before* admission to the ICU result in improved patient outcomes from critical illness? Likewise, there is a need to determine whether enhanced nutrition support provided to patients with sub-optimal nutrition status can improve outcome from critical illness. Furthermore, collection of reliable measures of nutrition status by ANZICS CORE could lead to improved insights into quality assurance initiatives.

SGA Fat Loss was found to be the single 'best' measure of body composition when modelled with all other measures of body composition in this analytic observational study. We recommend confirmation of this finding by repeating the evaluation of SGA Fat Loss and SGA Muscle Wasting in additional studies enrolling different populations of critically ill patients. These studies should compare the performance of SGA Fat Loss and SGA Muscle Wasting to other emerging measures of body composition such as abdominal CT scans or ultrasound determination of muscle layer thickness.

Finally, the results of this study identified BMI categorised according to the WHO criteria bordered on the verge of statistical significance. It is interesting to note that both the WHO and NIH BMI categories were designed to predict risk of adverse consequences in healthy populations. Future research should explore novel BMI categorisations that may capture risk of outcome better for ICU patients.

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14.0 APPENDIX

Appendix A: Author's final version of published Journal of Parenteral and Enteral Nutrition manuscript.

Appendix B: Anthropometry Procedures Manual.

Appendix C: Poster and talks related to the thesis.

Appendix D: Site investigators and hospitals participating in the Early Parenteral Nutrition Trial.

Appendix E: Ethics letter, Sydney University.

Appendix F: Inclusion and exclusion criteria, Early Parenteral Nutrition Trial.

Appendix G: Score sheet, APACHE acute physiology variables, Early Parenteral Nutrition Trial.

Appendix H: APACHE III ICU admission diagnosis categories, Early Parenteral Nutrition Trial.

Appendix I: Shapiro Wilk test for normality for continuous variables.

Author's final version of: Simpson F and Doig GS for the Early PN Trial Investigators Group. Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: An analytic observational study. *Journal of Parenteral and Enteral Nutrition* 2015; 39(3):313-321. *Complete reference*: Doi: dx.doi.org/10.1177/0148607113515526

APPENDIX A

Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: An analytic observational study.

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Short title:

Physical assessment and anthropometric measures. Their association with mortality in the ICU.

Non-standard abbreviations:

LR Likelihood ratio, Chi-square χ^2, Cl confidence interval.

Keywords

Intensive care unit, Critical care, Physical assessment, Anthropometric measurements, Clinical research, Baseline confounding

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Abstract

Background

Accurate assessment of nutritional status is essential in identifying subpopulations of critically ill patients that are malnourished and at higher mortality risk. The aim of this analytic observational study was to assess the performance of physical assessment and anthropometric measures commonly used in clinical research.

Methods

A prospective study was undertaken in 31 intensive care units (ICU) with a focus on patients with short-term contraindications to enteral nutrition. Within 24 h of admission to the ICU, the following measures were collected: The Subjective Global Assessment (SGA) components measuring subcutaneous fat loss and muscle wasting; height; weight; mid upper arm circumference and; triceps skinfold thickness (TSF). Mid arm muscle circumference (MAMC) and body mass index (BMI) were calculated. BMI was assessed as both a continuous variable, and categorized according to the World Health Organization (WHO) categories. The primary outcome was hospital discharge mortality.

Results

1,363 patients were enrolled. BMI, analyzed according to WHO categories (P=0.09), and TSF (P=0.32) failed to demonstrate statistically significant predictive ability. TSF failed to demonstrate statistically significant clinical utility (area under the Receiver Operating Characteristic curve (aROC) 0.52, 95% CI 0.48-0.56). All other individual measures demonstrated statistically significant predictive ability and statistically significant clinical utility.

Conclusions

Based on the results of our ICU cohort, we recommend caution when using BMI categorized according to WHO definitions. We cannot recommend collection of TSF. More research is required to understand reliability, performance and use before our results are able to be generalized to other ICU populations.

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Clinical Relevancy Statement

Baseline assessment of nutritional status in critically ill ventilated patients can be difficult. We sought to assess the performance of individual bedside physical assessment and anthropometric measures that did not require communication with the patient.

Based on the results of our ICU cohort which was composed of patients with relative short-term contraindications to enteral nutrition, ICU researchers aiming to assess risk of hospital mortality should be aware that our findings show triceps skinfold thickness should not be collected in this population. We would also recommend that where body mass index is recorded, it should be analyzed as a continuous measure rather than categorized according to the World Health Organization categories.

Other individual physical assessment and anthropometric measures collected in this analytic observational project (physical assessment of subcutaneous fat loss and muscle wasting, mid upper arm circumference, and mid arm muscle circumference) demonstrated statistically significant predictive ability and clinical utility. However, as the strength of the clinical utility was questionable, further study is required to investigate their reliability, performance and use.

Author's final version of: Simpson F and Doig GS for the Early PN Trial Investigators Group. Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: An analytic observational study. *Journal of Parenteral and Enteral Nutrition* 2015; 39(3):313-321. *Complete reference*: Doi: dx.doi.org/10.1177/0148607113515526

Introduction

Clinical research evaluating nutritional interventions in critically ill populations is increasing in frequency, sample size and methodological rigor.[1-3] Meta-analyses of clinical trials evaluating nutritional interventions demonstrate mortality benefits in critically ill patient populations.[4] Observational studies suggest there are subpopulations of patients that may benefit more from nutritional interventions than others.[2] Recent randomized controlled trials report unanimously no effect on mortality[1,3,5,6] from various interventions. While the results of cluster randomized trials are conflicting.[7,8] The value of nutritional status in identifying subpopulations that may benefit the most remains to be established. However, determining which physical assessment and anthropometric measures are associated with worse outcomes such as mortality, independent of nutrition therapy, may prove useful for future ICU researchers designing clinical trials.

The assessment of nutritional status within clinical research conducted in critically ill patient populations is usually undertaken at baseline enrolment into the project.[1,3] Body mass index (BMI) is the most commonly used construct to show groups are well balanced with regards to nutritional status.[9] Due to sedation and loss of consciousness, ventilated ICU patients are unable to report their own current weight or provide recent dietary histories early in their ICU admissions, making extensive and complete nutritional assessments difficult.[10]

Besides BMI, other measures of nutritional status that do not require communication with the patient can be used in studies conducted in the intensive care unit (ICU).[11] For example, mid arm circumference[12,13] and the Subjective Global Assessment (SGA) physical assessment measures of muscle wasting and subcutaneous fat loss[11,14] are both recommended by highly respected authorities.[11,12] The aim of this analytic observational study was to assess the predictive ability and clinically utility of *individual* baseline physical assessment and

anthropometric measures in the context of clinical research conducted in critically ill patient populations, where mortality is the primary outcome of interest. Additionally we sought to identify the 'best' combination of measures for use in research conducted in critically ill patients.

Materials and Methods

We assessed the predictive ability and clinical utility of commonly used bedside physical assessment and anthropometric measures. For the purposes of our manuscript, predictive ability was defined as a statistically significant relationship ($p<0.05$) with the outcome of interest, hospital mortality. Whilst a statistically significant relationship is the most basic and necessary condition required of any risk prediction marker,[15] it does not infer clinical utility.

Clinical utility, which can be defined as the ability to discriminate between patients who will eventually develop the event of interest from those who will not, was assessed using the area under the receiver operating characteristic curve (aROC).[15] The statistical concept of clinical utility *does not* however infer clinical usefulness at the individual patient level rather this concept describes performance at the population level.

The following physical assessment and anthropometric measures were included in the analytic observational study: physical evidence of subcutaneous fat loss as defined by the SGA tool, physical evidence of muscle wasting as defined by the SGA tool,[11,16] BMI,[12,17] mid upper arm circumference,[12] and, so to be able to calculate mid arm muscle circumference,[18] we also assessed triceps skinfold thickness.[19]

Data for this analytic observational study was collected in conjunction with a multicentre randomised controlled trial conducted in Australia and New Zealand (Australian and New Zealand Clinical Trials Registry, Number: ACTRN012605000704695).[5,20] In brief, eligible adult participants were enrolled within 24 hours of ICU admission if they were expected to remain in the ICU at least two additional calendar days and were not expected to be fed (enterally, parenterally or orally) for at least one calendar day after enrolment. As the study intervention in the main trial had no effect on hospital mortality, study intervention and

standard care patients were analyzed as one group in this analytic study. The analysis is therefore presented independent of nutrition therapy.

Ethics approval was obtained from each participating site's Human Research Ethics Committee, and from the University of Sydney, Sydney, Australia.

Measurement and Calculation of Measures of Nutritional Status

Full details on the procedures used to collect the baseline physical assessment and anthropometric measures have been published previously.[21] The following represents a summary of procedures used.

Patient height was calculated using demispan,[22] defined as the distance between the midpoint of the sternal notch and the middle and ring finger web root of the patients hand.[12] A non-stretch metal tape measure (Lufkin, Coopertools, Apex, NC, USA) was used, and the patient's arm was supported throughout the measurement by the attending nurse. Where demispan was not able to be measured, height was obtained from other measurement methods or estimated by trained research assessors.

Weight was obtained from medical note documentation or estimated by trained research assessors. BMI was calculated according to the formula: weight in kilograms/height in m^2.[23]

Mid upper arm circumference was measured on a fully relaxed upper arm, at the midpoint between the acromion process and the radial head using a non-stretch metal tape measure (Lufkin, Coopertools, Apex, NC, USA). Measurement was recorded to the nearest 0.1 centimeter.

Triceps skinfold thickness (TSF) was measured using Slim Guide skinfold calipers (Mentone Educational, Moorabbin, Victoria, Australia). Calipers were applied to the posterior surface of a fully relaxed and lifted arm, at the midpoint between the acromion process of the scapula and the radial head, determined with a non-stretch metal tape measure. A fold of fat and skin was lifted away from the underlying muscle and held in place while the triceps skinfold was measured, with the caliper placed on the skin just below the fingers lifting up the fatfold. Measurement was recorded to the nearest millimeter. The international standards for anthropometric assessment were used to guide the measurement of mid upper arm circumference and TSF, adapted for use in critically ill bed-bound patients as per Ravasco.[19] Mid arm muscle circumference (MAMC) was calculated using the formula from Heymsfield.[18]

A preference was made to use the right side of the body for all anthropometric measurements as per the International Standards for Anthropometric Assessment. If this was inappropriate (e.g. Injury to the right arm), the left side of the body was used for measurements.

Trained research assessors graded each patient's physical evidence of subcutaneous fat loss and physical evidence of muscle wasting using one of the four SGA categories (normal, mild, moderate or severe) as per Detsky and Baker.[16] Research assessors graded loss of subcutaneous fat loss at the triceps skinfold area and under the fat pads of the eye. Muscle wasting was graded at the clavicle and deltoids area.

Training of Assessors to collect baseline measures of nutritional status

Two hour, small group interactive workshops were held at each of eight two-day study start-up meetings to train research assessors on how to correctly measure and document the measures of nutritional status. Two formally trained anthropometrists described the

anatomical landmarks used in each measurement, and then demonstrated the correct measurement techniques using two different supine volunteer adult 'models'. Research assessors then practiced taking TSF, mid upper arm circumference and demispan measurements on the models, and then on at least two other research participants, with supervision and assistance from the trained anthropometrists. Both male and female adult examples were used.

A standardized subjective global assessment video (Baxter Healthcare Renal Division, Illinois, United States of America)[24] was played and discussed to teach research assessors how to identify and categorize clinical signs of muscle wasting and subcutaneous fat loss as per the SGA.[16] Participants then practiced on live models and photographic examples contained in the hard copy study manual,[21] with support and supervision from trained anthropometrists.

Reinforcement of learning was conducted during study start-up visits, study data monitoring visits and education visits. Over 80 on-site visits were conducted by the trained anthropometrist (FS) throughout the project.

A hard copy photographic study manual supported the small group study start up sessions.[21] Additional copies of the study manual were available on the password protected study website for trained research assessors throughout the conduct of the project.

Outcome ascertainment

Mortality, the primary outcome of this analytic observational study, was determined at hospital discharge from hospital records.

Statistics

Predictive ability and clinical utility

Predictive ability was assessed by logistic regression, conducted to assess the univariate relationship between all potential risk predictors and the primary outcome, mortality at hospital discharge. Predictive ability was agreed to have been met at the (two sided) $p<0.05$ level.

An aROC of 0.5 is considered to represent performance that is no better than random chance. Therefore, as a minimum standard, the lower limit of the 95% confidence interval (CI) around the aROC needed to be greater than 0.5 to declare any *potential* for clinical utility.[25] Where a physical assessment or anthropometric measure demonstrated statistically significant clinical utility, the following guide by Hosmer and Lemeshow was used to assess the strength of performance: between 0.7 to 0.8, acceptable; 0.8 to 0.9, excellent; and greater than 0.9, outstanding.[25]

Continuous and Categorical Variables

BMI was analyzed both as a continuous variable and as a categorized variable. BMI was categorized using the recommended WHO categories.[17]

Using logistic regression, odds ratios, 95% Cl around the odds ratio, and likelihood ratio (LR) p-values were calculated for all continuous variables (TSF, mid upper arm circumference, MAMC and BMI analyzed as a continuous variable).

Dummy variables were used to analyze all categorized variables (SGA physical evidence of muscle wasting, SGA physical evidence of subcutaneous fat loss, and BMI analyzed a categorical variable).[26] No obvious subcutaneous fat loss, no obvious muscle wasting,[16] and BMI 18.50 to 24.99 kg/m^2 [17] were used as the referent categories during analysis.

Likelihood ratio (LR) chi-squared (χ^2) values were calculated for all categorized variables, and all p-values were calculated from LR tests.[27] Statistical significance was agreed to have been met at the (two sided) $p<0.05$ level.

Multivariate Logistic Regression

All physical assessment and anthropometric measures with a likelihood ratio p-value of <0.25 in univariate logistic regression were considered for inclusion in a *maximum* multivariate model to identify independent predictors of outcome.[27]

The *maximum* multivariate model was assessed for multicollinearity using Eigenanalysis. A condition index of >30 was accepted to indicate excessive multicollinearity.[28] If excessive multicollinearity was detected, highly correlated variables were removed from the *maximum* multivariate model one variable at a time until a *stable* multivariate model was identified, as indicated by a condition index of <30.

Stepwise backwards elimination was performed on the *stable* multivariate model, with a p-value to remain in the model set at $p < 0.10$.[29]

Results

The data was collected in 31 intensive care units from 31 unique hospitals. 1,363 patients were enrolled from October 2006 to June 2011. The majority of patients were male (60.2%), with an average age of 68.5 years and an APACHE II score of 21.1. Surgical patients accounted for 65.6% of participants, whilst the remaining 34.4% were medical admissions. Complete APACHE III admission diagnoses and patient demographics are presented in Table 1.

The average patient required 9.0 days (SD 10.0) in the study ICU and 25.1 days (SD 25.5) in the study hospital. Mortality at hospital discharge was 21.4% (291/1363).

There were no missing values for patient height, weight, BMI or hospital mortality. Height was measured using demispan in 90% (1228/1363) of patients. 5.4% (74/1363) of patients had their height measured using another direct technique, while 4.5% (61/1363) of patients had estimated heights recorded. A direct measured weight was available in 21.2% (289/1363) of patients, while weight was estimated in 78.8% (1074/1363) of patients.

Missing variables were evident for TSF (4.8%, 66/1363), mid upper arm circumference (4.5%, 62/1363), MAMC (5%, 68/1363), SGA physical evidence of subcutaneous fat loss (2.3%, 32/1363) and SGA physical evidence of muscle wasting (2.3%, 32/1363).

Predictive ability of baseline measures of nutritional status

When analyzed as a continuous variable, BMI was found to be significantly associated with hospital mortality during univariate analysis (odds ratio = 0.98, 95% Cl 0.96 to 0.99, P = 0.03), however, analyzed as a categorical variable, BMI was not significantly associated with

mortality at hospital discharge (LR χ^2_{4df} = 8.12, P = 0.09). TSF was also not significantly associated with hospital mortality (odds ratio = 1.01, 95% Cl 0.99 to 1.02, P = 0.32).

All other measures were significantly associated with hospital outcome, demonstrating acceptable predictive ability. See Tables 2 and 3 for complete details.

Clinical utility of baseline measures of nutritional status

TSF failed to demonstrate statistically significant clinical utility, as the lower boundary of its 95% confidence interval fell below the pre-defined threshold of 0.50 (aROC 0.52, 95% Cl 0.48 to 0.56). All other individual physical assessment and anthropometric measures demonstrated statistically significant clinical utility. See Tables 2 and 3 for complete details.

Multivariate analysis of baseline measures of nutritional status on hospital mortality

All variables, except for TSF, were considered for inclusion in the *maximum* multivariate model. Due to excessive multicollinearity, categorized BMI and mid upper arm circumference were eliminated, thus the *stable* multivariate model subjected to stepwise backwards elimination was composed of: BMI analyzed as a continuous variable, MAMC, SGA physical evidence of muscle wasting, and SGA physical evidence of subcutaneous fat loss.

Stepwise backwards elimination removed the following variables: BMI analyzed as a continuous variable (LR p-value = 0.80); and SGA physical evidence of muscle wasting (LR p-value for the dummy variable = 0.30).

The *final* multivariate model contained the following physical assessment and anthropometric variables, independently associated with outcome: MAMC (LR p-value = 0.05) and SGA physical evidence of subcutaneous fat loss (LR p-value = 0.004). The aROC for the final model was 0.60 (95% Cl 0.56 to 0.64). See table 4 for details.

Discussion

This analytic observational study was conducted using a prospectively collected database composed of 1,363 critically ill patients recruited from 31 ICUs throughout Australia and New Zealand. The results indicate that BMI analyzed as a continuous variable, mid upper arm circumference, MAMC, SGA physical evidence of subcutaneous fat loss and SGA physical evidence of muscle wasting demonstrated statistically significant predictive ability and clinical utility. TSF and BMI categorized according to WHO standards did not demonstrate acceptable performance.

Furthermore, using multivariate analysis we found the best *combination* of measures to be MAMC and SGA physical evidence of subcutaneous fat loss. Both demonstrated independent statistically significant predictive ability and clinical utility.

Our observational analytic study indicates SGA physical evidence of subcutaneous fat loss may be more strongly associated with mortality compared with SGA physical evidence of muscle wasting. However, as the 95% confidence intervals of the physical assessment measures overlap with one another, we cannot regard these results as significantly different. More research is needed to confirm these findings.

BMI is the most commonly used measure of nutritional status in critical care research.[1-3,9,19] The WHO defined BMI categories were originally proposed to capture the increased risk of being overweight and obese on preventable diseases such as coronary heart disease, in apparently healthy populations. In ICU populations, there is a need to identify patients at highest risk of mortality. We found WHO categorized BMI to be a poor risk predictor of mortality in this analytic observational study. Similar to our findings, Heyland and colleagues[30] reported that categorized BMI ($<20 kg/m^2$, and $\geq 20 kg/m^2$) had a non-significant relationship with 28-day mortality in their 597 critically ill patient observational study.

Furthermore, in two recently published randomized controlled trials that included pre-planned subgroups based on BMI categories, both the Early Parenteral Nutrition Trial and EPANIC found the effect of the nutritional intervention was the same regardless of BMI category.[1,5] The WHO acknowledges that the BMI categories "may not correspond to the...associated health risk in different individuals or populations".[17] This appears to be the case for our ICU cohort. In studies where BMI is the only measure of nutritional status available, we recommend analysis as a continuous variable in preference to WHO categorization. More research is clearly needed in this area before categorized BMI can be used reliably to guide practice in critically ill patient populations.[17]

Our findings of a significant relationship between baseline anthropometric measurements and mortality in critically ill patients are supported by others' studies.[19,31,32] For example, in 124 medical/surgical ICU patients, Sungurtekin and colleagues[31] reported a strong association between TSF, MAMC, and BMI, and ICU mortality. In a cohort of 116 ventilated patients aged 70 and older, Dardaine and colleagues[32] reported mid upper arm circumference to be a significant predictor of mortality six months after discharge from the ICU. Similarly, Ravasco and colleagues[19] reported mid upper arm circumference to be significantly associated with mortality in 44 medical ICU patients requiring respiratory support.

Likewise, the SGA has been shown to predict mortality in ICU patient populations in previous studies. In multivariate analysis, Fontes and colleagues[33] found the full SGA tool could be used to identify malnourished patients who were significantly more likely to die prior to hospital discharge compared with well nourished patients (OR 8.12, 95% Cl 2.94 to 22.42). It is interesting to note that none of these previous studies reported aROC as a measure of clinical utility. With regards to the strength of the clinical utility of the measures

assessed in our paper, although we found that BMI analyzed as a continuous variable, mid upper arm circumference, MAMC, SGA physical evidence of subcutaneous fat loss, and SGA physical evidence of muscle wasting demonstrated statistically significant clinical utility, they did not meet a minimum performance threshold (aROC >0.70) often used to define 'acceptable' performance.[25] This suggests that although these measures contribute towards our understanding of an individual patient's risk of mortality, other measures such as disease process, severity of illness, age, mechanism of injury etc. may also need to be considered to reach an acceptable level of clinical utility.

Nutritional screening is now considered mandatory in many hospitals throughout the world, and is often required to be completed within 24 hours of admission.[11] In response, much research has been undertaken in non-ICU populations to develop and validate screening tools to identify individuals who may be malnourished or at risk for malnutrition, to determine if detailed nutritional assessment is indicated.[34,35] There is, however, far less research focused on the investigation of simple and inexpensive baseline nutritional assessment measures for use in the critically ill ICU patient. Due to sedation and loss of consciousness, ventilated ICU patients are unable to give weight histories or dietary histories early in their ICU admissions, and may not have previous documentation of nutritional and weight histories to inform researchers.[10] Additionally, families are often unavailable to be contacted to provide accurate histories, resulting in missing data.

In a recent observational study Heyland and colleagues reported that histories of recent oral intake and weight loss were recorded in only 28.9% of mixed medical and surgical ICU patients.[30] Excessive missing data are extremely important and can invalidate clinical research results.[36,37] Because missing data can confound or mask any response to treatment, the tools evaluated in our study were selected because they include only a few key variables

to maximize data completeness and they are relatively time efficient and cost effective to collect.

Strengths and limitations

We collected a number of different baseline physical assessment and anthropometric measures in an attempt to gain a valid estimate of the association between each one and hospital mortality. As the project was undertaken in conjunction with a major clinical trial, there were sufficient resources available to ensure data accuracy and minimize missing variables through ongoing on-site training, monitoring and timely data queries.

There were few missing variables thus allowing a true assessment of performance. The enrollment of 1,363 critically ill patients from 31 intensive care units across Australia and New Zealand further increases generalisability to similar health care settings, however, since patients were recruited within 24 hours of ICU admission, it is possible these measures may perform differently in studies recruiting patients at a later time during their illness. Also, although patients were recruited across numerous ICUs during the conduct of a major clinical trial, it is possible the population is unique. It is important to consider that 90% of patients admitted to the participating ICU's were excluded from this clinical trial. In Australia and New Zealand, up to 80% of all eligible patients receive enteral nutrition within the first two days of ICU admission[8] thus it is likely that 50% of truly eligible patients were enrolled. A CONSORT flow diagram including all patients not enrolled at each ICU is unfortunately not available. The results found may not generalize to a broader selection of ICU patients, and thus need to be confirmed in additional studies.

Mortality was considered the most clinically relevant outcome in a critically ill patient population, however future studies should consider other outcome measures such as quality of life, infectious complications and physical function.

Height was measured using demispan, in our study. At the time of study planning, Hickson and colleagues[38] had shown that compared with other methods such as knee height, demispan was able to be measured in the largest proportion of acutely ill hospitalized patients over the age of 65 years (75.6%), and was highly correlated with measured (standing) height. More recently however, Luft and colleagues have shown use of a 'Luft ruler' for measurement of patient height in-bed to be more accurate than other methods, including demispan.[39] Consideration should be made to use the Luft ruler in future studies of bedbound patients.

Weight was directly measured, obtained from recent documented measurements, or estimated by trained research assessors. The inaccuracies of estimated weights in ICU populations are well documented.[40] Patient self-reports have been shown to be more accurate than estimated weights, but as the majority of study patients were ventilated at study baseline (82.2%), this was not feasible. Whilst directly measured weights would have been preferable in this study, site selection surveys conducted by the authors prior to study commencement indicated only 6% (2/31) of ICUs routinely used some form of bed scales to weigh their patients.

Ravasco and colleagues have shown positive associations between edema and BMI, and edema and TSF.[19] Although the effect of edema on our baseline measurements is a potential confounder, we did find significant independent associations between mid upper arm circumference, MAMC, BMI (analyzed as a continuous variable), SGA physical evidence of subcutaneous fat loss and SGA physical evidence of muscle wasting, and hospital mortality. It is possible the presence of edema interfered with the assessment of the performance of TSF in our study.

Recommendations

Based on the results of our analytic observational study, we recommend caution when using BMI categorized according to WHO definitions. Its poor predictive performance suggests it may not be a reliable tool for use in critically ill patient populations. More research is needed to identify categorization thresholds suitable to critically ill patient populations.

Other baseline physical assessment and anthropometric measures included in this analytic observational study demonstrated statistically significant predictive ability and clinical utility, however, the *strength* of the clinical utility of each single measure was questionable.[25] We recommend more research into understanding their reliability, performance and use in different populations.

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The NH&MRC played no role in the design conduct or analysis of this analytic observational study.

Conflict of interest statement

The authors report no conflicts of interest for this analytic observational study.

Statement of Authorship

FS conceived and designed the analytic observational study, analyzed the data and drafted the manuscript. GSD provided essential advice during study design, assisted with analysis and interpretation of the data and helped draft the manuscript. Final approval of the submitted version was given by GSD and FS.

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Tables

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Table 1: Patient characteristics.

Baseline characteristics	1363 patients
Age in years, mean (± SD)	68.5 (± 14.7)
Gender, n females (%)	543 (39.8)
BMI, kg/m^2, mean (± SD)	28.2 (± 6.9)
BMI < 18.5, n (%)	46 (3.4)
BMI 18.5 - 24.99, n (%)	400 (29.3)
BMI 25.0 - 29.99, n (%)	503 (36.9)
BMI 30.0 - 39.99, n (%)	337 (24.7)
BMI ≥40, n (%)	77 (5.7)
Triceps skinfold thickness, mm, mean (± SD)	15.5 (± 9.0)
Mid upper arm circumference, cm, mean (± SD)	31.9 (± 5.4)
Mid-arm muscle circumference, cm, mean (± SD)	26.5 (± 5.0)
SGA muscle wasting, n (%)	
No obvious loss	980 (73.6)
Mild loss	229 (17.2)
Moderate loss	96 (7.2)
Severe loss	26 (2.0)
SGA fat loss, n (%)	
No obvious loss	961 (72.1)
Mild loss	250 (18.9)
Moderate loss	95 (7.1)
Severe loss	25 (1.9)
APACHE II score, mean (± SD)	21.1 ± 7.6
Mechanically ventilated, n (%)	1121 (82.2)
Chronic health states, n (%)	
Insulin treated diabetes	107 (7.9)
Immuno-compromised	63 (4.6)
Respiratory disease	61 (4.5)
Cardiovascular disease	48 (3.5)
Hepatic cirrhosis	16 (1.2)
Chronic dialysis	15 (1.1)
Source of admission to ICU, n (%)	
Operating Room	894 (65.6)
Other hospital	161 (11.8)
Emergency Department	158 (11.6)
Hospital Ward	140 (10.3)
Transfer from ICU	10 (0.7)
ICU readmission	0 (0)
Surgical admission n (%)	
Emergency Surgery	625 (69.9)
Elective Surgery	269 (30.1)
APACHE III admission diagnosis, n (%)	

Gastrointestinal	821 (60.2)
Cardiovascular / vascular	271 (19.9)
Sepsis	97 (7.1)
Respiratory	78 (5.7)
Trauma	40 (2.9)
Neurological	17 (1.3)
Renal	9 (0.7)
Metabolic	7 (0.5)
Hematological	2 (0.2)
Gynecological	2 (0.2)
Orthopedic surgery	1 (0.1)
Other	18 (1.3)

SD: Standard Deviation; ICU: Intensive Care Unit; BMI: Body Mass Index; APACHE: Acute Physiology and Chronic Health Evaluation, APACHE II scores range from 0 to 71.

Table 2: Univariate analysis of categorized variables on hospital mortality.

Category	**Number of patients**	**Odds Ratio**	**95% CI around the odds ratio**	**P-value[a]**	**aROC (95% Cl)**
BMI Category (n=1363):				0.09	0.55 (0.51-0.58)
<18.50 kg/m^2	46	1.69	0.88 to 3.23		
18.50 to 24.99 kg/m^2 [b]	400	-	-		
25.0 to 29.99 kg/m^2	503	0.80	0.58 to 1.10		
30.0 to 39.99 kg/m^2	337	0.74	0.52 to 1.06		
≥ 40.0 kg/m^2	77	0.70	0.38 to 1.31		
SGA muscle wasting category (n=1331):				0.001	0.56 (0.53-0.59)
No obvious loss [c]	980	-	-		
Mild muscle wasting	229	1.89	1.36 to 2.62		
Moderate muscle wasting	96	1.40	0.86 to 2.32		
Severe muscle wasting	26	1.99	0.85 to 4.65		
SGA subcutaneous fat loss category (n=1331):				<0.001	0.57 (0.54- 0.60)
No obvious loss [d]	961	-	-		
Mild subcutaneous fat loss	250	1.84	1.34 to 2.54		
Moderate subcutaneous fat loss	95	1.64	1.00 to 2.64		
Severe subcutaneous fat loss	25	2.56	1.11 to 5.89		

[a]P-values were obtained from likelihood ratio tests for the entire dummy variable; aROC: Area under the receiver operating characteristic curve; Cl: Confidence Interval; BMI: Body Mass Index; [b]BMI 18.50 to 24.99kg/m^2 was the referent category; SGA: Subjective Global Assessment; [c]No obvious loss was the referent category; [d] No obvious loss was the referent category.

Table 3: Univariate analysis of continuous variables on hospital mortality.

Variable Name	N	Odds Ratio	95% CI around the odds ratio	P-value[a]	aROC[b] (95% Cl)
Body Mass Index	1363	0.98	0.96 to 0.99	0.03	0.54 (0.51-0.58)
Triceps skinfold thickness	1297	1.01	0.99 to 1.02	0.32	0.52 (0.48-0.56)
Mid upper arm circumference	1301	0.97	0.94 to 0.99	0.01	0.55 (0.51-0.59)
Mid arm muscle circumference	1295	0.95	0.93 to 0.98	<0.001	0.56 (0.52-0.60)

[a]P-value obtained from likelihood ratio test; [b]aROC: Area under the receiver operating characteristic curve; Cl: Confidence Interval.

Table 4: Final multivariate model: Physical assessment and anthropometric measures independently associated with hospital mortality.

Variable	Odds Ratio	95% CI around the odds ratio	Multivariate P-value[a]
SGA subcutaneous fat loss category			0.004
No obvious loss [b]	-	-	
Mild subcutaneous fat loss	1.83	1.31 to 2.55	
Moderate subcutaneous fat loss	1.54	0.92 to 2.57	
Severe subcutaneous fat loss	1.84	0.74 to 4.55	
Mid arm muscle circumference	0.97	0.94 to 1.00	0.05

[a]P-value obtained from likelihood ratio test from final multivariate model; SGA: Subjective Global Assessment; [b]No obvious loss was the referent category; CI: Confidence Interval.

Author's final version of: Simpson F and Doig GS for the Early PN Trial Investigators Group. Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: An analytic observational study. *Journal of Parenteral and Enteral Nutrition* 2015; 39(3):313-321. *Complete reference*: Doi: dx.doi.org/10.1177/0148607113515526

THE UNIVERSITY OF SYDNEY

Online-Only Supplement:

Physical assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: An analytic observational study.

Fiona Simpson and Gordon S. Doig

for the Early PN Trial Investigators Group.

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2nd October 2013

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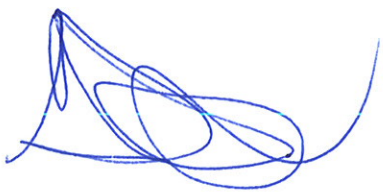
Statement of Authorship, Journal of Parenteral and Enteral Nutrition article.

Physical Assessment and anthropometric measures for use in clinical research conducted in critically ill patient populations: an analytic observational study. JPEN 2015; 39(3):313-321.

Fiona Simpson conceived and designed the analytic observational study, analysed the data and drafted the manuscript.

Gordon Doig provided essential advice during study design, assisted with analysis and interpretation of the data and helped draft the manuscript.

Final approval of the submitted version was given by Fiona and Gordon.

Gordon Doig  Date 22/5/15

Fiona Simpson  Date 22/5/15

Anthropometric Procedures Manual: Early parenteral nutrition vs. standard care in patients not expected to be fed within 24 h of ICU admission.

Fiona Simpson [1] and Gordon S. Doig [2]

The Early PN Trial

NHMRC Project Grant Number 402643

Australian and New Zealand Clinical Trials Registry Number 012605000704695

Endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group.

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Photographs of models used in this manual were obtained and used with permission.
References for other pictorial source material are provided. See reference list for more details.

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Title: **Anthropometric Procedures Manual: Early parenteral nutrition vs. standard care in patients not expected to be fed within 24 h of ICU admission.**
Edition: Version 1
Author/Contributor: Simpson, Fiona; Doig, Gordon S;
Date of Publication: 13 July 2011
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Size: 297x210
No. of Pages: 26
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Use of this Manual

This reference manual was designed for use in the Early PN Trial. It was not intended to be used for any other purposes. This reference manual has been released on the web after trial close-out as a resource text.

General Comments

Timing of measurements and position of patient

- Body composition measurements must be taken as baseline measurements *on the day of randomisation and then every MONDAY and THURSDAY* for the length of ICU stay.

- If the measurements are missed for some reason please ensure they are taken *the very next ICU working day* and continue the Monday/Thursday pattern thereafter.

- Use the *right hand side* of the body to take all body composition measurements.

- If any one of the body composition measurements *have* to be taken on the left side of a patient's body (Ex. the patient has no right arm or they have severe strictures in their right arm preventing accurate measurements), all measures *for that patient* should be taken using the left side of the body.

- All patients will be lying on their backs in bed when measurements are taken. For consistency, please ensure measurements occur whilst the patient is in that position.

- This manual has been deliberately written in layman's terms and designed for use in unconscious/semiconscious ICU patients.

Equipment

You have been provided with 1) two sets of slim guide calipers, 2) one ball of non-stretch string, 3) one tape measure and 4) one makeup pencil for use in this trial. When using the non-stretch string on a patient please cut an appropriate length and discard after use.

Anatomical Landmarks

Skeletal points ("landmarks") are used to identify the exact location of the site to be measured. All landmarks are identifiable with the thumb or forefinger. The site should be marked *directly over the landmark* using a fine tipped felt pen/makeup pencil.

A makeup pencil is useful for landmarking as it is not influenced by body oils and is non-permanent.

Version 1, 11 September 2006.
DOI: http://dx.doi.org/10.4451/EarlyPN_APM

CRF questions AD18, AD19, BC5 and BC6.

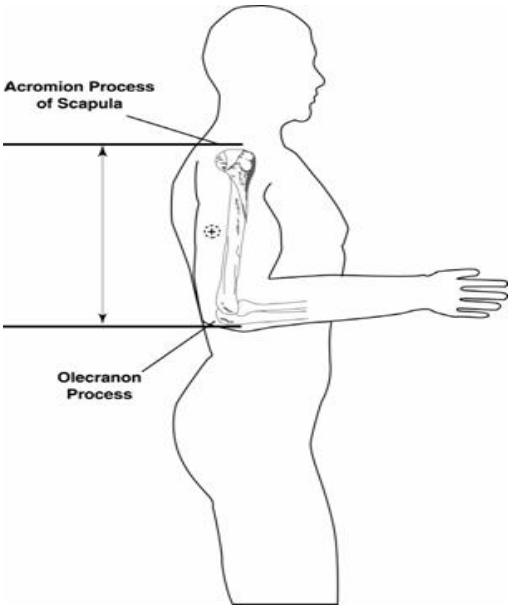
Preparation before measuring the Mid-Upper Arm Circumference and Triceps Skinfold Thickness.

Acromiale Landmark

(The acromion process of the scapula or "bump" on the upper shoulder)
Finding the acromiale landmark is the first step in being able to measure the mid-upper arm circumference and triceps skinfold.

Patient: In bed, lying on their back, right arm as relaxed as possible and straight by their side.
Measurer: Stand on the right-hand side of the patient so you can clearly see the patient's shoulder area.
Equipment Required: Fine felt tipped pen or a makeup pencil.

Figure 1 Skeletal image showing the Acromion process, Olecranon Process and Mid-point of arm. Right side standing view. From Phenxtoolkit, www.phenxtoolkit.org



- Find the spine of the scapula. This is located at the top of the patients' back. Run your fingers horizontally along the spine of the scapula, towards the back of the shoulder, moving away from the middle of the body.
- Once you run out of bone (scapula), move your fingers forward along the bone known as the acromion of scapula (i.e. towards the front of the patients' shoulder).
- Find the bony protrusion (bump) on the acromion. *This should be roughly in the middle of the patients' arm when looking from the side of the body. See figure 2 and 3*
- Mark the very edge of the acromion process (bump), at the site which is furthest away from the patient's head, on the side of the right arm. Mark the landmark with a horizontal line.

❖ This is the acromiale landmark.

Figure 2 Acromiale Landmark, supine patient.

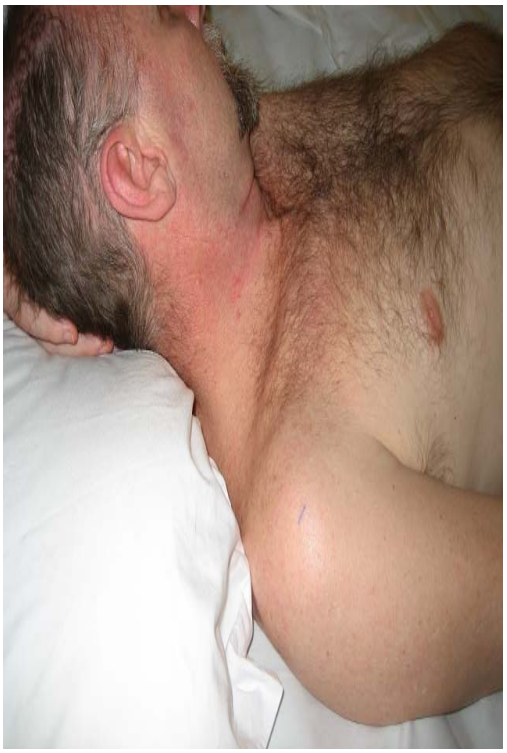
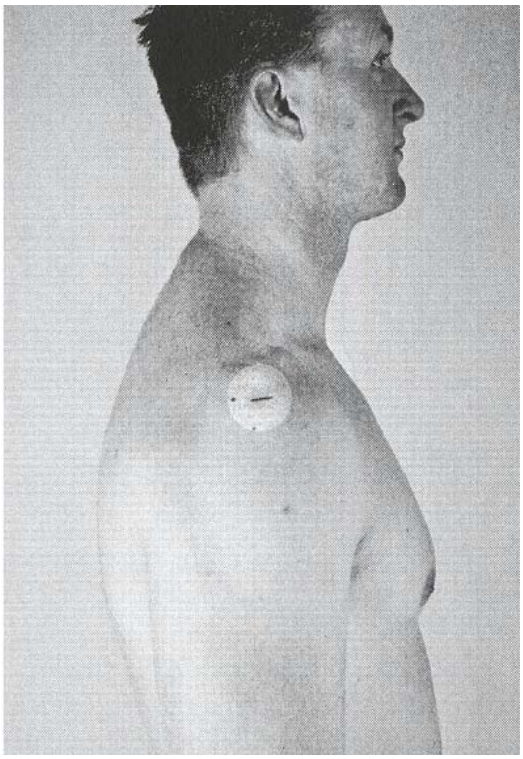


Figure 3 Acromiale Landmark, Standing View. ISAK 2001 page 24.



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Radiale Landmark

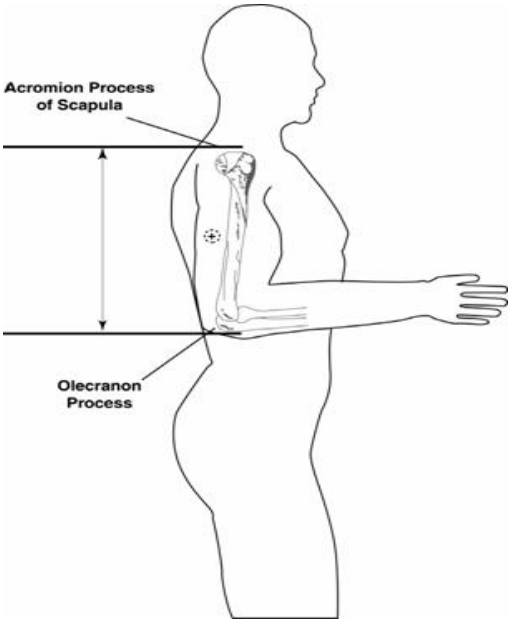
(Head of radius)

Finding the radiale landmark is the second step in being able to measure the mid-upper arm circumference and triceps skinfold.

Patient: In bed, lying on their backs, right arm relaxed, straight and slightly extended from the patient's side.
Measurer: Stand on the right hand side of the patient so to clearly see the patients elbow area.
Equipment Required: Fine felt tipped pen or a makeup pencil.

- Slightly raise the patient's right arm (approx. 30 degrees) and move it away from the patient's body.
- Find the bony tip of the elbow (olecranon process). See figure 4.
- Move your hand from the olecranon process to the "dimple" of the elbow. The "dimple" will be located slightly higher than the olecranon process, towards the patient's shoulder.
- Feel for the "space" between the humerus and the head (top) of the radius.
- Move your hand onto the head of the radius (of the two bones, the radius is the bone closer to the patients wrist). See figure 5.

Figure 4 Skeletal image showing the Acromion process, Olecranon Process and Mid-point of arm. Right side standing view. From Phenxtoolkit, www.phenxtoolkit.org.



NOTE: *To check if you have the correct landmark, keep your finger on the head of the radius and rotate the patient's wrist. You should be able to feel the radius rotating - if you can you have the correct landmark!*

- Mark the site on the head of the radius at the point furthest away from the middle of the patient's body.

❖ This is the radiale landmark.

DOI: http://dx.doi.org/10.4451/EarlyPN_APM

Figure 5 Radiale Landmark, Supine Patient.

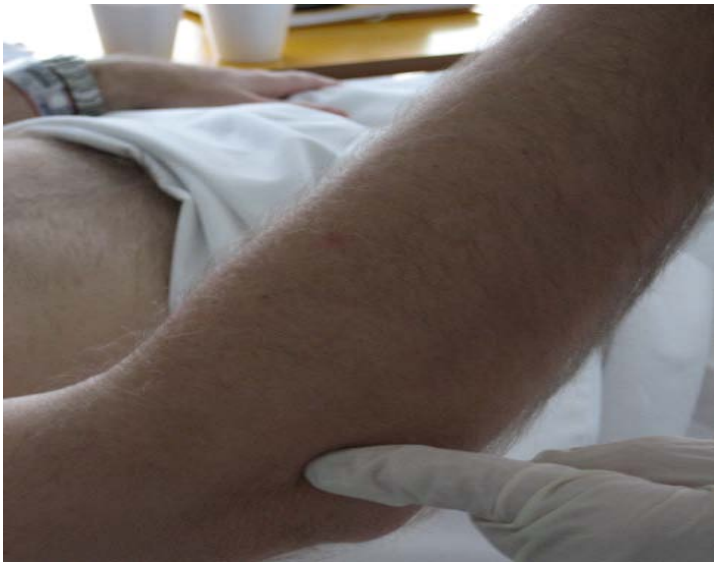


Figure 6 Supine Patient showing Radiale, Acromiale and Midpoint landmarks.

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Mid-acromiale-radiale Landmark

(The point exactly halfway between the Acromiale and Radiale landmarks).

Finding the Mid-acromiale-radiale landmark allows measurement of the Mid-upper arm circumference and triceps skinfold.

Patient: Lying on their back in bed. Right arm relaxed, straight and slightly extended from the patient's side.
Measurer: Stand on the right had side of the patient so to clearly see the patient's upper right arm.
Equipment Required: Fine felt tipped pen or a makeup pencil, non-stretch string or Lufkin metal tape measure.

- Using either non-stretch string or a metal tape measure, measure the linear distance between the Acromiale and Radiale landmarks.
- The tape/non-stretch string should follow the patients arm in a straight line, and not be twisted or at an angle. See figure 7.
- Divide the linear distance from the Acromiale and Radiale by two if using a tape measure. See figure 7.
- If using non-stretch string measure the distance between the Acromiale and Radiale landmarks, and then fold the string measurement in half. Put the halved string measure again on the Acromiale landmark and mark the skin where the string ends. See figure 8.
- Mark the mid-point on the patient with a horizontal mark.

❖ This is the Mid-Acromiale-Radiale landmark.

Figure 7 Measurement of Mid-acromiale-radiale landmark. Supine patient.

(Note: tape measure is at zero at Acromiale landmark)

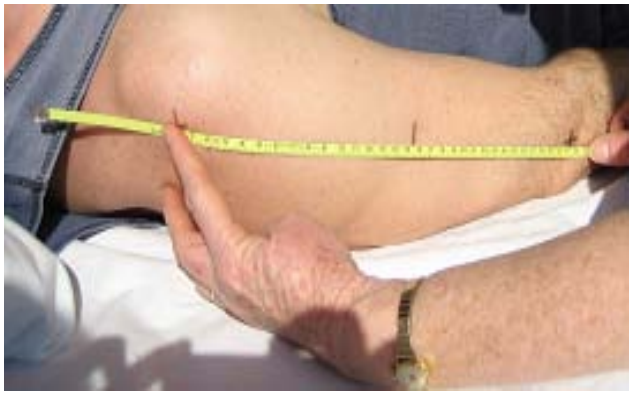
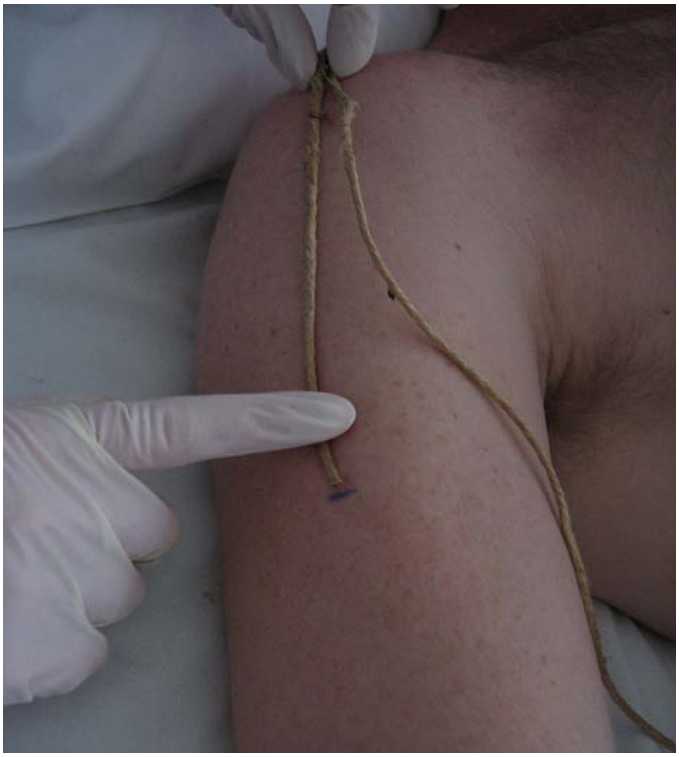


Figure 8 Measurement of Mid-acromiale-radiale landmark using string. Supine patient.



CRF questions AD18 and BC5. Mid-upper arm circumference

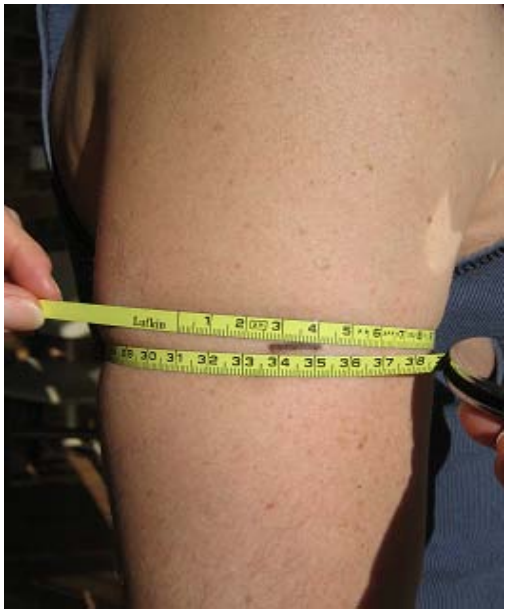
Mid Upper Arm Circumference Measurement (MUAC)

Patient: In bed, lying on back, right arm relaxed, straight and slightly extended from the patient's side
Measurer: Stand on the right had side of the patient so to clearly see the patient's upper right arm.
Equipment Required: Lufkin W606PM 2m flexible steel tape measure or non-stretch string and fine felt tipped pen or an eyeliner (makeup) pencil.

If using a tape measure to measure Mid Upper Arm Circumference:

- Hold the tape measure case in the right hand and the stub in the left.
- Ask the attending nurse to raise the patient's right arm slightly so you can pass the tape measure stub around the back of the arm.
- Put the patients arm back on the bed so it is "relaxed".
- Line up the tape measure with the Mid-Acromiale-Radiale landmark, so that the (horizontal) line is underneath but in the middle of the overlapped tape. See figure 9.
- Apply constant tension to the tape so to minimise gaps between the skin and tape, but avoiding skin compression
- Secure both pieces of tape with the right hand, allowing the left hand to manipulate the tape so that zero can be read. Read with eyes level to the tape.
- Record to the nearest 0.1cm on case report form.

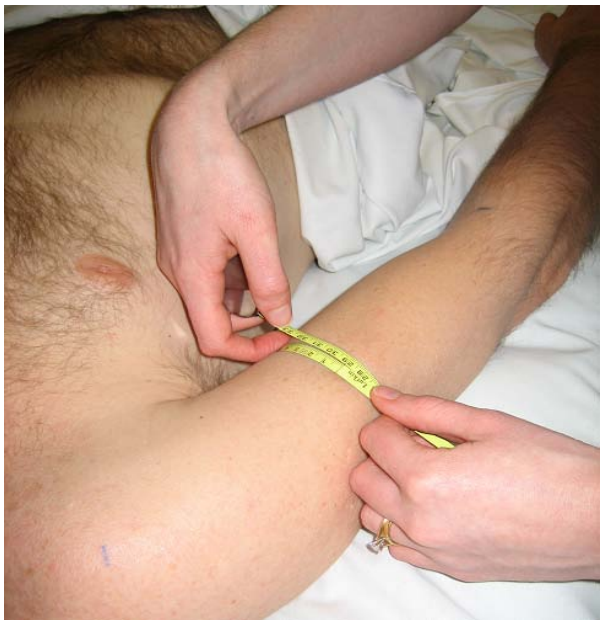
Figure 9 Lining up tape measure with Mid-acromiale-radiale landmark



DOI: http://dx.doi.org/10.4451/EarlyPN_APM

Figure 10 Measurement of Mid-upper-arm-circumference using tape measure. Supine patient

(Note: Arm relaxed and as straight as possible)



If using string to measure Mid Upper Arm Circumference:

- Cut a piece of non-stretch string more than large enough to go around the patient's arm. If you have already used string to measure the mid-acromiale-radiale landmark (mid-point of the arm) you could use the same piece.
- Ask the attending nurse to raise the patient's right arm slightly so you can pass the string around the back of the arm.
- Put the patients arm back on the bed so it is "relaxed".
- Line up the string with the Mid-Acromiale-Radiale landmark, so that the (horizontal) line is underneath but in the middle of the overlapped string (see figure 11).
- Apply constant tension to the string so to minimise gaps between the skin and string, but avoiding skin compression
- Secure both pieces of string with the right hand, allowing the left hand to manipulate the string. Find where the end of the string meets and mark that point.
- Measure the marked string against a tape measure and record on the case report form *to the nearest 0.1cm.*

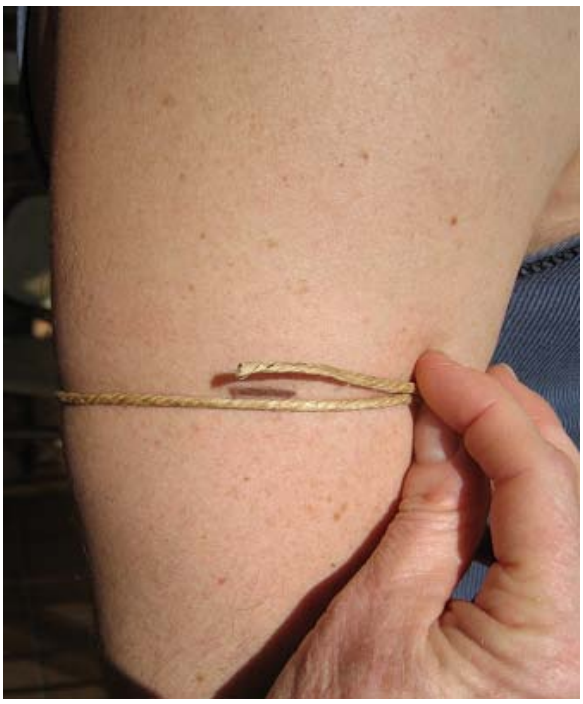
❖ This is the Mid Upper Arm Circumference Measurement.

NOTE: Whilst you still have the tape measure/string on the arm, mark the triceps skinfold site *(see triceps skinfold landmark).*

DOI: http://dx.doi.org/10.4451/EarlyPN_APM

Figure 11: Measuring Mid-upper arm circumference using string.

(Note: string lining up with Mid-acromiale-radiale landmark)



CRF questions AD19 and BC6.

Preparation before measuring the triceps skinfold thickness

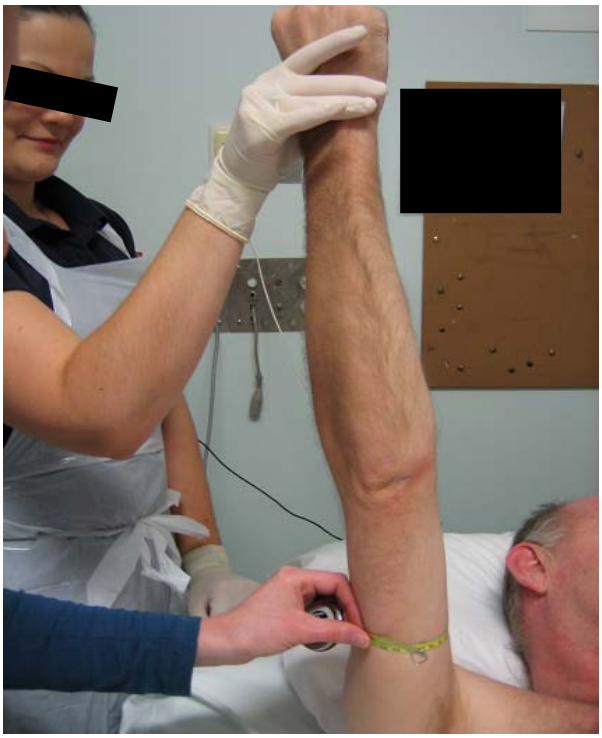
Triceps Skinfold Landmark

Finding the Triceps skinfold landmark allows measurement of the Triceps skinfold thickness.

Patient: In bed, lying on their back.
Attending nurse: Holding the right arm as straight up as possible (90 degrees to the floor, straight up in the air). Ensure that the attending nurse is taking all the weight of the arm (I suggest one hand holding the patients wrist and the other hand close to the patient's armpit to fully support the patients arm).
Measurer: The measurer will need to be able to clearly see the back of the arm. When the arm is held at 180 degrees the measurer should stand on the side of the arm which is closer to the patient's toes and the attending nurse closer to the patients head.
The measurer should still have the tape measure/string positioned at the Mid Upper Arm Circumference.
Equipment Required: Lufkin W606PM 2m flexible steel tape or non-stretch string. Fine felt tipped pen or a makeup pencil.

- After completing the measurement of the Mid-Upper Arm Circumference, keep the tape measure/string positioned at that landmark (Mid-acromiale-radiale landmark). Ask the attending nurse to hold up the patient's arm at 90 degrees to the floor. See figure 12.

Figure 12 Marking the triceps skinfold landmark. Supine patient. Attending nurse holding arm.



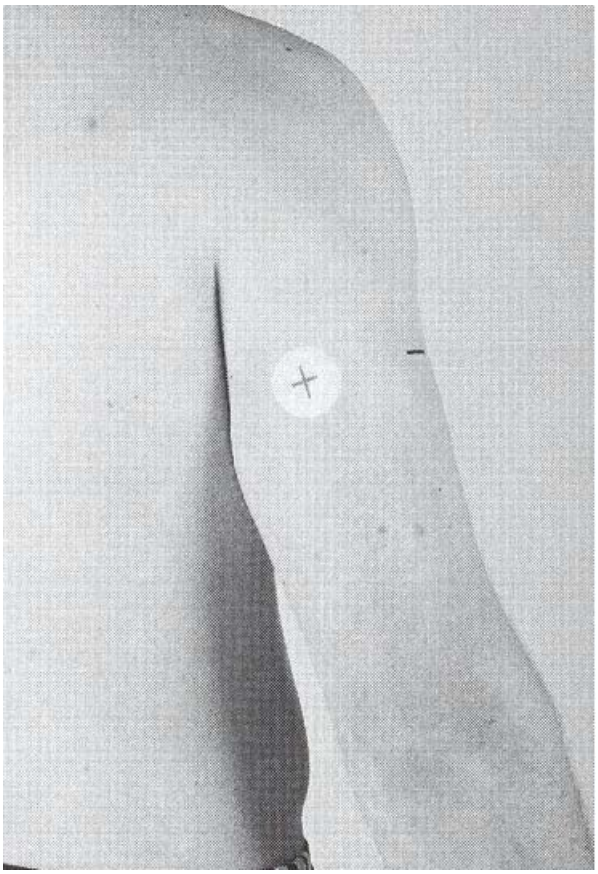
DOI: http://dx.doi.org/10.4451/EarlyPN_APM

- Using the tape measure/string as a template, make a horizontal mark in the middle of the *back* of the arm (triceps), between the two pieces of tape. The line should be at the same level as the Mid-acromiale-radiale landmark (midpoint of the front of the arm).

❖ This is the Triceps skinfold landmark site.

Figure 13 Marked triceps skinfold site. Standing patient. ISAK PAGE 27.

(Note: The Triceps skinfold landmark is at the same *level* as the Mid-acromiale-radiale landmark as shown in this photo)



NOTE: To save time, whilst the attending nurse is holding the arm up, remove the tape measure and take the triceps skinfold thickness measurement (see triceps skinfold thickness measurement section).

CRF questions AD19 and BC6. Triceps skinfold thickness

Triceps Skinfold Measurement

Patient: Lying on their back in bed.
Attending Nurse: Holding up the right arm straight up (90 degrees to the floor, straight up in the air). Ensure that the attending nurse is taking all the weight of the arm (I suggest one hand holding the patients wrist and the other hand close to the patient's armpit to fully support the patients arm).
Measurer: The measurer will need to be able to clearly see the back of the arm. When the arm is held at 90 degrees the measurer should stand on the side of the arm which is closer to the patient's toes and the attending nurse closer to the patients head.
Equipment Required: Slim Guide skinfold caliper.

- Hold calipers in your right hand, making sure the needle on the caliper is on zero.
- With your left hand, grasp and lift a fold of skin and underlying subcutaneous fat tissue at the marked Triceps skinfold site. The edge of the thumb and index finger should be in line with the marked site, palm facing away from you (see figure 14 and 15).
- The depth of the skinfold should allow the skin surface of the fold to be *parallel*.
- To ensure you don't include any underlying muscle tissue, roll the finger and thumb slightly before taking the triceps skinfold measurement. Remember subcutaneous fat has less tone and bulk than muscle tissue.
- The caliper should be held at 90 degrees to the surface of the skinfold site and applied 1cm below the thumb and finger at a depth equal to mid fingernail.
- The measurement is taken *2 seconds after* full pressure of the caliper is applied. *Continue to grip the skinfold throughout the measurement.* See figure 14 and 15.
- In the case of large skinfolds, the needle may still be moving when taking the measure. This is acceptable.
- Remove the caliper from the patients' arm. Don't forget to open the "contact faces" of the caliper otherwise you will pull the patients' skin!
- Record on the case report form to the nearest *millimeter*.

NOTE: **After taking the Triceps Skinfold Measurement, remove the calipers and look at whether there has been any loss of subcutaneous fat at the triceps skinfold site** (see "Subjective Global Assessment, Loss of Subcutaneous Fat" section for more details).

Version 1, 11 September 2006.
DOI: http://dx.doi.org/10.4451/EarlyPN_APM

Figure 14 Triceps Skinfold Measurement. Standing patient.

(Note: skinfold grasped at marked triceps skinfold landmark).

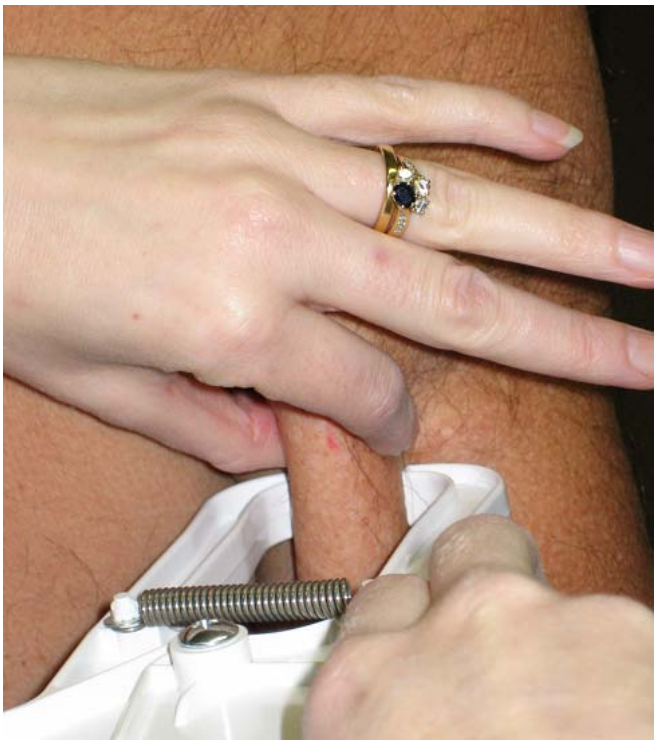
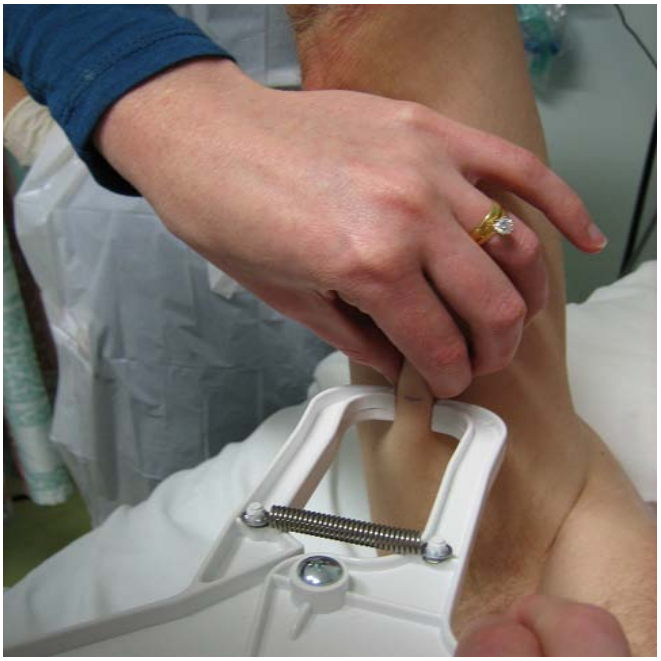


Figure 15 Triceps Skinfold Measurement, Supine Patient.

(Note: attending nurse fully supporting weight of arm throughout measurement).



Version 1, 11 September 2006.
DOI: http://dx.doi.org/10.4451/EarlyPN_APM

Height (Demi Armspan)

Height should be directly measured using Demi Armspan. This accurate measure of the patients' height is vital to determine the patients' body mass index. Height (Demi Armspan) needs to be measured only once during the hospital admission. The right arm is preferred but if it is not possible to use the right arm, use the left arm. Record the arm used on the case report form. If Demi Armspan measurement is *impossible* other acceptable measures of height are listed below, after the instructions for Demi Armspan.

CRF question AD17. Demi Armspan

Patient: Lying on their back in bed.
Attending nurse: Extending the patients' *right* arm until it is horizontal with the shoulder. Ensure the wrist is straight. The patients' arm may need to be supported.
Measurer: Standing on the right side of the patient.
Equipment Required: Lufkin W606PM 2m flexible steel tape or non-stretch string.

- Locate and mark the middle of the sternal notch (V at the base of the patient's neck). See figure 16.
- Place the metal tape measure between the middle and ring finger of the patients' right hand. The tape measure should be at zero at the base of the fingers (finger "web"). If using non-stretch string, the end of the string should be at the base of the finger "web". The tape/string should follow the patients arm in a straight line, and not be twisted or at an angle when measuring the distance.
- Extend the tape measure along the arm to the mid-point of the sternal notch.
- Record the measure to the nearest 0.5cm.
- Measures of the patients' height are taken *only once* during the trial.

NOTE: If neither the right or left arm can be used to measure Demi Armspan see details below for alternate measures of height.

Figure 16 Measurement of Demi Armspan. BAPEN 2003 page 14.

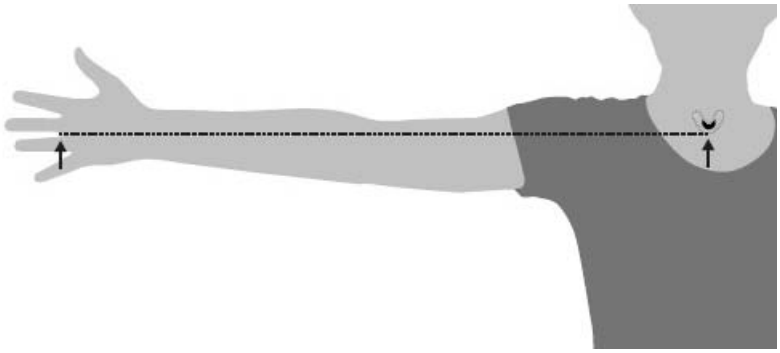
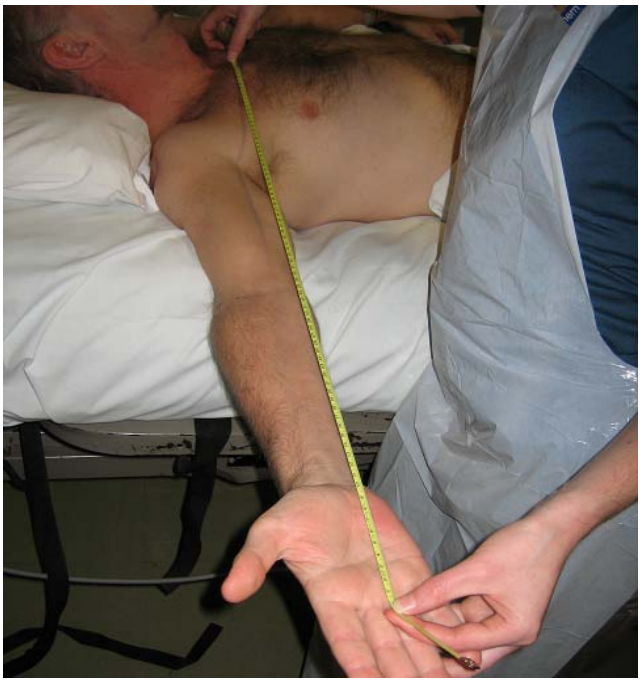


Figure 17 Measurement of Demi Armspan. Supine Patient.

(Note: Straight tape measure, following the patients arm. Wrist will need to be supported in an unconscious patient)



CRF question AD17a. Height

Total Height Measurement (only if Demi Armspan cannot be measured)

Demi Armspan should be used to measure height *if at all possible*. In the very small number of cases where Demi Armspan cannot be measured (e.g. when the patient has no arms) patient height can be measured directly (see below). Patient height is used to calculate body mass index (BMI).

Patient: Lying in bed on their back as flat and straight as possible.
Attending nurse: Standing at the patients' head.
Measurer: Standing at the lowest extremity of the patients' lower body. The measurer and the attending nurse should be standing at opposite extremes of the patient.
Equipment Required: Lufkin W606PM 2m flexible steel tape or non-stretch string. Clipboard or similar flat surface.

- Together with the attending nurse, use a clipboard or similar flat surface to each extend the perpendicular lines from the top of the head to lowest extremity of the patient. In many cases the lowest extremity will be the heel of the patients' foot.
- In cases such as where the patient has had an amputation please measure to the level of the lowest extremity

For example, a patient has had a double amputation with one leg amputated above the knee and the other leg amputated below the knee. Please measure to the lowest extremity. In this case this would be the leg amputated *below* the knee.

- Pull the tape measure/non flexible string out *in a straight line* until it is level with the lowest extremity of the patient.
- Please indicate on the case report form that the height was *measured* if using this technique.
- Measures of the patients' height are taken *only once* during the trial.
- Record to the nearest 0.5cm.

Estimating Height (Visual inspection)

If Demi Armspan and a full height measure cannot be undertaken please estimate the patient height.

- Visually inspect the patient in bed. It often helps if you know the length of your ICU's bed.
- Reports from family members may not be accurate so visual inspection is preferred. Check your visual inspection agrees with their report.
- Estimated heights should be as accurate as possible.
- Please indicate on the case report form that the height was *estimated* if using this technique.
- Estimates of the patients' height are taken *only once* during the trial.
- Please record to the nearest 0.5cm.

CRF questions AD16. Weight

We have asked for an estimate or direct measure of the patient's weight. This is vital to determine the patient's body mass index. Weight needs to be measured *only once* during the trial.

Weight Measure

Current body weight should be estimated from *direct observation or measured directly* (for example using bed scales or sling scales etc).

- If it is current ICU policy to weigh the patient, please continue with this policy and indicate on the case report form that weight was *measured.*
- Direct observation of weight is known to be accurate and is preferred to any historical weights or reports from family members.
- If an estimation of weight is made within a range of upper and lower limits, please record the upper limit of that range. Please also document on the case report form that the weight was *estimated*.
- Please record the patient's weight (in kilograms) to the nearest 0.1kg.

CRF questions AD20, AD21, BC 8 and BC9. Subjective Global Assessment of Nutritional Status: Physical Component.

CRF questions AD20 and BC7. Loss of Subcutaneous Fat stores.

The SGA is a validated and reliable instrument for detecting nutritional status *at a given point in time*. It is by very nature *subjective.* We are asking you to assess the patient at baseline *on the day of randomisation and on each Monday and Thursday thereafter* and decide *at that point in time* whether the patient shows evidence of subcutaneous fat loss. *Please do not try to remember all previous assessments when conducting a subsequent assessment*. These measures are part of the physical exam component of the SGA.

Physical Evidence of Loss of Subcutaneous Fat.

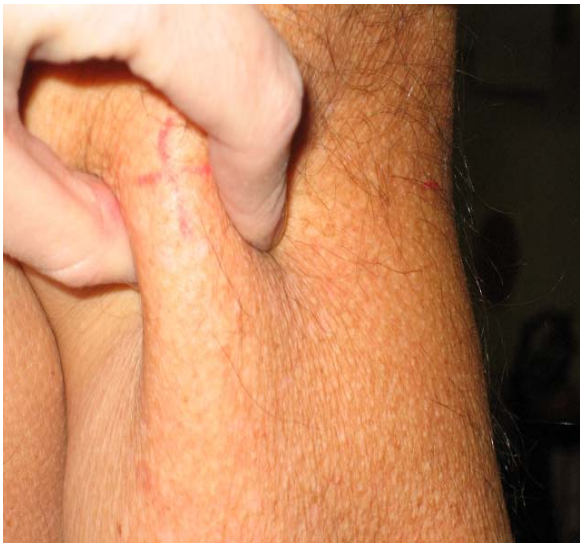
There are two areas to look at to assess whether there has been any loss of subcutaneous fat stores.

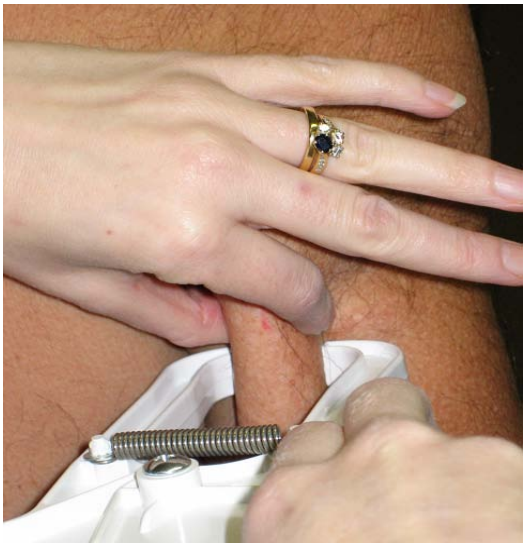
Fat Stored at the Triceps Skinfold Site

When grasping the skin at the triceps skinfold site, look to see the amount of subcutaneous fat stores. If your fingers *meet* when the triceps are grasped the loss of fat is *severe*; if the fingers *don't quite meet* the loss of stores would be regarded as *moderate*. If fingers don't touch there is ample subcutaneous fat tissue and the patient would be regarded as having *no obvious loss* of subcutaneous fat stores.

NOTE: Often determining the amount of subcutaneous fat present is easier when the skinfold is rolled between the fingers. This helps differentiate between fat and muscle. Subcutaneous fat stores lie directly under the skin. Muscle mass stores are deeper under the skin and have more tone and bulk than subcutaneous fat.

Figure 18 and Figure 19 No obvious Loss of Subcutaneous Fat Stores at Triceps Skinfold site.

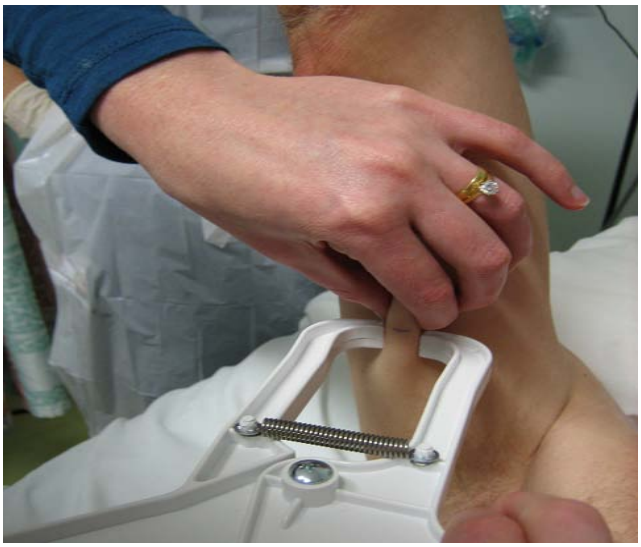




DOI: http://dx.doi.org/10.4451/EarlyPN_APM

Figure 20 Moderate Loss of Subcutaneous Fat Stores at Triceps Skinfold Site.

(Note: Fingers almost touching)



Loss of fat padding under the Eyes

- Look at the fat pads directly under the eyes. In normally nourished patients the fat pads appear as a slight bulge. In severely malnourished patients (severe loss of subcutaneous fat stores) *depressions or sometimes a darkened area* are seen under the eyes. Also look for *loose or hanging skin around the eyes and cheeks*.

Figure 21 Mild Loss of Subcutaneous Fat Stores

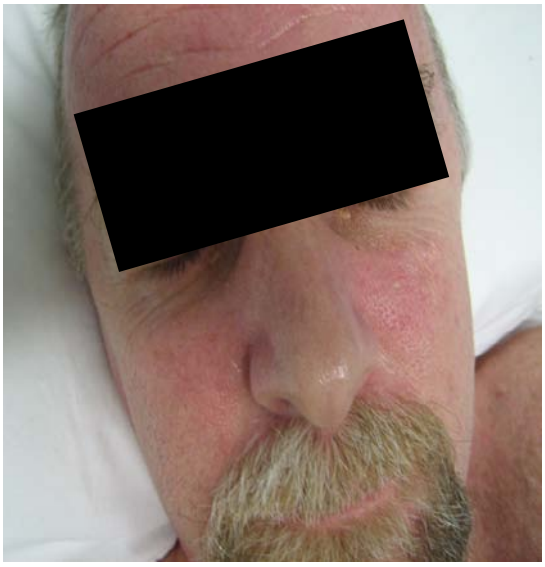
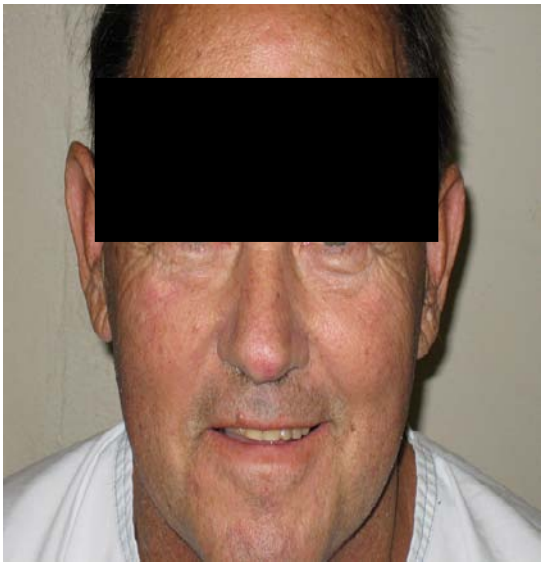


Figure 22 No Obvious Loss of Fat Stores



RANK THE PATIENT for physical evidence of loss of subcutaneous fat stores.
After examining the patients' subcutaneous fat stores (fat pads under the eyes, fat stores in the triceps area) please determine whether the patient shows any evidence of loss. If you are re-assessing the patient, *please do not try to remember previous assessments* and assess the patients' subcutaneous fat stores for only that calendar day.

Note: If the patient shows signs of subcutaneous fat loss in one area but not in the other, rank the patient in either the *mild or moderate category*, depending on the degree of subcutaneous fat loss in that ONE area

Please choose only ONE of the following categories to best represent *your overall* assessment of the patients' subcutaneous fat stores.

- **No obvious loss** (i.e. there is ample subcutaneous fat stores *in both areas),*
- **Mild loss** of subcutaneous fat stores (loss may vary between sites (see note above) OR loss is *slight in both areas*),
- **Moderate loss** of subcutaneous fat stores (loss may vary between sites (see note above) OR loss is moderate in *both areas),*
- **Severe loss** (the amount of subcutaneous fat store loss is severe *in each area).*

Please record your subjective assessment on the case report form.

CRF questions AD20, AD21, BC 8 and BC9. Subjective Global Assessment of Nutritional Status: Physical Component

CRF questions AD21 and BC8. Muscle Wasting

The SGA is a validated and reliable instrument for detecting nutritional status *at a given point in time*. It is by very nature *subjective.* We are asking you to assess the patient at baseline *on the day of randomisation and on each Monday and Thursday thereafter* and decide *at that point in time* whether the patient shows evidence of muscle wasting. *Please do not try to remember all previous assessments when conducting a subsequent assessment*. These measures are part of the physical exam component of the SGA.

Physical Evidence of Muscle Wasting

Muscles around the Clavicle

- Look along the line of the clavicle. *The smaller the muscle mass the more prominent the bone.* In the severely malnourished patient the bone can be quite prominent. Take note of the degree of muscle wasting in the clavicle area and inspect the shoulder area (see below).

NOTE: In well-nourished males the clavicle is usually not visible. In well-nourished females the clavicle *can* be visible so it is important to combine your findings with your assessment of the patients muscle mass around the shoulder area (see below).

Figure 23 Female. Normal (no muscle wasting).

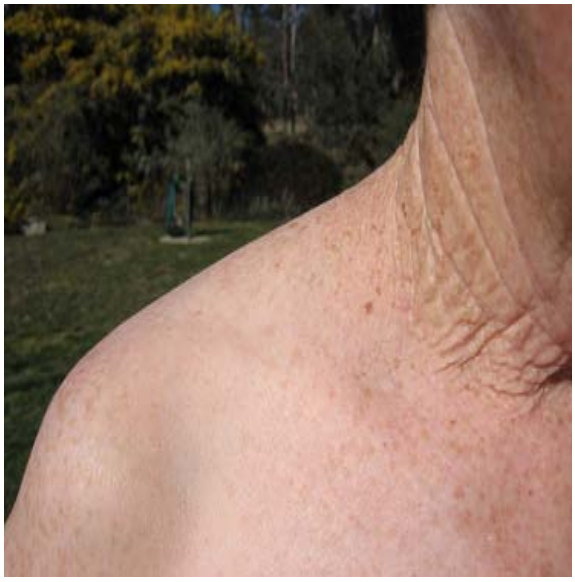


Figure 24 Male. Clavicle visible, normal muscle around shoulders. Mild muscle wasting.

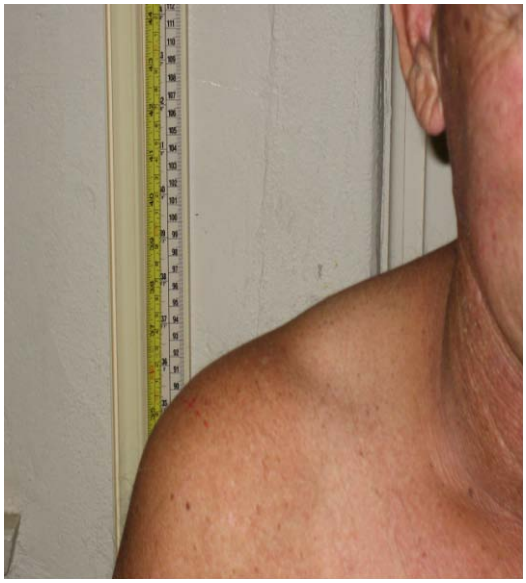
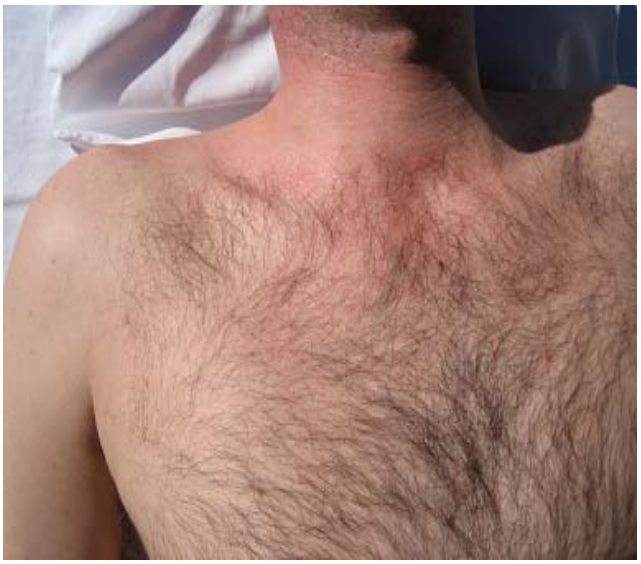


Figure 25: Male. Clavicle quite obvious. Acromion process visible. Shoulders slightly more square than above photo examples but still rounded. Good muscle bulk around biceps. Mild muscle wasting.



Muscles around the shoulder

- Position the patients arm down at his/her side if possible. The shoulders of a *severely* malnourished patient (i.e. severe muscle wasting) are *square rather than rounded*. The acromion protrusion can be quite pronounced. Normal shoulders are curved, especially at the junction between the neck and the shoulder, and at the shoulder joint. You also should be able to *grasp muscle tissue at the shoulder* joint.

Mildly or moderately malnourished patients will show some signs of muscle wasting and whilst the shoulders will not be square the acromion protrusion can be evident.

RANK the patient for physical evidence of muscle wasting.

After examining the muscle around the shoulder and clavicle, subjectively rate the degree of muscle wasting.

Note: If the patient shows signs of muscle wasting in one area but not in the other rank the patient in either the *mild or moderate category* depending on the degree of muscle wasting.

Please chose only *ONE* of the following categories to best represent your overall subjective assessment of the degree of muscle wasting:

- Normal (i.e. there is no physical evidence of muscle wasting *in either area*),
- Mild muscle wasting (the loss of muscle may vary between sites (see note above) OR muscle wasting is *slight in both areas*),
- Moderate muscle wasting (the loss of muscle may vary between sites (see note above) OR muscle wasting is moderate *in both areas*),
- Severe (the loss of muscle is severe *in both areas*).

Version 1, 11 September 2006.
DOI: http://dx.doi.org/10.4451/EarlyPN_APM

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International Standards for Anthropometric Assessment (2001). International Society for the Advancement of Kinanthropometry. ISBN 0 86803 712 5.

PhenxtoolKit: http://www.phenxtoolkit.org July 29 2011, Version 4.5

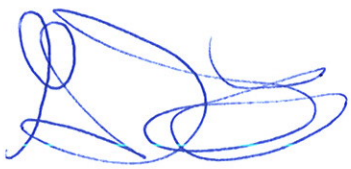
Statement of Authorship, Anthropometry Procedures Manual.

Anthropometric Procedures Manual. DOI: 10.4451/EarlyPN_APM

Fiona Simpson conceived and designed the Anthropometry Procedures Manual for the analytic observational study, which was in turn used in the Early Parenteral Nutrition Trial.

Gordon Doig provided essential advice during construction of the Anthropometry Procedures Manual, and helped draft the final PDF book.

Final approval of the Anthropometry Procedures Manual was given by Fiona and Gordon.

Gordon Doig  Date 22/5/15

Fiona Simpson  Date 22/5/15

APPENDIX C

Posters arising from this thesis

- **Simpson F,** Doig GS. "BMI is not a good measure of baseline mortality in intensive care clinical trials". Clinical Nutrition Week 2013, American Society for Enteral and Parenteral Nutrition, National; Phoenix, Arizona, USA, 9th to 12th Feb, 2013.

Presentations given by the candidate and related to the thesis

- **Simpson, F.** Keynote Presenter, Invited Speaker. "Early parenteral nutrition vs. standard care in patients not expected to be fed within 24 h of ICU admission: Methodology of a Multi-Centre Trial." Hot Topics Session. 34th European Society for Parenteral and Enteral Nutrition Congress on Clinical Nutrition and Metabolism (ESPEN), Barcelona, Spain; 8th to 11th Sept, 2012.
- **Simpson, F.** Invited Speaker. "Early Parenteral Nutrition in Critically Ill Patients with Short Term Contraindications to Enteral Nutrition (The Early PN Trial): Methodology of a Multi-Centre Clinical Trial". Breakfast Session. Australian New Zealand Intensive Care Society and Australian Critical Care Nurses (ANZICS/ACCN) 2012, 37th Australian and New Zealand Annual Scientific Meeting on Intensive Care, Adelaide, Australia, 25th to 27th October, 2012.
- **Simpson, F.** Plenary Session, Invited Speaker. "Early Parenteral Nutrition in Critically Ill Patients with Short Term Contraindications to Enteral Nutrition: Methodology of a Multi-Centre Clinical Trial". Clinical Trials Plenary Session. Clinical Nutrition Week 2013, American Society for Enteral and Parenteral Nutrition (ASPEN), Phoenix, USA, 9th to 12th Feb, 2013.

- **Simpson, F.** Invited Speaker. "Early Parenteral Nutrition in Critically Ill Patients with Short Term relative contraindications to early Enteral Nutrition: Methodology of a Multi-Centre Trial." Critical Care Nutrition Session. 39th Annual Scientific Meeting of the Australasian Society for Parenteral and Enteral Nutrition (AuSPEN), Sydney, Australia; 14th to 16th Sept, 2013.
- **Simpson, F.** Invited Speaker. "Nutrition in ICU and the Early Parenteral Nutrition Trial". New South Wales Nutrition Support Interest Group. Sydney, Australia, 6th March, 2014.

APPENDIX D

Early PN Trial Conduct and Management:
Study Management Committee: Gordon S. Doig (Chair), Fiona Simpson, Elizabeth A. Sweetman, Simon R. Finfer, D. Jamie Cooper, Philippa T. Heighes, Andrew R. Davies, Michael O'Leary, Tom Solano and Sandra Peake. ***PN protocol sub-committee:*** Gordon S. Doig (Chair), Fiona Simpson, Michael O'Leary. ***Infectious complications sub-committee:*** Gordon S. Doig (Chair), Tom Solano, Fiona Simpson. ***Data Quality and Management:*** Jennifer L. Hannam (Northern Clinical School Intensive Care Research Unit, University of Sydney, Australia). ***Statistical analysis:*** Gordon S. Doig. ***Independent Data Safety and Monitoring Committee:*** John Moran (Chair, Dept of Intensive Care, The Queen Elizabeth Hospital, Adelaide, Australia), Petra Graham (Dept of Statistics, Macquarie University, Sydney, Australia) and Andrew Bersten (Dept of Critical Care Medicine, Flinders University, Adelaide, Australia).

Early PN Trial Contributing Sites and Site Investigators, alphabetical by site: **Auckland City Hospital, New Zealand:** Jodi Brown, Heidi Buhr, Vicki Cochrane, Michelle Eccleston, Eileen Gilder, Shay McGuiness, Rachael Parke, Anna Whitley. **Austin Hospital, Victoria, Australia:** Rinaldo Bellomo, Glenn Eastwood, Donna Goldsmith, Inga Mercer, Kim O'Sullivan, Leah Peck , Helen Young. **Bendigo Hospital, Victoria, Australia:** Catherine Boschert, John Edington, Jason Fletcher, Gary Koch, Mainak Majumdar, Tracey Shard, Julie Smith. **Blacktown Hospital, New South Wales, Australia:** Kalpesh Gandhi, Kiran Nand, Treena Sara. **Box Hill Hospital, Victoria, Australia:** David Charlesworth, Suzanne Eliott, David Ernest, Angela Hamilton (deceased), Belinda Howe, Inga Mercer, Sam Radford, Jaspreet Sidhu. **Cabrini Hospital, Victoria, Australia:** Jonathon Barrett, Felicity Hawker, MariaGrazia de Luca. **Calvary Mater Hospital Newcastle, New South Wales, Australia:** Irene Bailey, Jorge Brieva, Katrina Ellem. **Campbelltown Hospital, New South Wales, Australia:** Gillian Bishop, Olivia Mulligan, Ray Eckhardt. **Concord Hospital, New South Wales, Australia:** David Milliss, Helen Wong. **Dandenong Hospital, Victoria, Australia:** Subhash Arora, Michael Buist, Bridget O'Bree, Kate Shepherd, Susan Van Dyk. **Frankston Hospital, Victoria, Australia:** Sharon Allsop, Subhash Arora, John Botha, Himangsu Gangopadhyay, David Lewis, Naomi Pratt, Fiona Turnbull, Jodi Vuat. **Geelong Hospital, Victoria, Australia:** Allison Bone, Claire Cattigan, Tania Elderkin, Melissa Fraser, Anne Kilmonth, Neil Orford, Tania Salerno. **Gold Coast Hospital, Queensland, Australia:** Alan Spencer, Mandy Tallott, Rosemary Whitbread. **Gosford Hospital, New South Wales, Australia:** Rob Cameron, Sheridan Hatter, Jackie Hyslop, Peter Rye. **John Flynn Private Hospital, Queensland, Australia:** Robin Holland, Roslyn van der Vooren. **John Hunter Hospital, New South Wales, Australia:** Elise Crowfoot, Miranda Hardie, Peter Harrigan, Sam Jenkins. **Liverpool Hospital, New South Wales, Australia:** Deepak Bhonagiri, Sharon Micallef, Michael Parr. **Lyell McEwin Hospital, South Australia, Australia:** Rajaram Ramadoss, Josette Wood, Julie Zuppa. **Middlemore Hospital, New Zealand:** Marilyn Beggs, Peter Dzendrowskyj, Chantal Hogan, Judy Tai, Anna Tilsley, Tony Williams. **Monash Medical Centre, Victoria, Australia:** Jonathon Barrett, Sue Burton, Tim Crozier, Pauline Galt, Ainsley Gillies, Rebecca Ioannidis, Marnie Reilly, Carly Thornhill. **Nepean Hospital, New South Wales, Australia:** Cheryl Cuzner, Rebecca Gresham, Larissa Hoyling, Tony Maclean, Maria Nikas, Phoebe Palejs, Ian Seppelt, Leonie Weisbrodt, Sarah Whereat. **Royal North Shore Hospital, New South Wales, Australia:** Anthony Delaney, Gwen Hickey. **Royal Hobart Hospital, TAS:** David Cooper, Kathryn Marsden, Rick McAllister, Ram Sistla, Andrew Turner. **St George Hospital, New South Wales, Australia:** Vanessa

Dhiacou, Deb Inskip, Theresa Jacques, Alina Jovanovska, Michael O'Leary, Rebecca Sidoli. **St Vincent's Hospital Melbourne, Victoria, Australia:** Nicole Groves, Jenny Holmes, John Santamaria, Roger Smith, Antony Tobin. **St Vincent's Hospital Sydney, New South Wales, Australia:** Jeff Breeding, Priya Nair, Claire Reynolds, Karen Storer. **Sydney Adventist Hospital, New South Wales, Australia:** Roger Harris, Linley Shields, Hui (Whay) Yang. **The Prince of Wales Hospital, New South Wales, Australia:** Frances Bass, Michelle Campbell, Pam Edhouse, Naomi Hammond, Maryam Sana, Yahya Shehabi, Victoria Stockdale, Barb Trytko. **The Queen Elizabeth Hospital, South Australia, Australia:** Catherine Kurenda, Sandra Peake, Patricia Williams. **Wellington Hospital, New Zealand:** Lynn Andrews, Dick Dinsdale, Peter Hicks, Diane Mackle. **Wollongong Hospital, New South Wales, Australia:** Michael Davis, Michelle Gales, Francisco Hill, Bronwyn Johnson, Adam Purdon, Martin Sterba, Renee Xu.

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9 December 2005

Dr G Doig
Intensive Therapy Unit
Royal North Shore Hospital
E25

Dear Dr Doig

Title: **Early parenteral nutrition versus standard care in the critically ill patient: A level 1 randomised controlled trial**
Granting Body: *NHMRC (ID 402643)*

Ref. No.: 8827

Your recent application has been noted by the Executive Committee of the Human Research Ethics Committee and in doing so accepts the final approval from the Northern Sydney Central Coast Health Human Research Ethics Committee (Northern).

In considering the ethical content of the study, the Committee acknowledges the right for you to proceed under the authority of the Northern Sydney Central Coast Health Human Research Ethics Committee (Northern).

It is the responsibility of the Chief investigator to provide a progress report every twelve months for the duration of the study and a final report on the completion of the study. Your report will be due on 31 December 2006.

The responsibility for complaints by participants about the research process will remain with the Northern Sydney Central Coast Health Human Research Ethics Committee (Northern).

Yours sincerely

Gail Briody
Manager, Ethics Administration

APPENDIX F: Study Inclusion and Exclusion Criteria

Inclusion Criteria (All YES answers for enrolment)

1. Is the patient expected to remain in ICU today and tomorrow?
2. Is the patient 18 years of age or older?
3. Has the patient been admitted to the study ICU less than 24 hours?
4. Does the patient have a central venous access line through which parenteral nutrition could be delivered?
5. Is this patient **not** expected to receive enteral, parenteral or oral nutrition today or tomorrow?

Exclusion Criteria (All NO answers for enrolment, YES to any for exclusion)

1. Known pregnancy or currently breastfeeding.
2. Has the patient previously been enrolled and randomised into this study?
3. Is the patient to receive palliative care only and is not expected to survive ICU or hospital discharge?
4. Was the patient admitted to this, or another, ICU during this current hospitalisation?
5. Was the patient admitted to the study ICU directly from another ICU?
6. Is the patient moribund and not expected to survive 24 hours?
7. Is the patient brain dead or suspected to be brain dead?
8. Are there long term contraindications to enteral or oral nutrition such that the patient would normally be supported with parenteral nutrition (Ex. Home TPN patient)?
9. Does the patient require treatment of thermal injury to greater than 20% of total body surface area?
10. Is the primary reason for admission to the ICU for the treatment of a condition that requires timely nutritional support (Ex. Anorexia nervosa.)?
11. Body weight < 35 Kg
12. Height < 140 cm (Demi armspan < 59 cm)
13. Is there a contraindication to treatment with Kabiven G19%?

NB - see next page for contraindications to Kabiven G19% based on TGA licensing indications.

Contraindications to Kabiven G19% based on TGA Licensing Indications.

c1. Known hypersensitivity to egg or soya protein or to any of the ingredients of the study PN (for full ingredients see Product Information, MIMS TGA Document Appendix 1).

c2. Severe hyperlipidaemia (Documented serum total cholesterol >7mmol/L and/or triglycerides >3 mmol/L).

c3. Severe liver insufficiency (Biopsy proven cirrhosis, or documented portal hypertension with a known past history of either upper GI bleeding attributed to portal hypertension or of hepatic failure leading to encephalopathy / coma.)

c4. Severe blood coagulation disorders (Documented INR > 3.0 not due to coumarin therapy, platelet count <15,000).

c5. Inborn errors of amino acid metabolism (Ex. PKU etc)

c6. Severe renal insufficiency without access to haemofiltration or dialysis.

c7. Acute shock as defined by arterial systolic blood pressure ≤ 90mmHg or mean arterial pressure ≤ 70mmHg despite adequate fluid resuscitation (i.e. following rapid infusion of ≥ 500mL crystalloid or 200mL colloid solution and /or PAOP ≥ 12mmHg, CVP ≥ 8mmHg) **or** increasing need for noradrenaline / adrenaline / dopamine to maintain blood pressure where the infusion rate has **increased by more that 50%** over the previous hour **to greater than 0.6mg/hour (10 mcg/min)** norad / adrenaline or **30mg** dopamine.

*Patients are **not excluded** if their initial shock responds to fluid therapy or if the catecholamine infusion rate has not increased by more than 50% over the previous one hour period or if the current infusion rate is less than 0.6mg norad / adrenaline per hour .*

c8. Hyperglycaemia (blood sugar > 10 mmol/L) that currently requires the administration of more than 6 units of insulin/hour **at the time of enrolment**.

c9. Pathologically elevated serum levels of any of the electrolytes included in Kabiven G19% a**t the time of enrolment. Documented** Sodium >155 mmol/L, potassium > 6.2 mmol/L, magnesium > 2.0 mmol/L, ionised calcium > 1.5 mmol/L, phosphate >2.0 mmol/L, chloride > 120 mmol/L.

The patient may become eligible if these pathologically elevated electrolyte levels can be corrected within 24 hours of admission to the study ICU.

c10. General contraindications of infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency and hypotonic dehydration

The patient may become eligible if these general contraindications to fluid therapy can be corrected within 24 hours of admission to the study ICU.

c11. Haemophagocytic syndrome

c12. Severe trauma with acute shock (see **Exclusion Criteria c7** for definition of acute shock).

c13. Diabetes mellitus with ketoacidosis or non-ketotic hyperosmolar state.

c14. Acute myocardial infarction with acute shock (see **Exclusion Criteria c7** for definition of acute shock) or pulmonary oedema.

c15. (Metabolic acidosis or severe sepsis) with acute shock (see Exclusion Criteria c7 for definition of acute shock. Use Bone Criteria for definition of Severe Sepsis).

c16. Coma (GCS ≤8) in association with hyperosmolarity of the blood (≥320mOs/kg) from any cause.

APACHE Score: ICU Early PN Trial

Data obtained from **24 hours immediately prior to study enrolment**.

AD1:Patient Code | | | | | | | **AD2**:Patient Initials | | | **AD8**:ICU Admit Date | | |

Hospital ID Patient Number

Abnormal Value Guide

Record Most Abnormal Value available over 24hours prior to enrolment

PHYSIOLOGIC VARIABLE	Most abnormal Value	High Abnormal Range				Normal	Low Abnormal Range			
		worst	Severe	moderate	mild		mild	moderate	severe	worst
AP4: Temperature central preferred *°C*		≥ 41	39 – 40.9		38.5 – 38.9	36 – 38.4	34 – 35.9	32 – 33.9	30 – 31.9	≤ 29.9
AP5: Mean arterial pressure *mmHg*		≥ 160	130 – 159	110 – 129		70 – 109		50 – 69		≤ 49
AP6: Heart rate *ventricular beats per min*		≥ 180	140 – 179	110 – 139		70 –109		55 – 69	40 – 54	≤ 39
AP7: Respiratory rate *total breaths per min*		≥ 50	35 – 49		25 – 34	12 – 24	10 – 11	6 – 9		≤ 5
AP8: Oxygenation: a. for $FiO_2 \geq 0.5$, record worst A – a gradient		> 500	350 – 499	200 – 349		< 200		A – a gradient = $(713 * FiO_2) – (1.25*PaCO_2) – PaO_2$		
b. for $FiO_2 < 0.5$, record lowest PaO_2 *mmHg*						≥ 71	61 – 70		55 – 60	< 55
AP9: Arterial *pH*		≥ 7.7	7.6 – 7.69		7.5 – 7.59	7.33 – 7.49		7.25 – 7.32	7.15 – 7.24	< 7.15
AP10: Serum sodium *mMol/L*		≥ 180	160 – 179	155 – 159	150 – 154	130 – 149		120 – 129	111 – 119	≤ 110
AP11: Serum potassium *mMol/L*		≥ 7	6 – 6.9		5.5 – 5.9	3.5 – 5.4	3 – 3.4	2.5 – 2.9		< 2.5
AP12: Serum creatinine *µMol/L*		≥ 300	171–299	121 – 170		50 – 120		< 50		
AP13: Presence of Acute Renal Failure	☐ Yes ☐ No	Creatinine increase by minimum 20% to at least more than 120 *µ*mol/L compared to the last known creatinine (this hospital admission) and presence of a risk factor for ARF.								
AP14: Haematocrit (%)		≥ 60		50 – 59.9	46 – 49.9	30 – 45.9		20 – 29.9		< 20
AP15: Haemoglobin g/L (record only if Haematocrit **not** available)		≥ 200		167 – 199	153 – 166	100 – 152		67 – 99		< 67
AP16: White blood count $x10^9/L$		≥ 40		20 – 39.9	15 – 19.9	3 – 14.9		1 – 2.9		< 1
AP17: Glasgow Coma Scale Score		Record *lowest* Glasgow Coma Scale score.								
AP18: Serum HCO_3 venous *mMol/L* (record only if **no** arterial blood gasses are available)		≥52	41 – 51.9		32 – 40.9	22 – 31.9		18 – 21.9	15 – 17.9	<15

Completion Signature: _____

Baseline Demographics: ICU Early PN Trial

AD1:Patient Code | | | | | | | **AD2**:Patient Initials | | | |

Hospital ID | Patient Number

AP1: Select the *single most specific reason* for this ICU admission:

Note – If the patient was admitted from the Operating Theatre or Recovery Room, you must choose a Postoperative Category.

Postoperative Categories

Vascular / Cardiovascular

☐1: Dissecting / ruptured aorta
☐2: Peripheral vascular disease (no bypass graft)
☐3: Valvular heart surgery
☐4: Elective abdominal aortic aneurysm
☐5: Peripheral artery bypass graft
☐6: Carotid endarterectomy
☐7: Other cardiovascular disease

Respiratory

☐8: Respiratory infection
☐9: Lung neoplasm
☐10: Respiratory neoplasm (mouth, sinus, larynx, trachea)
☐11: Other respiratory diseases

Trauma

☐12: Head trauma (with / without multiple trauma)
☐13: Multiple trauma (excluding head trauma)

Gastrointestinal

☐14: GI perforation / rupture
☐15: GI inflammatory disease
☐16: GI obstruction
☐17: GI bleeding
☐18: Liver transplant
☐19: GI neoplasm
☐20: GI cholecystitis / cholangitis
☐21: Other gastrointestinal diseases

Neurological

☐22: Intracerebral haemorrhage
☐23: Subdural / epidural haematoma
☐24: Subarachnoid haemorrhage
☐25: Laminectomy / other spinal cord injury
☐26: Craniotomy for neoplasm
☐27: Other neurologic disease

Renal

☐28: Renal neoplasm
☐29: Other renal diseases

Gynaecological

☐30: Hysterectomy

Orthopaedic

☐31: Hip or extremity disorder

Other surgical category

☐32: Burns (thermal injury)
☐33: Other procedure

Nonoperative Categories

Cardiovascular / vascular

☐34: Cardiogenic shock
☐35: Cardiac arrest
☐36: Aortic aneurysm
☐37: Congestive cardiac failure
☐38: Peripheral vascular disease
☐39: Rhythm disturbance
☐40: Acute myocardial infarction
☐41: Hypertension
☐42: Other nonsurgical cardiovascular disease

Respiratory

☐43: Parasitic pneumonia
☐44: Aspiration pneumonia
☐45: Respiratory neoplasm (including larynx, trachea)
☐46: Respiratory arrest
☐47: Pulmonary oedema (non-cardiogenic)
☐48: Bacterial / viral pneumonia
☐49: Chronic obstructive pulmonary disease
☐50: Pulmonary embolism
☐51: Mechanical airway obstruction
☐52: Asthma
☐53: Other respiratory diseases

Sepsis

☐54: Sepsis other than urinary tract
☐55: Sepsis of urinary tract origin

Trauma

☐56: Head trauma (with / without multiple trauma)
☐57: Multiple trauma (excluding head)

Gastrointestinal

☐58: Hepatic failure
☐59: GI Perforation / obstruction
☐60: GI Bleeding – varices
☐61: GI Inflammatory disease (ulcerative colitis, Crohn's, pancreatitis)
☐62: GI Bleeding (ulceration / laceration)
☐63: GI Bleeding (diverticulitis)
☐64: Other gastrointestinal disease

Neurological

☐65: Intracerebral haemorrhage
☐66: Subarachnoid haemorrhage
☐67: Stroke
☐68: Neurologic infection
☐69: Neurologic neoplasm
☐70: Neuromuscular disease
☐71: Seizure
☐72: Other neurological disease

Metabolic

☐73: Metabolic coma
☐74: Diabetic ketoacidosis
☐75: Drug overdose
☐76: Other metabolic disease

Haematological

☐77: Coagulopathy / neutropenia / thrombocytopenia
☐78: Other haematological diseases

Renal diseases

☐79: Any renal disorder

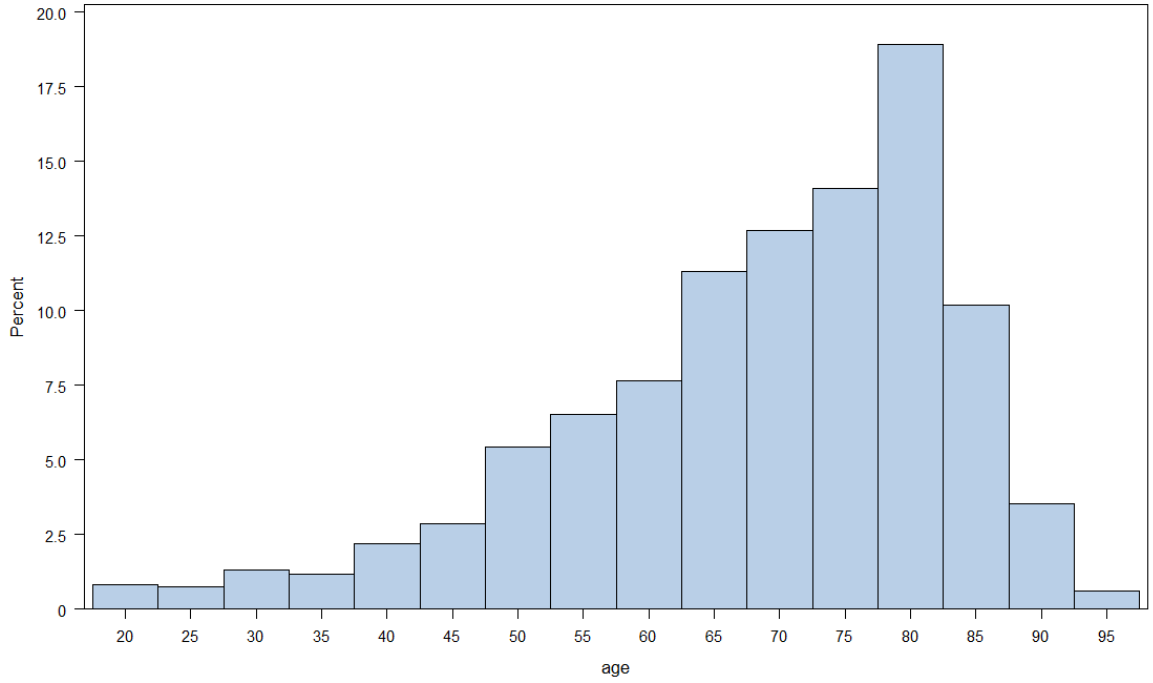
Other medical category

☐80: Burns (thermal injury)
☐81: Other disease

Completion Signature: _____

APPENDIX I: Shapiro Wilk test for normality for continuous variables.

1) Age.

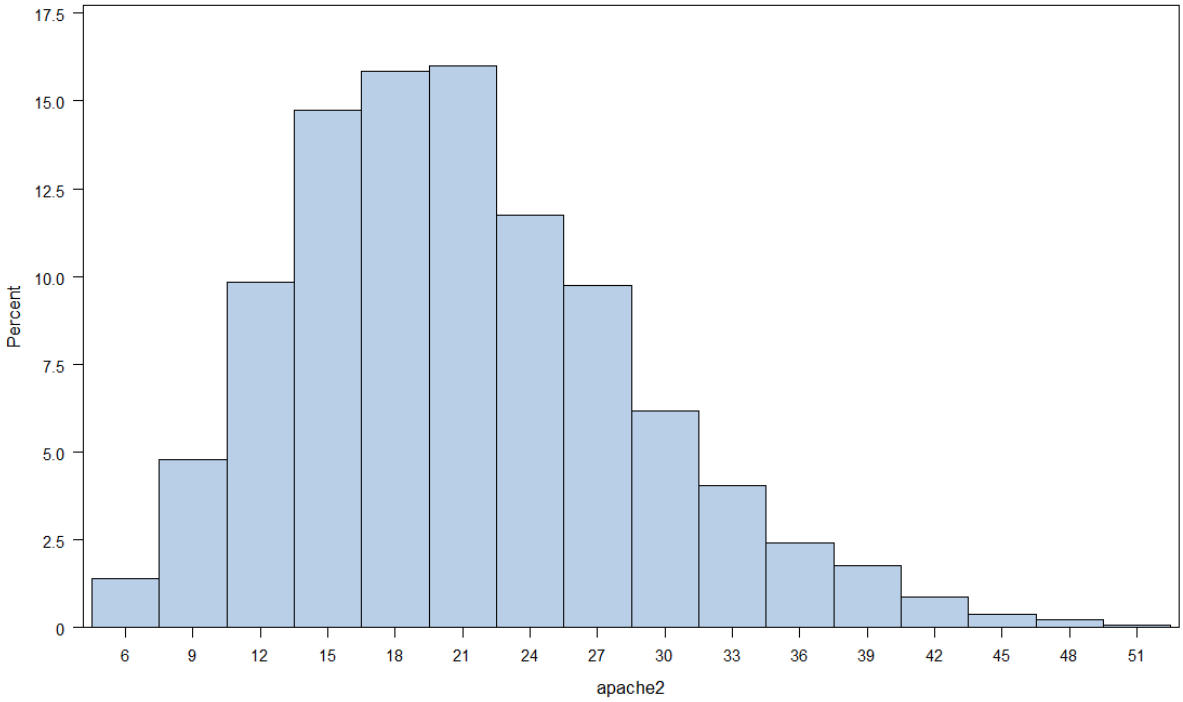


Shapiro-Wilk 0.937696 Pr < W <0.0001

Median 71.33151 years

Quantile	Estimate
100% Max	96.3233
99%	91.9260
95%	86.9123
90%	84.2438
75% Q3	79.7205
50% Median	71.3315
25% Q1	60.4959
10%	48.2959
5%	39.1781
1%	23.5260
0% Min	18.2877

2) APACHE II Score

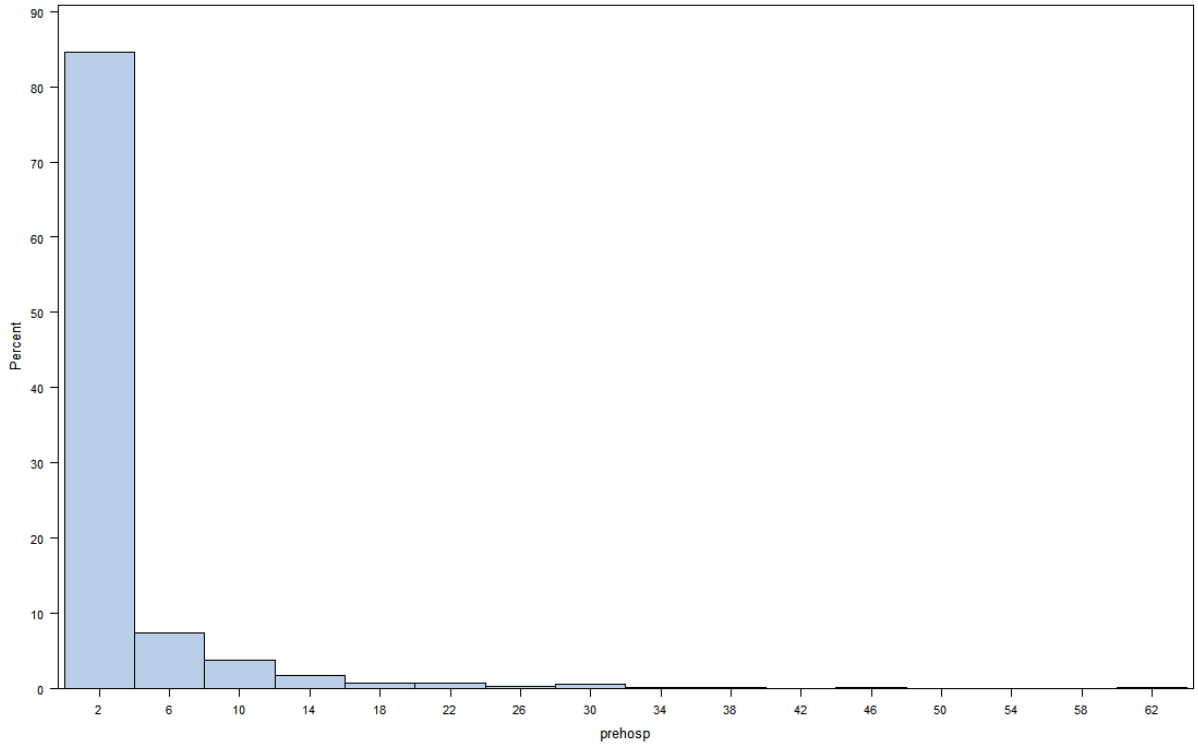


Shapiro-Wilk 0.973668 Pr < W <0.0001

Median 20.0000

Quantile	Estimate
100% Max	51
99%	43
95%	35
90%	31
75% Q3	26
50% Median	20
25% Q1	15
10%	12
5%	10
1%	7
0% Min	5

3) Days in hospital prior to ICU admission.

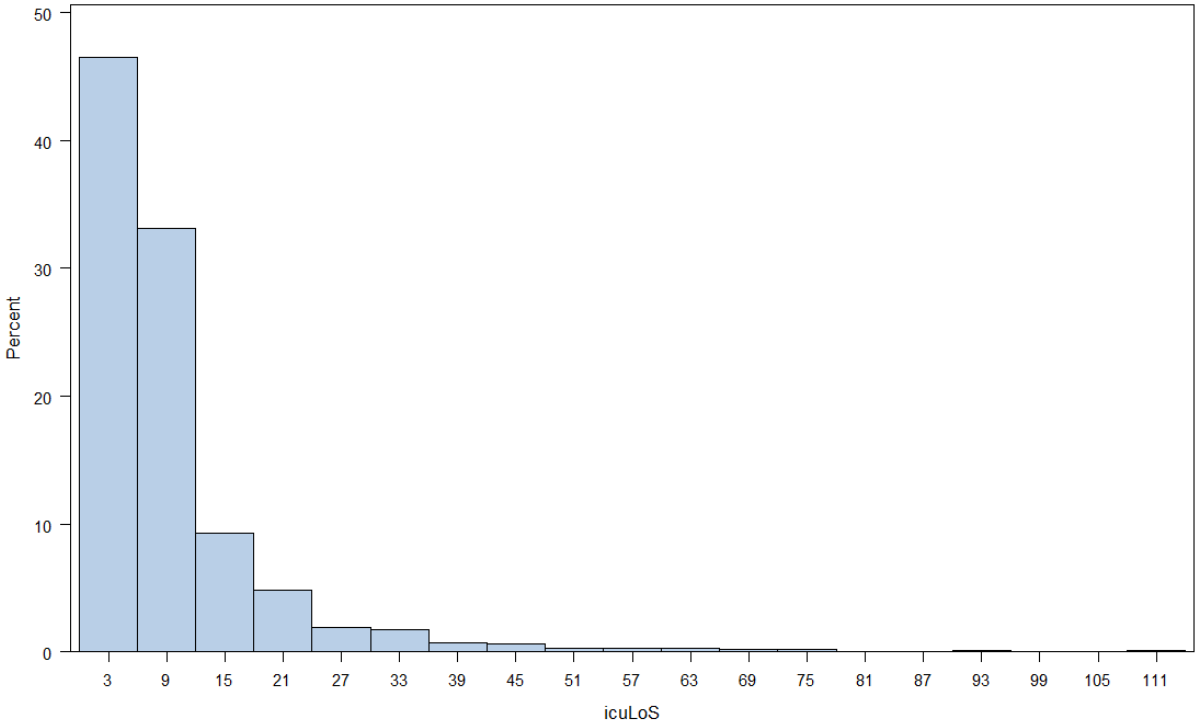


Shapiro-Wilk 0.464194 Pr < W <0.0001

Median 1.0 day

Quantile	Estimate
100% Max	63
99%	25
95%	10
90%	6
75% Q3	2
50% Median	1
25% Q1	1
10%	0
5%	0
1%	0
0% Min	0

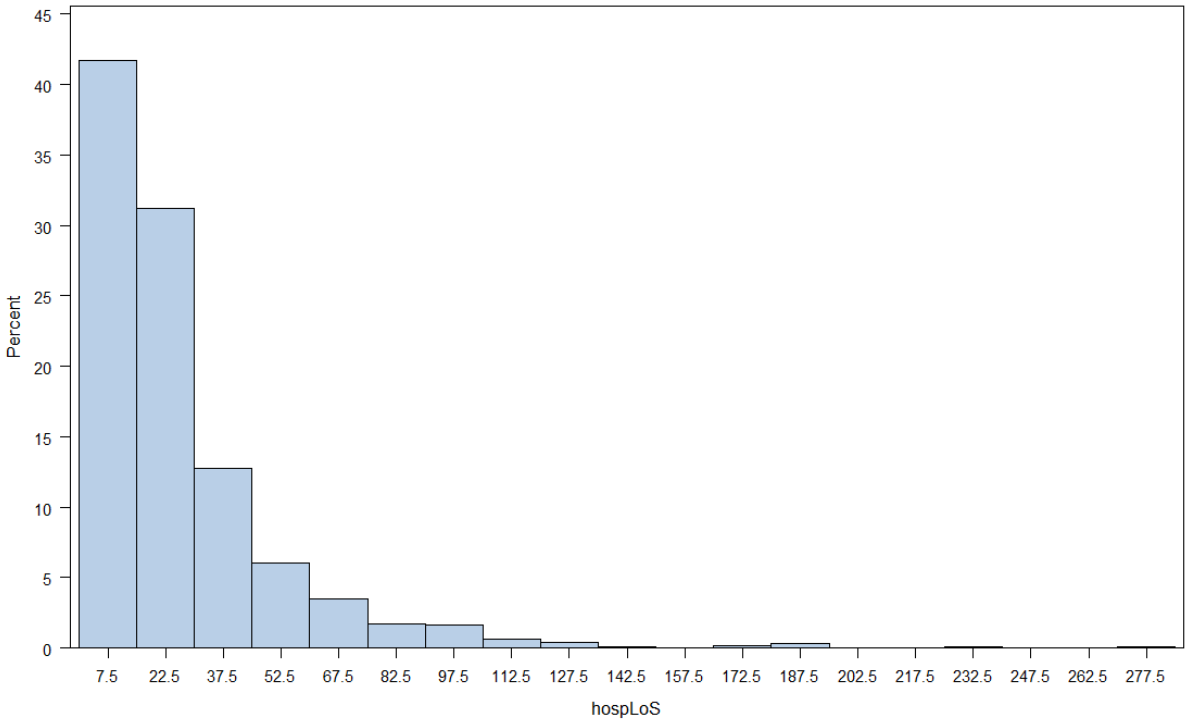
4) ICU length of stay



Shapiro-Wilk 0.625466 Pr < W <0.0001
Median 6.0 days

Quantile	Estimate
100% Max	112
99%	57
95%	27
90%	19
75% Q3	10
50% Median	6
25% Q1	3
10%	2
5%	2
1%	2
0% Min	1

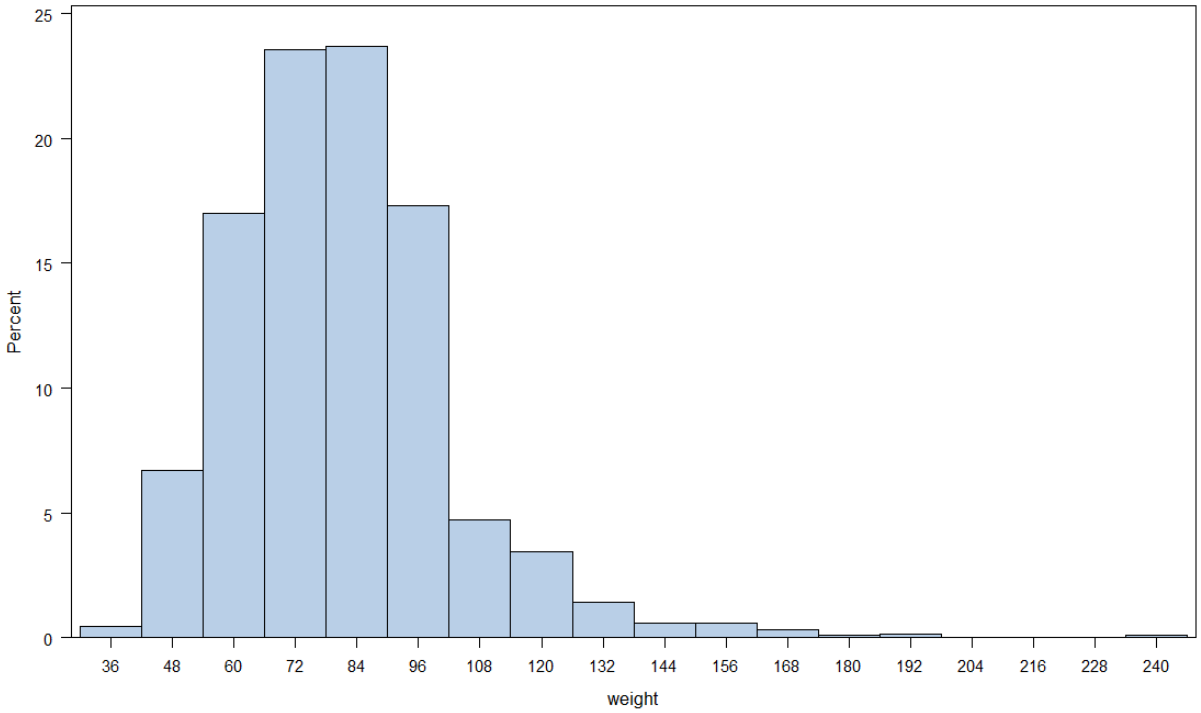
5) Hospital length of stay



Shapiro-Wilk 0.704378 Pr < W <0.0001
Median 16.0 days

Quantile	Estimate
100% Max	277
99%	120
95%	73
90%	53
75% Q3	31
50% Median	16
25% Q1	10
10%	7
5%	4
1%	2
0% Min	1

6) Weight

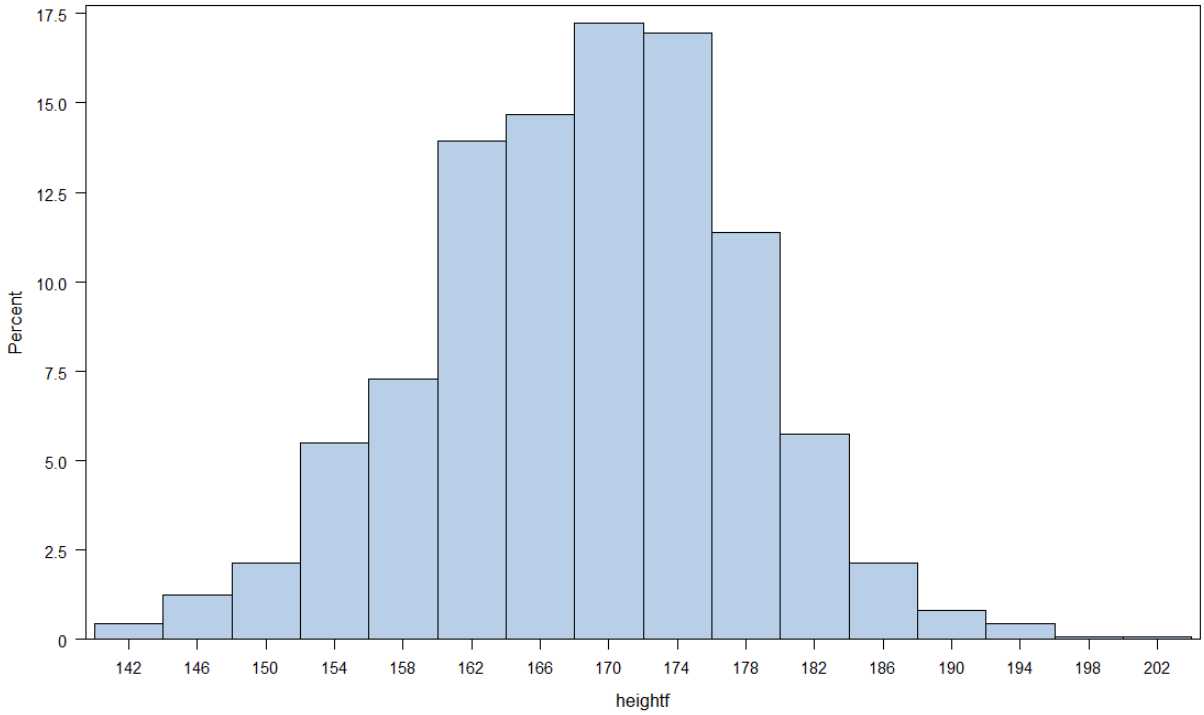


Shapiro-Wilk 0.923291 Pr < W <0.0001

Median 80.00000 kilograms

Quantile	Estimate
100% Max	235.0
99%	158.0
95%	120.0
90%	105.0
75% Q3	90.0
50% Median	80.0
25% Q1	67.7
10%	55.0
5%	50.0
1%	45.0
0% Min	35.0

7) Height

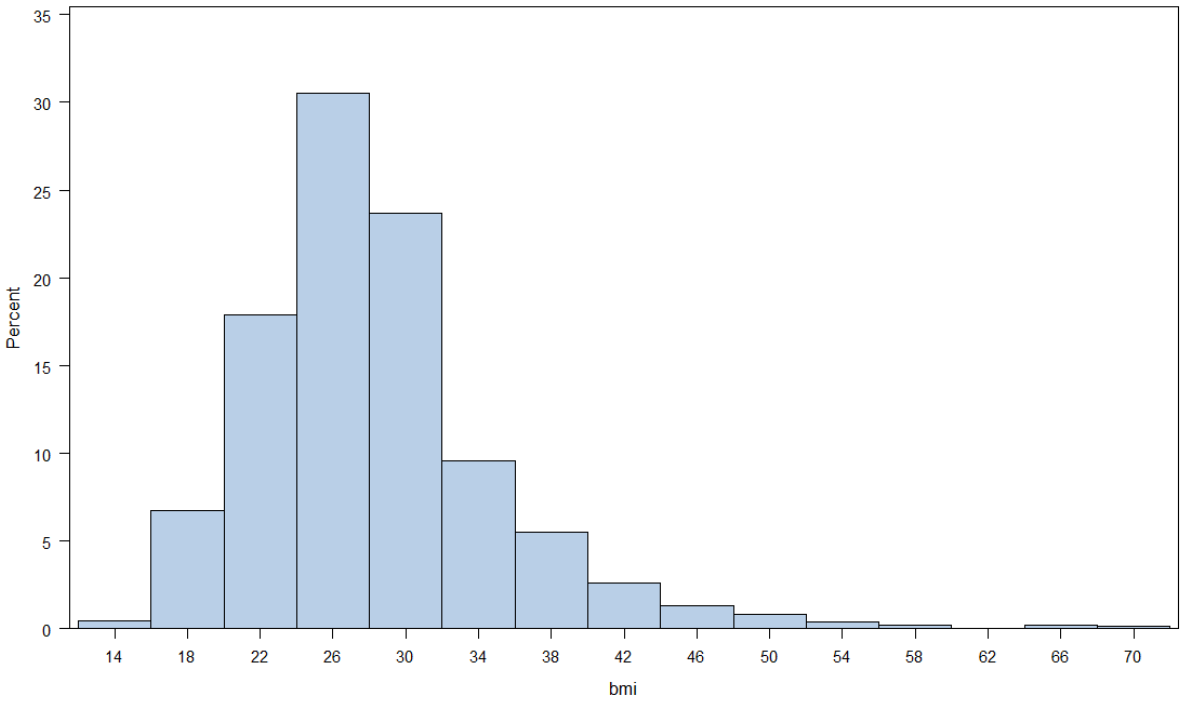


Shapiro-Wilk 0.996606 Pr < W 0.0045

Median 168.4000 centimetres

Quantile	Estimate
100% Max	203.40
99%	188.00
95%	182.50
90%	179.60
75% Q3	175.40
50% Median	168.40
25% Q1	161.40
10%	157.30
5%	153.25
1%	146.00
0% Min	140.00

8) Body Mass Index

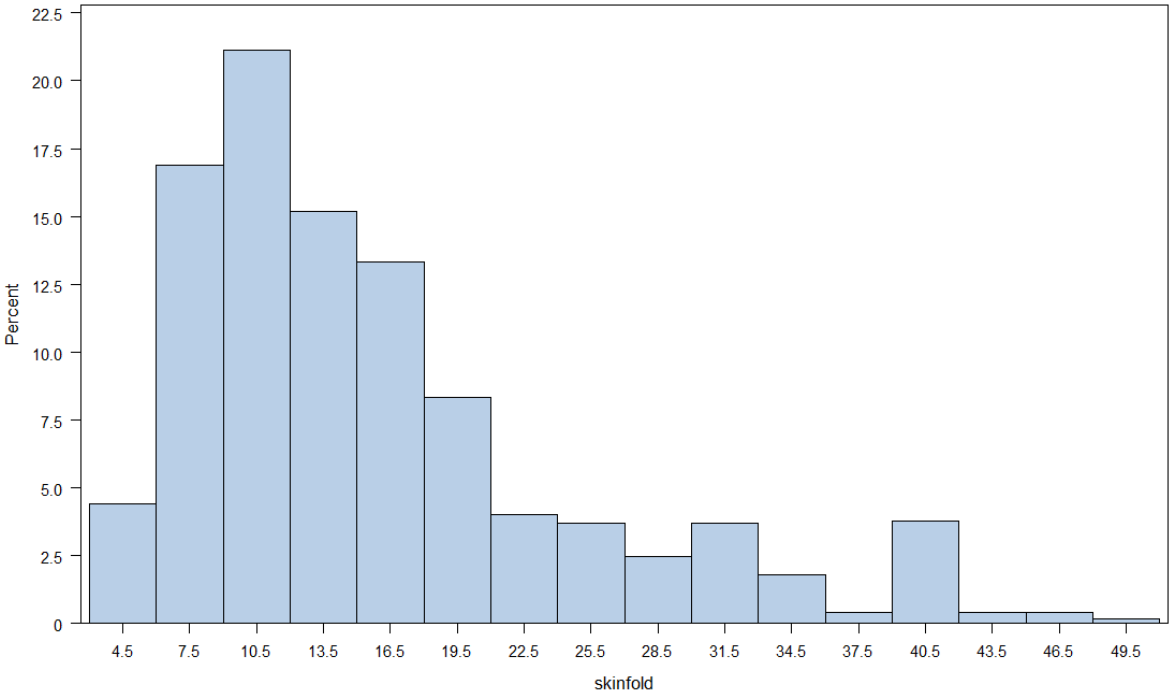


Shapiro-Wilk 0.903038 Pr < W <0.0001

Median 27.29496 kg/m^2

Quantile	Estimate
100% Max	70.6347
99%	51.9563
95%	40.6250
90%	36.5972
75% Q3	31.0204
50% Median	27.2950
25% Q1	23.9937
10%	20.8889
5%	19.0661
1%	16.6904
0% Min	14.5671

9) Triceps skinfold thickness

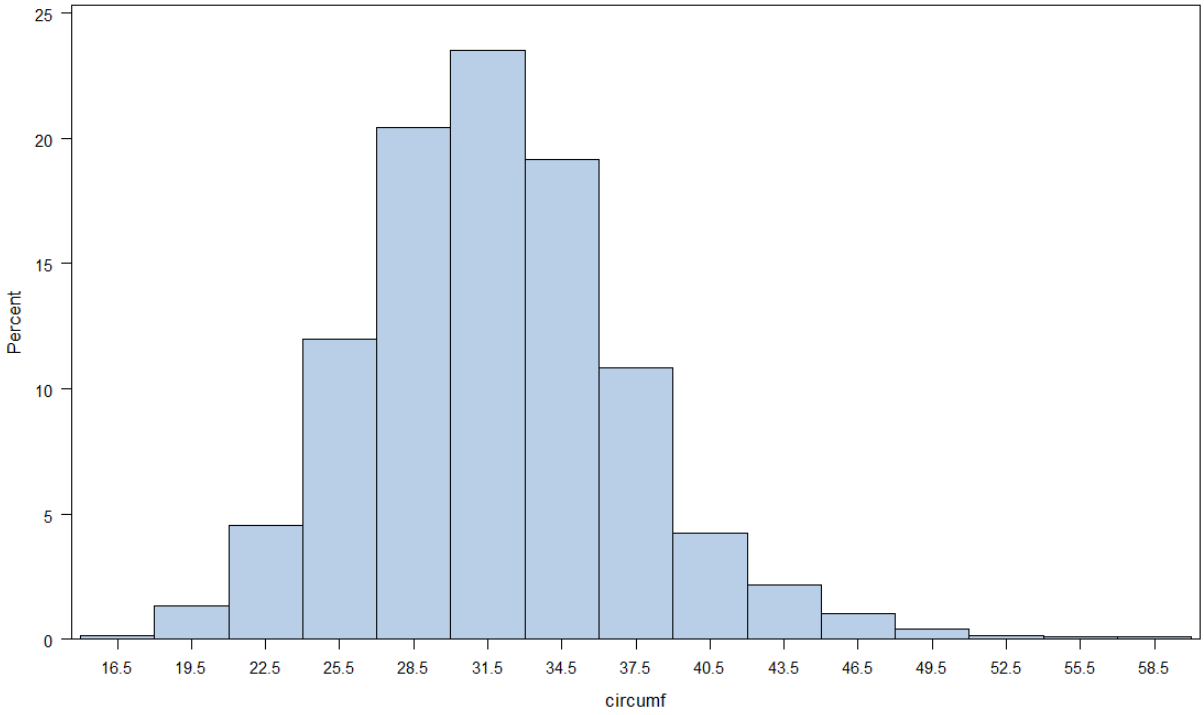


Shapiro-Wilk 0.86595 Pr < W <0.0001

Median 13.00000 millimetres

Quantile	Estimate
100% Max	50
99%	41
95%	36
90%	30
75% Q3	19
50% Median	13
25% Q1	9
10%	7
5%	6
1%	5
0% Min	4

10) Mid upper arm circumference

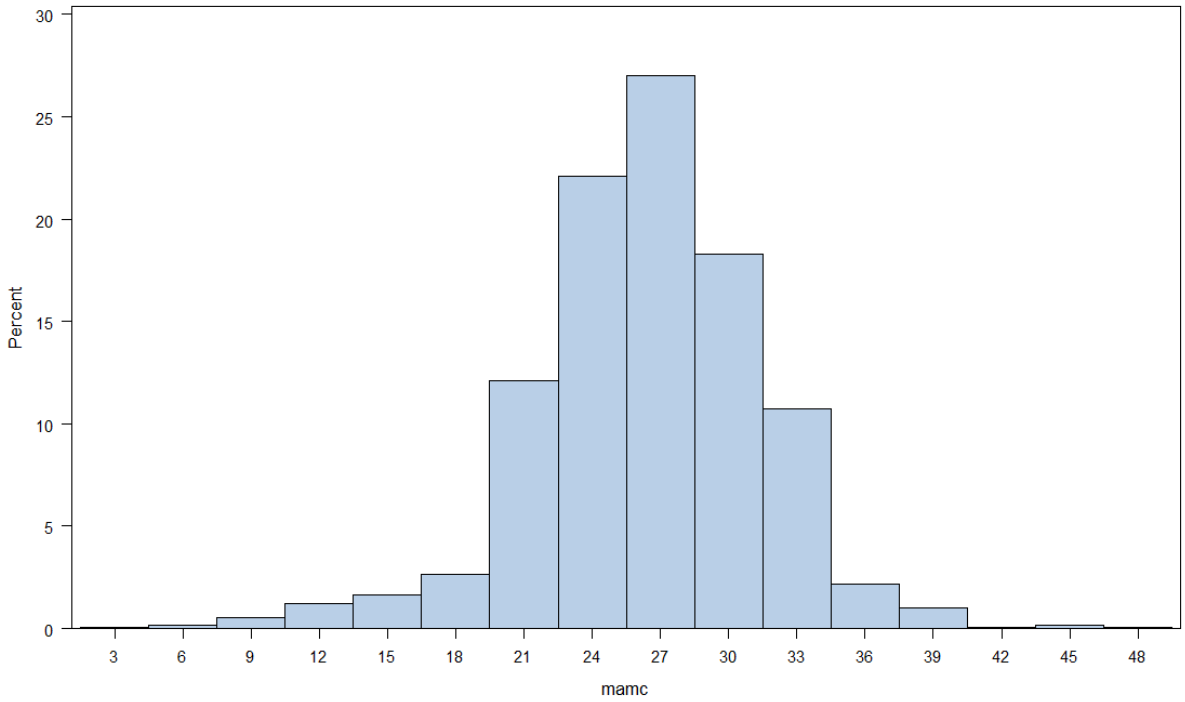


Shapiro-Wilk 0.982152 Pr < W <0.0001

Median 31.00000 centimetres

Quantile	Estimate
100% Max	58.0
99%	46.0
95%	41.0
90%	38.0
75% Q3	34.5
50% Median	31.0
25% Q1	28.0
10%	25.0
5%	23.0
1%	20.0
0% Min	16.0

11) Mid Arm Muscle Circumference



Shapiro-Wilk 0.978156 Pr < W <0.0001

Median 26.71681 centimetres

Quantile	Estimate
100% Max	48.14602
99%	38.23009
95%	33.85841
90%	32.35841
75% Q3	29.60177
50% Median	26.71681
25% Q1	23.65929
10%	20.80089
5%	18.43363
1%	11.57522
0% Min	3.43363