DETERMINING THE BEST PREDICTIVE EQUATION FOR RESTING ENERGY EXPENDITURE AMONG MECHANICALLY VENTILATED CRITICALLY ILL PATIENTS IN A MALAYSIAN TERTIARY HOSPITAL

BY

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ABSTRACT

Introduction: Measurement of resting energy expenditure using indirect calorimetry in intensive care unit patient is the gold standard as recommended by guidelines. Unfortunately, technical difficulties and high cost prevent its widespread adoption by medical facilities. Predictive equations are largely used instead. We aim to validate commonly used predictive equation at different period of acute phase of critical illness.
Methods: Patients hospitalized from November 2019-August 2020 in a general ICU of Sultan Ahmad Shah Medical Center, a university affiliated, tertiary care hospital who had been ventilated with GE Carescape R860 to assess caloric targets were included. Measurement was done up to 3 times per day from day 1 of ICU admission to day 7 of ICU admission. Equation performance was assessed by comparing means, standard deviations, correlation, concordance and agreement, which was defined as a measurement within 90-110% of measured REE by indirect calorimetry. A total of 18 equations was evaluated.
Results: A total of 49 patients were recruited. Mean patient age was 63 years, 63.6% were male and 90.9% were Malay ethnic. Medical admission comprises of 69.7% of patients category. The mean of REE as measured by IC was 1176±332 kcal during early acute phase and 1222±321 kcal during late acute phase. There was no significant difference of REE during the two acute phases of critical illness. During acute phase, the Mifflin-St. Jeor have the highest accuracy (33.33%) but no agreement. In the late acute phase, WHO predictive equation shows the highest accuracy but poor agreement with IC. The Mifflin-St. Jeor equation demonstrates the second highest accuracy and moderate agreement with IC. None of the predictive equations have level of accuracy of more than 50% across both phases. Lack of sample size due to COVID-19 pandemic and technical issues affect the overall result of this study.
Conclusions: From this study, no predictive equation can be recommended during the early acute phase of critical illness. The Mifflin-St. Jeor can be recommended to be used in late acute phase of critically ill patients. This predictive equation include static variables of height, weight and age. Incorporation of dynamic variables such as maximum temperature, minute ventilation does not increase the accuracy of predictive equation such as Faisy and Ireton-Jones. Recommendations cannot be concluded due to lack of sample size.

APPROVAL PAGE

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LIST OF ABBREVIATIONS

ICU	Intensive Care Unit
REE	Resting Energy Expenditure
TEE	Total Energy Expenditure
IC	Indirect Calorimetry
REE-IC	Resting Energy Expenditure Measured by Indirect Calorimetry
REE-PE	Resting Energy Expenditure Estimated by Predictive Equation
BW	Body Weight
IBW	Ideal Body Weight
AdjBW	Adjusted Body Weight
BMI	Body Mass Index
ht	Height
wt	Weight
APACHE II	Acute Physiology and Chronic Health Disease Classification System II
SOFA	Sequential Organ Failure Assessment
mNUTRIC	Modified Nutrition Risk in Critically Ill
Ve	Minute Ventilation
Tmax	Daily Maximal Temperature
MSJ	Mifflin-St. Jeor
PSU	Penn State University
HB	Harris-Benedict
IMNA	Institute of Medical of. National Academies

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Nutritional therapy is an important component of managing critically ill patients and have been accepted as part of standard care in intensive care unit (ICU). What was once known as nutritional support have been shown to positively impact patient's morbidity and mortality while being relatively inexpensive and available for doctors in different settings and level of healthcare. Efforts have been made to study nutrition as therapy, and from there we are beginning to understand its true potential in modern medicine. The full benefit however can only be achieved when the therapy is tailored to the individual, using individual resting energy expenditure to target caloric feeding (Waele & Honore, 2018). Achieving individual optimal target calorie and protein intake has been associated with reduction in mortality of critically ill patient and a ratio of 70% survival advantage (Waele & Honore, 2018). Nutritional therapy is indeed part of 'medication' for treatment.

Nutritional therapy can be prescribed by enteral or parenteral feeding. When prescribing enteral or parenteral feeding, measured or predicted resting energy expenditure (REE) is the parameter used to determine the amount of feeding. REE is the largest component of total energy expenditure (TEE) in hospitalized patient, more so in critically ill patient as most of them are bed bound, mechanically ventilated or sedated in ICU.

1.2 MALNUTRITION IN ICU

Malnutrition (include both under and overfeeding) is common in critically ill patients and have been associated with poor clinical outcome (Zusman et al., 2016). Reports of the rate of malnutrition differed according to geographical, patient population and assessment tools. An international, multicenter study involving 26 countries reports that majority of critically ill patients did not manage to get adequate intake of nutrition (define as >80% requirement). In Asia region, 82% was reported to received iatrogenic underfeeding in 2015, compared with 57% in Europe and South Africa (Heyland, Dhaliwal, Wang & Day, 2015). A study by Yip et al (Yip, Rai & Wong, 2014) regarding prevalence of underfeeding of critically ill patients in a Malaysian ICU shows 66% achieved 80% of caloric requirement within 3 days of ICU stay.

1.3 INDIRECT CALORIMETRY

Indirect calorimetry is the gold standard, the most precise way to determine resting energy expenditure in critically ill patient in ICU (Schlein & Coulter, 2014). It is suggested that to determine resting energy expenditure, indirect calorimetry is to be used when available (McClave et al., 2016). Despite this recommendation, its usage still limited worldwide and not routinely used. The complexity and the high cost of equipment have disrupted their adoption around the world in spite of its value for wide range of patients (Oshima et al., 2017).

1.4 PREDICTIVE EQUATION

Predictive metabolic rate equation is an alternative way to estimate resting energy expenditure in the absence of indirect calorimetry. Its accuracy however is varied from 30% up to 80%. Multiple guidelines have recommended the usage of predictive

equation to guide nutritional therapy in critically ill patients if indirect calorimetry not available (McClave et al., 2016).

1.5 STATEMENT OF THE PROBLEM

Nutritional therapy is highly dependent on accurate measurement of REE using indirect calorimetry or prediction of REE using equations, as underfeeding or overfeeding can lead to increase morbidity and mortality. Indirect calorimetry however is not widely available to be used by clinicians in Malaysian ICU. Meanwhile, predictive equations have been shown to be limited by severity and phase of illness, interindividual variabilities of bodies composition, rate of metabolism, gender and age. Despite this limitation, degrees of accuracy up to 80% can still be obtained. This however is limited by studies done on western population. In Malaysia, previously study done to assess the accuracy of predictive equation. It is however among the healthy volunteer, and not representative of ICU patient which is critically ill.

1.6 PURPOSE OF THE STUDY

As the determination of accurate REE will influence the quality of nutritional therapy, multiple studies have been done to find out the best predictive equations for it. Ismail (Ismail et al., 1998) have conducted studies to determine best predictive equation using healthy volunteer among Malaysia. ICU patients however is a critically ill population with deranged physiology compared to healthy population. As nutritional therapy is used extensively in ICU, it is important to investigate the accuracy of predictive equations in critically ill population as they have deranged physiology compared to healthy population. Deranged physiology will lead to altered REE. This difference is affected by severity and acuteness of diseases, rate of metabolism and drugs. The purpose of these study is to explore the best predictive equation to be used in critically ill patients in ICU of Malaysian population.

1.7 RESEARCH OBJECTIVES

General objectives of this study are to assess the best predictive equation in critically ill patients against indirect calorimetry during early acute and late acute phase.

1.7.1 Specific objectives

To find out accuracy and correlations of predictive equations in comparison to indirect calorimetry in critically ill patients based on ASPEN definition (Singer et al., 2019) on

a. Early acute phase, defined as day 1 to 2
b. Late acute phase, defined as day 3 to 7

1.8 RESEARCH QUESTIONS

a. Which predictive equations have the highest accuracy and agreement in critically ill patient?

b. Does early acute and late acute phase of illness have different best predictive equation?

1.9 THEORETICAL FRAMEWORK

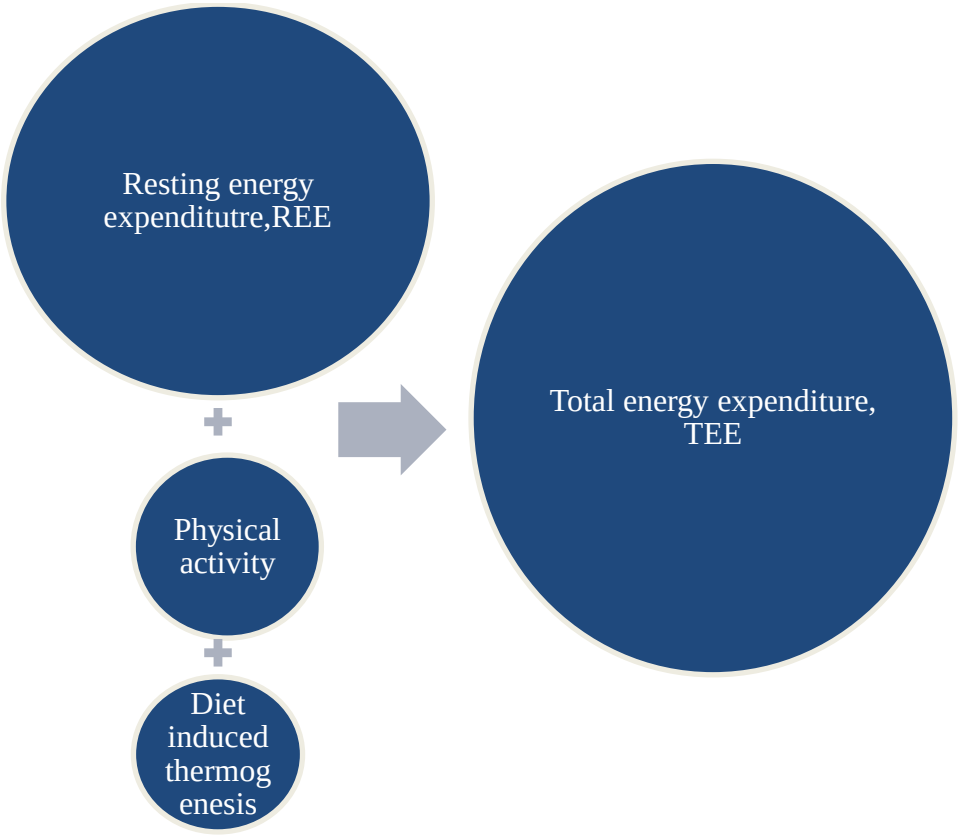

Figure 1.1 Diagram describing association between REE and TEE

1.10 SIGNIFICANCE OF THE STUDY

This study hopes to help guide the clinicians in Malaysian ICU in providing their patients with nutrition especially in settings where indirect calorimetry is not always available.

Despite indirect calorimetry is the gold standard for determination of energy requirement, it is not widely available for clinicians in Malaysian ICU. By using best predictive equations suited to the patient, we can aim for more accurate energy requirement. More accurate energy requirement determination will reduce patient mortality and morbidity rate, and length of stay in ICU by improving the effectiveness of nutritional therapy.

1.11 LIMITATIONS OF THE STUDY

The study sample was limited to patients admitted to intensive care unit of Sultan Ahmad Shah Medical Center. This study was confined to intubated patient, ventilated with GE Carescape R860 with indirect calorimetry module installed. The time scope of the study is between November 2019 till August 2020. The subject of the study comprised patients age more than 18, ventilated with GE Carescape R860 and BMI $\leq$ 35. The population of patients was 49.

1.12 DEFINITIONS OF TERMS

1.12.1 Critically ill

Patients who are in severe respiratory, cardiovascular or neurological derangement, usually in combination, where the derangement is reflected in abnormal physiological observations.

1.12.2 Resting energy expenditure

Resting energy expenditure is body metabolism during a time period of steady resting conditions that are defined by a combination of assumptions of physiological

homeostasis and biological equilibrium. REE includes activities needed to sustain life, such as respiration, circulation, and body temperature.

1.12.3 Indirect calorimetry

A technique used to measure energy expenditure in critically ill patients which are mechanically ventilated, by measuring gaseous O^2 consumption and CO^2 production and using Weir's equation. Multiple conditions have to be fulfilled in order to ensure the energy measured is a resting energy expenditure.

1.12.4 Predictive equations

Equations developed to estimate individuals resting energy expenditure by using static variables and/or dynamic variables such as temperature, minute ventilations.

1.13 CHAPTER SUMMARY

This chapter provides the reader with an insight into nutritional therapy as part of management in ICU. This chapter also provides information on the purpose of the study, the research objectives, the research questions and also the significance of the study. Finally, this chapter outlines the theoretical framework of this study.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

Accurate estimation of energy expenditure is important for nutritional therapy. The most widely available and literally costless method is by using predictive equations. Hundreds of predictive equations have been developed. Generally, they can be divided into three groups. First group, formulas based on static variables (e.g. height, weight, gender) only e.g. Harris-Benedict, Fusco, Mifflin. Second group, formulas in which dynamic variables (e.g. body temperature, tidal and minute volume) was taken into account, reflecting their metabolism state e.g. Penn State, Swinamer, Faisy. Third group, formulas that adapt patient's pathology (e.g. burn, trauma) and type of patient (e.g. obesity). Examples of this include Ireton-Jones (Spapen et al., 2014).

2.2 DIFFERENCES OF REE BETWEEN INDIVIDUAL

Each individual has different percentage of visceral, muscle and fat tissues. As each tissue use different amount of energy, this leads to error in REE predicted. Different gender will have different composition of tissues types. Person with the same gender, height and weight as well will have variable composition of tissues (Wang, Heshka, Heymsfield, Shen & Gallagher, 2005). Increasing BMI is shown to reduce physician's accuracy in estimating requirement (De Waele & Honore, 2016). Even if bodies composition is known, genetic factor will play a role as different individual have different metabolism rate.

Trauma and disease will cause hypermetabolism. Trauma can increase EE up to twice the REE due to the hypermetabolism that occurs. Disease such as

hyperthyroidism will greatly increase REE. The metabolic response to stress include sequential changes in energy expenditure, stress hyperglycemia, changes in body composition, and psychological and behavioral problems (Preiser et al., 2015) . Taking these factors when predicting REE also cannot be simply done as we need to take into account their severity and time lapse. Hypermetabolism cause by trauma usually will peak between week 1 and 2 and begin to wean to about half.

All these factors influencing REE is not reflected by every predictive equation. And thus, reducing their accuracies. Individual optimization of nutritional therapy will be difficult(Oshima et al., 2016).

2.3 REE IN DIFFERENT PHASES OF ILLNESSES

Critical illness has different phases, usually described as ‘ebb’ and ‘flow’ phase. The ‘ebb’ phase includes hyperacute early phase of hemodynamic instability during which patient admitted to ICU. The ‘flow’ phase meanwhile follows the period after that with metabolic instability and catabolism and later period of anabolism. The acute phase can be divided into two periods: the early period, the ‘ebb’ phase and the late period, the ‘flow’ phase. ASPEN further divide the acute phase into early acute and late acute (Singer et al., 2019). The early acute phase is defined as day 1 to day 2 while the late acute phase is defined as day 3 to day 7.

2.4 REE IN ELDERLY

Aging cause physiological changes in the body. There will be decline at a rate of 1-2% per decade after the second decade of life for. Resting energy expenditure (Wang et al., 2005). This could be account due to decline in. Both the mass and cellular fraction of tissues and organs. The fat free mass particularly declines as people get older. The

changes occur despite body weight remain unchanged. The applicability and accuracy of commonly used REE equations among have been investigated before. For example, study done among octogenarian Swedish man found out that Mifflin-St. Jeor is the most accurate equation (Karlsson et al., 2017).

2.5 REE IN CRITICALLY ILL

A severely ill patients undergoes dynamic changes during its course of illness. The changes are the consequences of prolonged bed rest, atrophy of the metabolically active lean tissue, stress and effect of medications e.g. inotropes, sedatives, neuromuscular blocking agent (Finnerty, Mabvuure, Kozar & Herndon, 2013). Even therapies such as mechanical ventilation, renal replacement therapies and liver support therapies can modify the resting energy expenditure. Due to these dynamic changes throughout patient treatment in ICU, IC measurement is recommended to be repeated to define energy target.

2.6 REE IN PATIENTS WITH CHRONIC CONDITION

Chronic conditions and their treatments can alter lean body mass and the level of physical activity, both of this will in turn alter the resting energy expenditure (Oshima et al., 2016). Respiratory diseases like COPD and cystic fibrosis will increased respiratory effort and enhanced the level of activity. Metabolic diseases such as thyroid and adrenal gland can change the level of metabolism by altering the hormonal activity. Muscle diseases can reduce the REE by disuse or atrophy of the muscles. Presence of seizure can increase the muscle activity and hence the REE. Anorexia and malnutrition affect the REE by reducing the lean body mass.

In view of the broad chronic condition patients can present with in ICU, IC is recommended to confirm the REE for optimal nutrition therapy. The energy needs are challenging to be estimated with.

2.7 REE IN WOMEN

Women have different body composition compared to men. They have less muscle mass and more fat tissues percentage. This differences in body compartment can reduce the metabolic activity and so the REE. Women also are more predispose to obesity compared to men. Depending on the menstrual cycle also, the metabolic activity will differ (Mauvais-jarvis, 2015). Due to these reasons, the accuracy of predictive equation is affected by the gender of its subject.

2.8 ACCURACY OF PREDICTIVE EQUATIONS

All the factors influencing metabolic activity, necessitates the usage of IC for accurate measurement of REE. However, as explained before, IC is rarely routinely used in the medical institution around the world. Estimating the REE using predictive equation is an alternative for clinical practice. Unfortunately, multiple studies have shown these predictive equations to be variable in their reliability.

Table 1.1 Studies done on predictive equation accuracy

Authors	Population	Design	Result
Neelemaat et al., 2012	Malnourished older patient n = 194	Observational 23 predictive equations evaluated	Best equation have accuracy of 40% All equations under predict the measured REE
Weijs et al., 2018	Obese adult of US and Dutch n = 239	Retrospective analysis 27 predictive equations evaluated	Best equation have accuracy of 79%, only for US population
Campbell et al., 2005	Critically ill, underweight male n = 42	Retrospective analysis 4 predictive equations evaluated	Best equation have accuracy of 42%
Kross et al., 2012	Critically ill n = 927	Retrospective analysis 5 predictive equations evaluated	Best equation have accuracy of 31% Mostly underestimate
Lee et al., 2012	Healthy policemen n=28	Observational 12 predictive equations evaluated	Best equation have accuracy of 35.7%
Kruizenga et al., 2016	General hospital patient n=513	Observational 15 predictive equations evaluated	Best equation have accuracy of 49%
Zusman et al., 2018	Critically ill n = 1440	Retrospective analysis 8 predictive equations evaluated	Best equation have accuracy of 50%

Systematic literature review has been conducted to assess the accuracy of predictive equations for mechanically ventilated, critically ill patients. From 18 studies included out of 160 variation of predictive equations, 38% of equations underestimated and 12% equations overestimated energy expenditure by more than 10%. At an individual patient level, predictive equations underestimated and

overestimated energy expenditure in 13–90% and 0–88% of patients (Tatucu-babet, Hons, Ridley & Tierney, 2015).

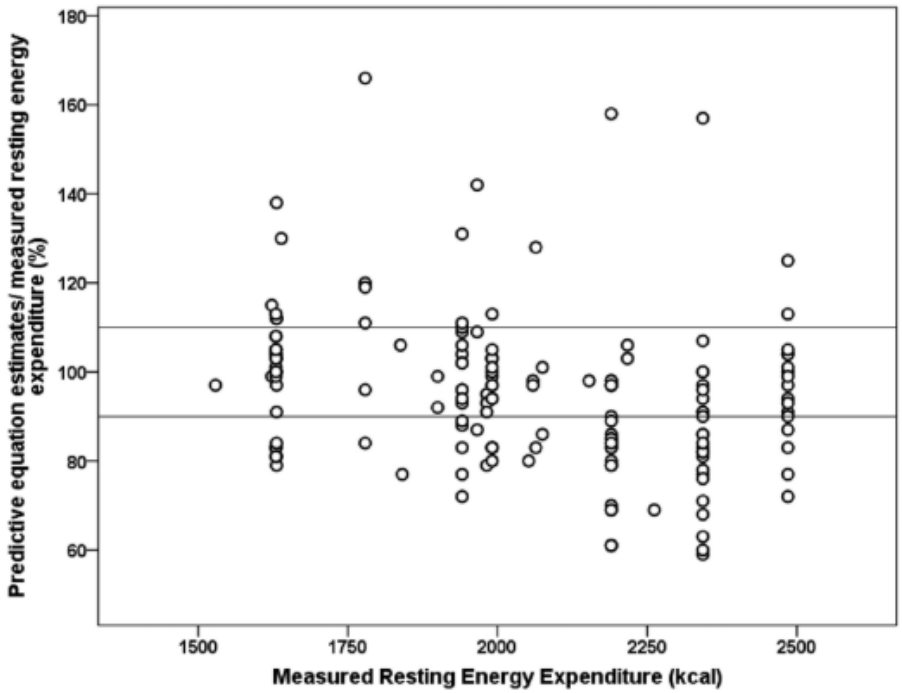

Figure 2.1 Degree of under prescription and over prescription of energy needs among all reviewed predictive equations

(N = 160) based on mean values of predicted and measured resting energy expenditure.

2.9 INDIRECT CALORIMETRY AS THE GOLD STANDARD

Indirect calorimetry (IC) remain the gold standard in measuring REE. With it, we are able to individualize the prescription of energy despite genetic variability, stages of trauma and composition of tissues(Schoeller, 2007). If adequate test stability can be achieved, IC measurements of only 15 minutes duration can successfully predict energy requirements with less than a 4% error in critically ill patients (McClave, Martindale & Kiraly, 2013).

Despite the IC is non-invasive, highly accurate to measure REE, due to cost factor and technical limitation, it is still not widely used in ICUs. Predictive equations

still hold its place, more so in Malaysian public hospitals setting where cost is commonly a limiting factor.

2.10 TECHNICAL CONCEPTS OF INDIRECT CALORIMETRY

Energy expenditure is calculated using IC by measuring the inspired and expired gas exchange. Heat production is closely correlated with O^2 consumption and CO^2 production according to type of energy substrate. To measure the resting energy expenditure, subject must be in resting state that is free of psychological and physical stress, in a thermally neutral environment, in a fasting state. In practical, REE reflects the patient energy needs (Oshima et al., 2016).

IC requires the measurement if inspired and expired O^2 and CO^2 concentrations and volumes. Energy expenditure are then calculated using Weir's equation (Schlein & Coulter, 2014):

Metabolic rate (kcal per day) = 1440 (3.94 VO^2 + 1.11 VCO^2)

For a mechanically ventilated patient, the gas sampling is obtained via sampling line from the endotracheal tube and measured either using breath-by-breath analysis or mixing chamber. Air leaks can alter the accuracy of the measurement and must be avoided (Oshima et al., 2016).

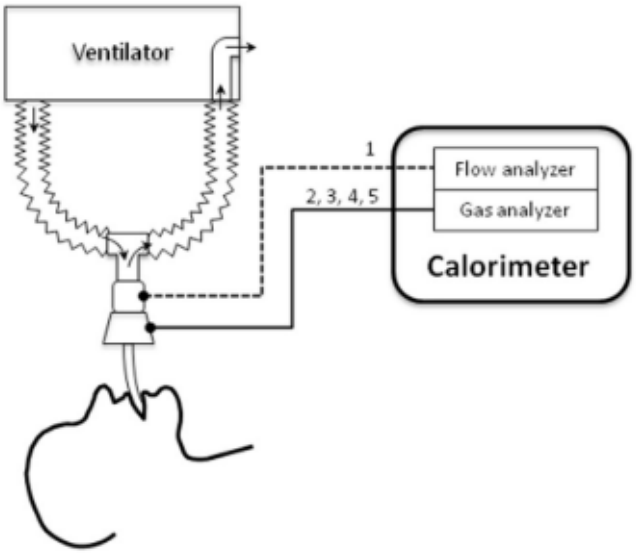

Figure 2.2 Schematic diagram showing the connection of calorimeter to a mechanically ventilated patient

2.11 PRACTICAL CONDITION TO USE INDIRECT CALORIMETRY

2.11.1 Patients

The most important condition is for air leak in the respiratory circuit not to be present. This includes patients with air leaking chest drainage and mechanically ventilated patients with high pressure settings. Any measurement in unstable patient is less useful as it will not represent their true metabolic characteristics. Examples include agitated patients and patient with seizures. This is because the measurement will include also the energy expenditure for body movement and therefore not represent the true REE. Patient must be in calm and resting conditions (Lambell., 2020).

2.11.2 Treatments

Mechanical ventilation with FiO^2 >60%is likely to produce inaccurate measurements because of the Haldane transformation. Special considerations must be given also to patients on organ support that supply O^2 to blood or CO^2 removal, and therapy that

alter acid-base homeostasis such e.g. renal replacement therapy. Other than that, liver support therapies also require special consideration (Schlein et al., 2014).

2.12 GUIDELINES AND RECOMMENDATIONS

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) (Singer et al., 2019) in 2019 recommends indirect calorimetry to be used to determine energy requirements when available, or in the absence of it, predictive equation or simplistic weight based equation 25-30kcal/kg/day be used (McClave et al., 2016).

The Asia-Pacific and Middle East Working Group on nutrition in ICU in 2017 has recommended indirect calorimetry as gold standard and to be used when available. Weight based predictive equations can be used as alternative (Sioson et al., 2018).

Current practice as recommended by Malaysia Society of Intensive Care and Ministry of Health, published in August 2012 suggest a target energy intake of 25 kcal/kg/day and at least 1.2-1.5 g/kg/day of protein. For obese patients, use 120% of ideal body weight (IBW) or (Actual Body Weight - IBW) X 0.25 + IBW. For underweight patients, actual body weight is use. Energy intake should be adjusted according to the severity and type of illness. No guidelines given for the adjustment (Malaysian Society of Intensive Care, 2012).

2.13 CHAPTER SUMMARY

This chapter provides with an in-depth information regarding factors that influence the resting energy expenditure in a critically ill patients and technical working aspect of indirect calorimetry. Predictive equations are a valid alternative to IC but not as

reliable as IC. Despite that, it is still recommended to be used where IC is not available.

CHAPTER THREE

METHODOLOGY

3.1 INTRODUCTION

This chapter gives an outline of the research methodology used in the study. It provides detailed information on the research design, inclusion and exclusion criteria, and sample size calculation. Furthermore, this chapter also describes in detail the conduct of the study including the data collection method. Finally, this chapter provides an explanation of the statistical analysis used for this study.

3.2 RESEARCH DESIGN

A cross-sectional study to compare validity of several predictive equations used to predict REE in critically ill adult patients by using indirect calorimetry (IC) as the reference.

The study conducted involved all patients who is admitted to General Intensive Care Unit of Sultan Ahmad Shah Medical Center. Approval from IIUM research ethics committee was obtained before start of research.

3.3 RECRUITMENT AND CONSENT

All patients admitted to the General ICU were screened for inclusion criteria

Inclusion criteria are:

a. 18 years old and older
b. Stay in ICU more than 48 hours
c. Mechanically ventilated
d. BMI ≤ 35

Information leaflets was given and informed consent was taken from patient or their legally approved representative if patient unable to give consent on day 1 of ICU admission. A copy of informed consent form was given to patient's legally approved representative.

3.4 WITHDRAWAL OF PARTICIPANTS FROM STUDY

Participants can withdraw at any time for any reason from studies.

This includes but not limited to

a. Subject's (or guardian's) request
b. Adverse event, at investigator's request
c. A concomitant therapy which could interfere with the results of the study
d. Technical limitation

3.5 EXCLUSION CRITERIA

Technical limitation that exclude the REE measurement by indirect calorimetry

a. $FiO^2 > 0.6$
b. PEEP >12
c. Leaks in the sampling (e.g pneumothorax, tracheostomy or chest tube)

3.6 DATA COLLECTION

The following data will be collected from patient throughout investigation

a. Gender
b. Age

c. Weight - measured using calibrated ICU bed. Calibration will be done before patient transferred to bed.

d. IBW, Ideal body weight

Female: (ht-152.4)0.91 + 45.5

Male : (ht-152.4)0.91 + 50

e. Adj BW, Adjusted body weight

IBW + 0.4(BW-IBW)

f. Height - measured using standard measuring tape.

g. BMI, Body mass index

(weight in kg)/(height in meter)^2

h. Daily maximal temperature – measured using infrared thermometer at forehead

i. Minute ventilation

j. APACHE II

k. SOFA

l. mNUTRIC score

m. Admission category, medical or surgical

3.7 RESEARCH TOOLS

Research tools involve in this study includes:

a. GE Carescape R860

b. Spirometry module E-SCAIOV

c. Water D-Fend

d. Spirometry kit

e. Endotracheal tube

Figure 3.1 GE Carescape R860

Figure 3.2 Spirometry module E-SCAIOV

Figure 3.3 Water trap D-Fend

Figure 3.4 Spirometry kit

Figure 3.5 Endotracheal tube

3.8 STUDY PROTOCOL

Eighteen predictive equations to estimate energy expenditure were tested simultaneously.

Table 3.1 Predictive equations evaluated

Name	Equation (kcal)
Standard weight based	25 x wt
Harris Benedict (Harris & Benedict, 1918)	Males: 13.75*(ht)+5*(wt)-6.8*(age)+66 Females: 1.8*(ht)+9.6*(wt)-4.7*(age)+655
Harris Benedict with adjusted weight (Flancbaum, Choban, Sambucco, Verducci & Burge, 1999)	Males: [66.5+(13.8*AdjBW)+5*(ht)-(6.8*age)]*1.5 Females: [655+(9.6*AdjBW)+1.8*(ht)−4.7*age)]*1.5
Penn State (Frankenfield, Smith & Cooney, 2004)	0.96*(MSJ) + 167*(Tmax)+31*(Ve)-6212
Penn State modified (Frankenfield et al., 2004)	0.71*(MSJ) + 85*(Tmax)+64*(Ve)-3085

Ireton-Jones (Ireton-Jones, Turner, Liepa & Baxter, 1992)	1784+5*(wt)-11*(age)+244*(male) +239*(trauma)+804*(burns)
Ireton–Jones for obesity (Mifflin et al., 1990)	Men:606+9*(wt)−12*(age)+400(if ventilated)+1400 Women: wt−12*(age)+400(if ventilated)+1444
Faisy (Faisy, Guerot, Diehl, Labrouuse & Fagon, 2003)	8*(wt)+ 14*(ht)+42*(Ve)+94*(T)-4834
Mifflin-St. Jeor (Mifflin et al., 1990)	Males: 10*(wt)+6.25*(ht)-5*(age)+5 Females: 10*(wt)+6.25*(ht)-5*(age)-161
Jolliet (Jolliet et al., 1998)	Males, age > 60: 25*(wt) Males, age < 60: 30*(wt) Females, age > 60, 20*(wt) Females, age <60, 25*(wt)
Liu (Liu et al., 2001)	Men: 13.88*(wt)+4.16*(ht)-3.43*(age) Women: 13.88*(wt)+4.16*(ht)-3.43*(age)-112.40
Owen	Men: 879+10.2*(wt)

(Boullata, Williams, Cottrell, Hudson & Campher, 2007)	Women: 795+7.2*(wt)
WHO (Report of a joint FAO/WHO/UNU Expert Consultation)	18-30y:13.3*(wt)+334*(ht)/100+35 30-60y:8.7*(wt)–25*(ht)/100+865 >60 y: 9.2*(wt)+637*(ht)/100–302
Schofield (Schofield, 1985)	15.057*(wt)+692.2
Schofield with height (Schofield, 1985)	15.057*(wt)+0.1*(ht)+705.4
IMNA (Trumbo, Schlicker, Yates & Poos, 2002)	204–4*(age)+4.505*(ht)+11.69*(wt)
Henry (Henry, 2005)	14.4*(wt)+3.13*(ht)+113

Henry with height (Henry, 2005)	16.0*(wt) + 545

ht- height (cm), wt – weight (kg), Tmax – daily maximal temperature (C), Ve – minute ventilation (ml)

Patients were mechanically ventilated by GE Carescape R860 where indirect calorimetry measurement was done. Spirometry module E-SCAIOV, water trap D-Fend and spirometry kit is installed. No water was ensured to be present inside the water trap D-Fend and spirometry kit.

Resting energy expenditure (REE) was measured by indirect calorimetry for every patient. Maximum of three measurement done for each day.

a. At least 5 hours after the previous meal, or under continuous feeding
b. Minimum 2 hour after alcohol and nicotine ingestion, 4 hours after caffeine ingestion
c. After 30 minutes of resting period
d. Resting in supine position and free of physical stress
e. Awake and free of psychological stress
f. Comfortable environmental condition
g. Ensure average RQ within physiological range 0.67-1.3
h. (VCO^2 -VO^2) less or equal to 5%
i. Average energy expenditure that displays is the calculated calorie requirement for the patient in a day
j. Patient received 1.2 to 1.5g/kg/day of protein (according to ideal body weight).

If protein inside feeding is inadequate, myotein will be added to servings. Eligible patients were followed in ICU for a maximum of 7 days or until death or discharge from ICU. All patients detail and data collected will recorded in a case report form along with the informed consent form and compiled in a file stored in locked cabinet.

3.9 SAMPLE SIZE

Previous study by Kross et al (Kross et al., 2012) showed that predictive equations have the highest accuracy of 31% in a sample of 927 patients. Expecting the accuracy of 31% with precision of 10% using α of 0.05, the sample size, n is 100 taking into account 20% drop rate.

$$n = \frac{\left(\frac{Z\alpha}{2}\right)^2 p(1-p)}{d^2} \text{ x } 100/80$$

p : expected outcome

d : precision required

z : value for confidence

α : confidence level

n : sample size

3.10 INFORMED CONSENT AND INFORMATION SHEET

An information sheet was provided to patient together with the informed consent. This was to provide general information regarding the study to the patients. The informed

consent was obtained from patients or Legally Accepted Representative (LAR) for their agreement to be enrolled into the study.

This study does not present any direct benefit to the participants. However, the study does provide a better understanding of the disease/condition studied. The study procedures are all routine procedures for the disease/condition studied. There is thus minimal risk for the subjects.

Patients were allowed to withdraw from the study during the study period if they feel so. The withdrawal form was also provided together in the information sheet and the informed consent.

Patient's data were kept confidential and only accessible by the investigators and team members only. It will be stored by primary investigator for 10 years for further review or analysis if needed. It will be destroyed after 10 years provided no review and further analysis needed.

No specific details of any specific subject will be mentioned in any publication other than in form of figures and analysis This will maintain patient's confidentiality and protect patient's personal information.

3.11 STATISTICAL ANALYSIS

All data analysis was analyzed using Statistical Package for the Social Sciences (SPSS) software version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive analysis was used to describe the data of sociodemographic characteristics and clinical assessment. Descriptive data are reported as mean ± SD (standard deviation) and/or median (interquartile range) for skewed distributions or as frequency and percentage.

Comparison of mean resting energy expenditure measured by indirect calorimetry (REE-IC) and resting energy expenditure predicted by equation (REE-PE) was performed using paired *t* test.

Intraclass correlation coefficient (ICC) test was performed to assess the correlation between the predicted REE by each of the predictive equations and the measured REE by indirect calorimetry in critically ill adult patients. ICC based on single rater measurement, absolute agreement, two-way random effects model was performed to assess the agreement between REE-PE and REE-IC. A narrower 95% CIs for ICC expressed greater precision. The following range of ICC value was considered: ICC less than 0.20, no agreement; 0.20 less than or equal to ICC less than 0.40, poor agreement; 0.40 less than or equal to ICC less than 0.60, moderate agreement; 0.60 less than or equal to ICC less than 0.80, good agreement; and ICC greater than or equal to 0.80, very good agreement .

The rate of accuracy was defined as the percentage of patients whose REE-PE was within ± 10% of the REE-IC. Underestimation was defined as less than 10% of REE-IC, and overestimation was defined as greater than 10% of REE-IC.

3.12 CHAPTER SUMMARY

This chapter provides the readers with in-depth information of the methodological aspect of the study including the research design, sample size calculation, data collection process, data storage and also the methods used to analyze the study data.

CHAPTER FOUR

RESULTS AND ANALYSIS

4.1 INTRODUCTION

This chapter describes in detail the results and analysis of this study. The time scope of the study is between November 2019 till August 2020. The subject of the study comprised patients age more than 18, ventilated with GE Carescape R860. A total of 66 patients were recruited according to inclusion criteria. However, 4 patients were dropped from the study as 4 required different ventilator for treatment purpose and 13 was dropped due to technical limitations. Eventually, 49 patients were enrolled into this study. There were no deviations from the study protocol and data from all 49 participants were analyzed. In this study, 33 patients were assessed during the early acute phase. 36 patients were assessed during the late acute phase. They were followed until extubated from ventilator or death. The numbers are higher in late acute phase as some patients were recruited during late acute phase only, as no measurement done during early acute phase.

Due to COVID-19 pandemic starting March 2020, patient recruitment had to be withheld for 2 months before resumption of data collection. A new standard operating procedure was applied in ICU. Patients need to be cleared from COVID-19 by PCR testing which can take up to 2 days before proceeding with measurement if no PCR testing done before admission to ICU.

Descriptive statistics were used to summarize the data set across all patients within the two groups. Numerical data were checked for normality using distribution curve and histogram. If the data showed normal distribution, it was presented as mean with standard deviation (SD). If the data did not show normal distribution, then it was

presented as median with interquartile range (IQR). Categorical data was presented as frequency and percentage.

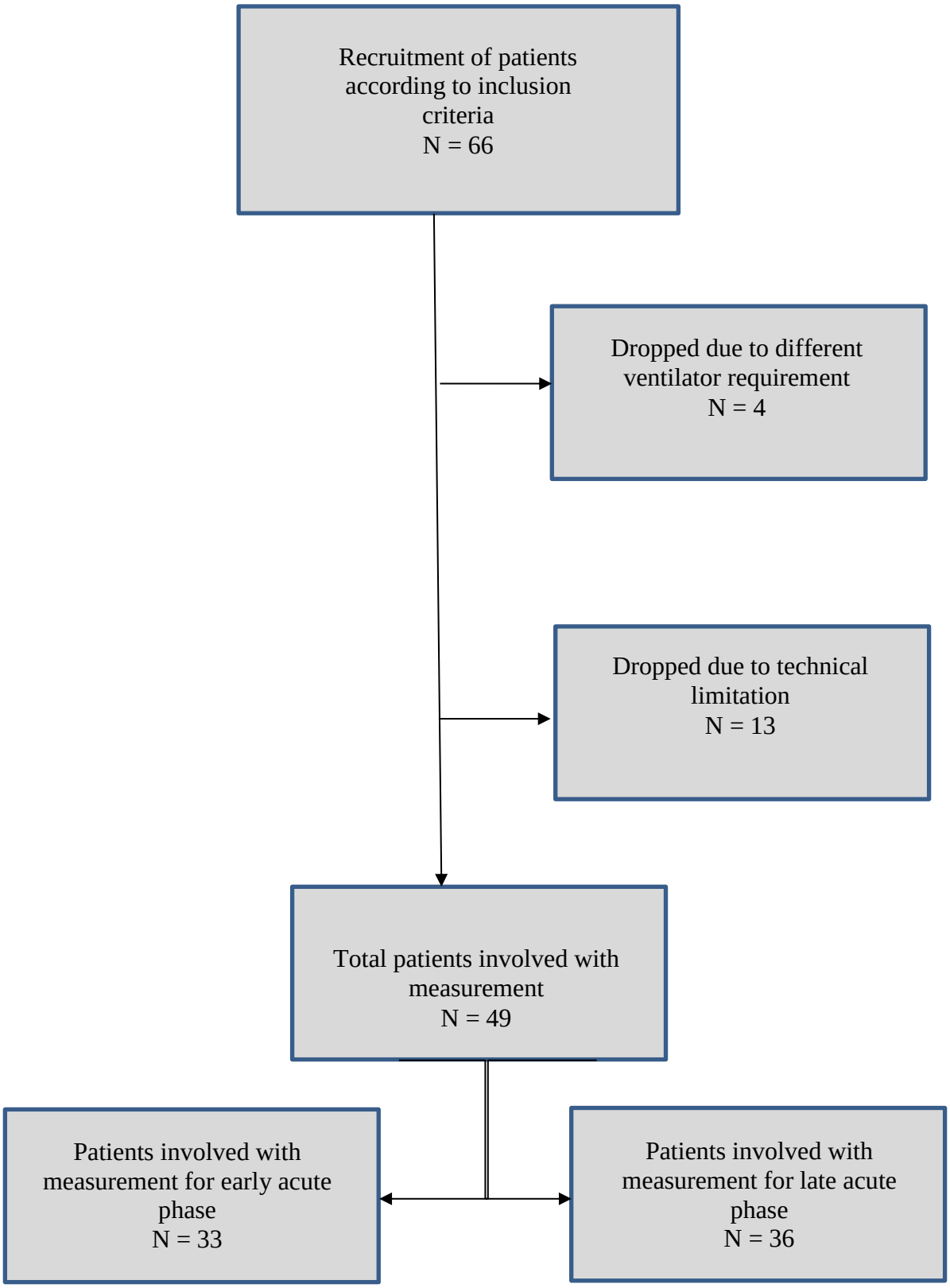

Figure 4.1 CONSORT flow diagram for patients recruitment and measurement

4.2 BACKGROUND CHARACTERISTICS OF PATIENTS AT BASELINE

Table 4.1 Demographic and clinical characteristics of patients

Variable	Early cute (n=33)	Late acute (n=36)
Age	62.72 ± 12.44	61.36 ± 11.82
Age, year old		
<60	9 (27.3)	13 (36.1)
≥ 60	24 (72.7)	23 (63.89)
Gender		
Male	21 (63.6)	23 (63.9)
Female	12 (36.4)	13 (36.1)
Ethnicity		
Malay	30 (90.9)	34 (94.4)
Chinese	0 (0)	0 (0)
Indian	2 (6.1)	1 (2.8)
Others	1 (3.0)	1 (2.8)
Admission category		
Medical	23 (69.7)	23 (63.9)
Surgical	10 (30.3)	13(36.1)
Weight, kg	66.82 ± 14.05	66.50 ± 16.38
Height, cm	160.94 ± 8.69	161.47 ± 8.09
BMI, kg/m^2	25.39 ± 5.02	25.11 ± 4.86
BMI group		
≥ 30	6 (18.2)	7 (19.44(
<30	27 (81.8)	29 (80.56)
m-NUTRIC	4.42 ± 2.17	4.56 ± 2.13
<5	22 (66.70)	25 (69.44)
≥ 5	11 (33.3)	11 (30.56)
SOFA Score	7.24 ± 3.10	7.67 ±3.33
APACHE II score	17.52 ± 6.60	18.42 ± 6.52
Hospital days of IC measurement	2 (1.5 - 2)	1 (1 - 4)

BMI = body mass index, IC = indirect calorimetry, m-NUTRIC = modified Nutrition Risk in Critically Ill score, SOFA = Sequential Organ Failure Assessment, APACHE II = Acute Physiology and Chronic Health Evaluation II .

Continuous variables are presented as mean ± SD or median (Q1–Q3). Categorical variables are presented as number of subjects, n (%).

The baseline characteristics including age, gender, race, admission category, height, weight, body mass index, m-NUTRIC score, Sequential Organ Failure Assessment Score, Acute Physiology and Chronic Health Evaluation II score were shown. Majority of the patients recruited were more than 60 years old, 62.72 ± 12.44 years old during early acute and 61.36 ± 11.82 years old during late acute phase. Majority are male; 63.6% during early acute and 63.9% during late acute phase. Almost all are Malay ethnicity; 90.9% during early acute and 94.4% during late acute. Medical admission were twice more than surgical admission; 69.7% during early acute and 63.9% during late acute phase. Patients were normal to overweight BMI; 25.39 ± 5.02kg/m^2 during early acute and 25.11 ± 4.86kg/m^2 during late acute. They presented majority with low risk m-NUTRIC score; 66.7% in early acute and 69.4% in late acute phase, with SOFA score of 7.24 (±3.10) during early acute phase and 7.67 (±3.33) during late acute.

4.3 COMPARISON BETWEEN REE IC AND REE PREDICTIVE EQUATIONS

Table 2.2 Proportions of accuracy, underestimation and overestimation of the REE-PEs compared with REE-IC during early acute phase

		Early acute (n=33), %		
No	Predictive Equations	Accuracy[a]	Underestimation[b]	Overestimation[c]
1	Standard	12.12	6.06	81.81
2	Harris-Benedict	9.09	15.15	75.75
3	Harris-Benedict with AdjBW	3.03	3.03	93.93
4	Mifflin-St. Jeor	33.33	15.15	51.51
5	Penn State	33.33	3.03	63.63
6	Penn State modified	27.27	3.03	69.7
7	Ireton-Jones	9.09	3.03	87.88
8	Ireton-Jones for obesity	21.21	0.00	78.78
9	Faisy	3.03	3.03	93.93
10	Jolliet	15.15	6.06	78.78
11	Owen	21.21	9.09	69.68
12	WHO	30.3	6.06	63.63
13	Liu	24.24	15.15	60.6
14	Schofield	6.06	3.03	90.9
15	Schofield with height	3.03	3.03	93.93
16	IMNA	21.21	6.06	72.72
17	Henry	21.21	6.06	72.72
18	Henry with height	15.15	6.06	78.78

AdjBW = adjusted body weight, WHO = World Health organization, IMNA = Institute of Medicine of National Academies

[a]Percentage of mean energy REE-PE from day 1 to day 2 within 90% to 110% of mean REE-IC from day 1 to day 2
[b]Percentage of mean energy REE-PE from day 1 to day 2 < 90% of mean REE-IC from day 1 to day 2
[c]Percentage of mean energy REE-PE from day 1 to day 2 >110% of mean REE-IC from day 1 to day 2

Table 4.3 Proportions of accuracy, underestimation and overestimation of the REE-PEs compared with REE-IC during late acute phase

No	Predictive Equations	Late acute (n=36), %		
		Accuracy[a]	Underestimation[b]	Overestimation[c]
1	Standard	11.11	8.33	80.56
2	Harris-Benedict	19.44	11.11	69.44
3	Harris-Benedict with AdjBW	2.77	0.00	97.22
4	Mifflin-St. Jeor	33.33	16.67	50.00
5	Penn State	25.00	5.56	69.44
6	Penn State modified	22.22	5.56	72.22
7	Ireton-Jones	11.11	0.00	88.89
8	Ireton-Jones for obesity	22.22	2.78	75.00
9	Faisy	5.55	2.78	91.67
10	Jolliet	16.67	5.56	77.78
11	Owen	19.44	11.11	69.44
12	WHO	36.11	11.11	52.78
13	Liu	33.33	13.89	52.78
14	Schofield	8.33	2.78	88.89
15	Schofield with height	5.56	2.78	91.67
16	IMNA	30.57	5.56	63.89
17	Henry	19.44	5.56	75.00
18	Henry with height	19.44	5.56	75.00

AdjBW = adjusted body weight, WHO = World Health organization, IMNA = Institute of Medicine of National Academies.

[a]Percentage of mean energy REE-PE from day 1 to day 2 within 90% to 110% of mean REE-IC from day 3 to day 7

[b]Percentage of mean energy REE-PE from day 1 to day 2 < 90% of mean REE-IC from day 3 to day 7
[c]Percentage of mean energy REE-PE from day 1 to day 2 >110% of mean REE-IC from day 3 to day 7

Predictive equation for resting energy expenditure with highest accuracy were Mifflin-St. Jeor (33.33%) and Penn State (33.33%) for early acute phase. While for late acute phase, WHO (36.11) had the highest accuracy, followed by Mifflin-St. Jeor (33.33%) and Liu (33.33%).

All predictive equations have ≥50% overestimation during early acute and late acute phase. Harris-Benedict with adjusted body weight (93.93%), Faisy (93.93%) and Schofield with height (93.93%) have the highest overestimation in early acute phase. While in late acute phase, Harris-Benedict with adjusted body weight (97.22%) were the highest.

All predictive equations have <20% underestimation during early acute and late acute phase. Harris-Benedict (15.15%), Mifflin-St. Jeor (15.15%) and Liu (15.15%) have the highest underestimation during early acute phase. While in late acute phase, Mifflin-St. Jeor (16.67%) were the highest.

Only Mifflin-St. Jeor consistently predicted REE-IC more than 30% accuracy across both early acute and late acute phase. None of the predictive equations had level of accuracy more than 50% across both phases.

4.4 COMPARISON OF MEANS BETWEEN REE-IC AND REE PREDICTIVE EQUATIONS

Table 4.4 Comparison of means between REE-IC and REE PEs and their p value

		Early acute (n=33), %			Late acute (n=36), %		
No	Predictive Equations	n	kcal/d[a]	p value	n	kcal/d[b]	p value
	IC	33	1176±332	-	36	1222±321	-
1	Standard	33	1652±321	<0.001	36	1671±366	<0.001
2	Harris-Benedict	33	1594±334	<0/001	36	1640±312	<0.001
3	Harris-Benedict with AdjBW	33	1889±251	<0.001	36	1930±252	<0.001
4	Mifflin-St. Jeor	33	1301±209	0.051	36	1320±226	0.057
5	Penn State	33	1417±237	0.001	36	1431±239	<0.001
6	Penn State modified	33	1460±222	<0.001	36	1485±236	<0.001
7	Ireton-Jones	33	1673±153	<0.001	36	1684±155	<0.001
8	Ireton-Jones for obesity	33	1942±569	<0.001	36	1898±547	<0.001
9	Faisy	33	1728±235	<0.001	36	1740±242	<0.001
10	Jolliet	33	1669±449	<0.001	36	1700±487	<0.001
11	Owen	33	1479±207	<0.001	36	1479±229	<0.001
12	WHO	33	1353±156	0.007	36	1370±155	0.004
13	Liu	33	1343±241	0.018	36	1357±264	0.016
14	Schofield	33	1698±213	<0.001	36	1707±235	<0.001
15	Schofield with height	33	1727±212	<0.001	36	1735±235	<0.001
16	IMNA	33	1458±193	<0.001	36	1475±205	<0.001
17	Henry	33	1578±218	<0.001	36	1590±238	<0.001
18	Henry with height	33	1614±225	<0.001	36	1624±249	<0.001

AdjBW = adjusted body weight, WHO = World Health organization, IMNA = Institute of Medicine of National Academies.

Significant different between average REE-IC and REE-PE when $p < 0.05$.
[a]Mean energy ± SD from day 1 to day 2
[b]Mean energy ± SD from day 3 to day 7

Paired *t* test was performed to detect significant difference between REE-IC during early acute phase and REE-IC during late acute phase by using 25 patients that were measured in both early acute and late acute phase. The result is no significant difference between REE-IC during early acute and late acute phase with p=0.122. The mean REE-IC for all critically ill patients were 1176±332 kcal/day during early acute phase and 1222±321 kcal/day during late acute phase

Paired *t* test was performed to detect significant difference between REE-PEs and REE-IC during early acute phase and between REE-PEs and REE-IC during late acute phase. All REE-PEs showed significant difference with REE-IC during both early acute and late acute phase with the exception of Mifflin-St. Jeor (MSJ) equation. Only MSJ are not significantly different with REE-IC across both phases. The mean REE for MSJ are 1301±209 kcal/day during early acute phase with no significance difference with REE-IC (p=0.051). For late acute phase, the mean REE for MSJ are 1320±226 kcal/day with no significance difference with REE-IC (p=0.057). The mean difference for MSJ between early acute and late acute phase is 9.4kcal and are not significant (p=0.842)

4.5 CORRELATION ANALYSIS

Table 4.5 Correlation analysis by intraclass correlation coefficient for REE-IC and REE-Pes.

			Early acute		Late acute
No	Predictive Equations	n[a]	ICC (95% CI)	n[b]	ICC (95% CI)
1	Standard	33	-0.045 (-0.196 - 0.169)	36	0.181 (-0.090 - 0.457)
2	Harris-Benedict	33	-0.073 (-0.255 - 0.173)	36	0.073 (-0.104 - 0.295)
3	Harris-Benedict with AdjBW	33	0.047 (-0.057 - 0.209)	36	0.131 (-0.059 - 0.419)
4	Mifflin-St. Jeor	33	0.168 (-0.149 - 0.466)	36	0.409 (0.111 - 0.643)
5	Penn State	33	0.152 (-0.112 - 0.428)	36	0.482 (0.043 - 0.737)
6	Penn State modified	33	0.069 (-0.149 - 0.327)	36	0.390 (-0.048 - 0.680)
7	Ireton-Jones	33	0.108 (-0.079 - 0.355)	36	0.148 (-0.086- 0.429)
8	Ireton-Jones for obesity	33	0.117 (-0.087 - 0.367)	36	0.116 (-0.088 - 0.358)
9	Faisy	33	0.013 (-0.088 - 0.169)	36	0.200 (-0.087 - 0.526)
10	Jolliet	33	0.065 (-0.120 - 0.300)	36	0.227 (-0.083 - 0.514)
11	Owen	33	0.051 (-0.148 - 0.298)	36	0.192 (-0.077 - 0.458)
12	WHO	33	0.071 (-0.200 - 0.362)	36	0.297 (-0.002 - 0.557)
13	Liu	33	0.096 (-0.197 - 0.395)	36	0.372 (0.071 - 0.616)
14	Schofield	33	-0.015 (-0.120 - 0.146)	36	0.126 (-0.085 - 0.382)
15	Schofield with height	33	-0.013 (-0.110 - 0.139)	36	0.118 (-0.082 - 0.369)
16	IMNA	33	0.062 (-0.149 - 0.316)	36	0.283 (-0.051 - 0.564)
17	Henry	33	-0.012 (-0.158 - 0.193)	36	0.184 (-0.090 - 0.462)
18	Henry with height	33	-0.020 (-0.154 - 0.175)	36	0.162 (-0.091 - 0.433)

AdjBW = adjusted body weight, WHO = World Health organization, IMNA = Institute of Medicine of National Academies

[a]n = number of patients during day 1 to day 2
[b]n = number of patients during day 3 to day 7

Intraclass Correlation Coefficient (ICC) based on single rater measurement, absolute agreement, two-way random effects model was performed to assess the agreement between REE-PE and REE-IC. A narrower 95% CIs for ICC expressed greater precision. The following range of ICC value was considered: ICC less than 0.20, no agreement; 0.20 less than or equal to ICC less than 0.40, poor agreement; 0.40 less than or equal to ICC less than 0.60, moderate agreement; 0.60 less than or equal to ICC less than 0.80, good agreement; and ICC greater than or equal to 0.80, very good agreement

During early acute phase, no agreement exist between REE-IC and REE-PEs as all ICC of the predictive equation is <0.2.

For late acute phase, no good or very good agreement exist between REE-IC and REE-PEs as none of the ICC is >0.6. Moderate agreement however were shown by Mifflin-St. Jeor (ICC,0.409; 95% CI, 0.111 - 0.643) and Penn State (ICC,0.482; 95% CI, 0.043 - 0.737) during these phase with Penn State equation showing the highest agreement. Poor agreement were also shown by Penn State modified (ICC,0.390; 95% CI, -0.048 - 0.680), Faisy (ICC, 0.200; 95% CI, -0.087 - 0.526), Jolliet (ICC, 0.227; 95% CI, -0.083 - 0.514), WHO (ICC, 0.297; 95% CI, -0.002 - 0.557), Liu (ICC, 0.372; 95% CI, 0.071 - 0.616) and IMNA (ICC, 0.283; 95% CI, -0.051 - 0.564). The rest of REE-PEs however showed poor agreement with REE-IC.

During the early acute phase, Faisy have the narrowest limits of agreement and Mifflin-St. Jeor with the widest limit of agreement. During the late acute phase, Harris-Benedict have the narrowest limits of agreement and Penn State have widest limits of agreement.

4.6 CHAPTER SUMMARY

This chapter elaborates in detail the results of the primary and secondary outcomes of this study. Findings have been summarized into tables and figures.

CHAPTER FIVE

DISCUSSIONS

5.1 INTRODUCTION

This chapter, by using the data from the study, will interpret and elaborate on the significant findings of these study and conclude the answers to the research questions of the study. Results will be analyzed in comparison of the previous research on predictive equations. Any limitations of the study will be discussed and improvement suggested for future trials.

To the best of our knowledge, this is the first study done to determine the best predictive equation for resting energy expenditure among mechanically ventilated patients in Malaysian population, at different phases of illness using ASPEN definition (Singer et al., 2019). However, the results of these study cannot be extrapolated to Malaysia population as it was only involving single center tertiary hospital in Pahang.

Furthermore, due to the ongoing COVID-19 in Malaysia, patient recruitment was limited from March 2020 to June 2020. This is due to change in standard operating procedure in ICU to prevent an outbreak of COVID-19 in hospital.

The discussion in the chapter will attempt to answer the research questions:

a. Does early acute and late acute phase of illness have different best predictive equation?
b. Which predictive equations have the highest accuracy and agreement in critically ill patient?

5.2 ACCURACY AND AGREEMENT

As shown in results of these study, there is no significant difference in the resting energy expenditure of critically ill patients when measured using indirect calorimetry during early acute and late acute phase.

None of the predictive equations perform particularly well with no accuracy above 40% in both early acute and late acute phase. We also found that only a few REE-PEs have poor to moderate agreement during late acute phase while the rest have no agreement. Our study shown that Mifflin-St. Jeor have the highest accuracy in early acute phase but no agreement. While in the late acute phase, Mifflin-St. Jeor is the relatively best equation with high accuracy and agreement.

Mifflin-St Jeor is an equation with static variables that was developed from healthy adult population (Mifflin et al., 1990). It outperform REE-PEs that was developed for critically ill mechanically ventilated patient such as Faisy (Faisy et al., 2003) and Penn State (Frankenfield et al., 2004). This is despite Mifflin- St. Jeor using only static variables such as weight, height and age in its calculation while Faisy and Penn State also incorporates dynamic variables such as minute ventilation and temperature in its equation which may better reflect the state of metabolism of the body at different phase of illnesses. This might be explained by the mean age of the patient recruited > 60 years old (Spapen et al., 2014) which previous study by Weijs et al.m 2018 reported the same finding. Other equation with static variables such as standard, Harris-Benedict, Jolliet and WHO have poor accuracy and no to poor agreement. Previous study by Frankenfield et al., 2012 showed that REE-PEs with dynamic variables perform better compared to static variables in critically ill patients, contradicting the results of these study.

The large difference between REE-IC and REE-PEs may be explained by heterogeneity of ICU patients, inaccuracy of predictive equations or IC measurements. Patients might also have variable nutrition absorption, nutritional status and pharmacological treatment. Presence of oedema can alter the body composition of patient and accuracy of REE-PEs.

According to ASPEN (Lambell et al., 2020), target energy for early acute phase is ~70% for well nourished and moderately malnourished, and ~50% for severely malnourished. In view of this, accuracy of predictive equation during this period does not have high influence to the energy provided. In contrast to late acute phase where 70% estimated or 80-100% measured requirement need to be given.

5.3 OVERESTIMATION AND UDERESTIMATION

This study found that most of the REE-PEs tend to overestimate the REE. The rate of overestimation during both early acute and late acute range from 50 to 97%. The result is different compared to systematic review previously done by Tatucu et al (Tatucu-babet et al., 2015) where only 13% of equation overestimate the REE. Only up to 15% of equation from both early acute and late acute phase underestimate the REE-IC.

Mifflin-St. Jeor have the lowest mean difference between REE-IC and REE-PE with 125kcal during early acute phase and 98kcal during late early phase. It is the best performing equation. Ireton-Jones for obesity have the highest mean difference between REE-IC and REE-PE during early acute phase with 766kcal while Harris-Benedict with adjust body weight have the highest mean difference at 708kcal during late early phase.

5.4 STRENGTH

The main strength of this study was that measurement via indirect calorimetry and calculation of predictive equation were done at different period of acute phase of critical illness. This allowed variable, often unpredictable metabolic changes of critically ill patients to be considered. This study however found no significant difference between resting energy expenditure of early acute and late acute phase. Furthermore, 18 predictive equations were evaluated their accuracy and agreement.

5.5 LIMITATIONS

Several limitations exist and need to be considered when the result of this study is interpreted. First, the generalizability of the results is limited because this is a single-center study. Second, accurate anthropometry data such as height and weight is dependent on the nurses which change every day and in charge of different patient, making measurement consistency less optimal. Third, the different modes of ventilation and settings may alter the VO^2 and VCO^2, hence affecting the accuracy of IC. Fourth, the accuracy of REE-IC and REE-PEs is affected by variable nutrition absorption, nutritional status and pharmacological treatment. Fifth, the sample size targeted was not achieved. The findings from this study might only be applicable to Malay population as majority of the patient (>90%) was Malay ethnic.

5.6 CONCLUSION

The relatively most accurate predictive equation for critically ill patients during late acute phase was Mifflin-St. Jeor and none during early acute phase. The incorporation of dynamic variables does not improve predictive equation as expected.

When IC not feasible, REE-PE with highest agreement and accuracy should be used.

No suitable REE-PE can be applied across different phases of critical illness.

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APPENDIX A: INFORMED CONSENT

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT FORM

(for adult subjects and interventional studies)

Title of study: Determination of the best predictive equations for resting energy expenditure among mechanically ventilated patients in an intensive care unit

Name of investigator and institution: Dr. Khairul Anam Bin Mansor, International Islamic University of Malaysia

Introduction:

You are invited to participate in a research study because you have been mechanically ventilated that requires ICU admission. The details of the research trial are described in this document. It is important that you understand why the research is being done and what it will involve. Please take your time to read through and consider this information carefully before you decide if you are willing to participate. Ask the study staff if anything is unclear or if you like more information. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form. To participate in this study, you may be required to provide your doctor with information on your health history; you may harm yourself if you are not truthful with the information provided.

Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may also refuse to answer any questions you do not want to answer. If you volunteer to be in this study, you may withdraw from it at any time. If you withdraw, any data collected from you up to your withdrawal will still be used for the study. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

1. **What is the purpose of the study?**

The purpose of this study is to determine the best predictive equations for resting energy expenditure among mechanically ventilated patients.

Malnutrition is common in critically ill patients and have been associated with poor clinical outcome. When prescribing enteral or parenteral feeding, measured or predicted resting energy expenditure is the major parameter used. The most widely available estimation of energy expenditure is by using predictive equations. Predictive equation have been shown to be limited by severity of illness and variabilities of bodies composition, rate of metabolism, gender and age. Despite this, degrees of accuracy up to 80% can still be obtained. This however is based on studies done on western population, not Asian.

A total of 102 subjects like you from International Islamic University of Malaysia Medical Center will be invited into this study. The whole study will last about 12 months and your participation will be about three days

2. **What kind of intervention will I receive?**

If you agree to participate in the study, the doctor may need to collect data from you during your mechanically ventilated period in ICU.

3. **What will happen if I decide to take part?**

a) You will be mechanically ventilated in ICU as per your management.

b) You will be connected to a ventilator that can measure resting energy expenditure

c) Every morning, measurement of resting energy expenditure will be taken via the ventilator by indirect calorimetry

d) Measurement will be done for 3 consecutive days

e) Data like gender, age, weight, height, daily maximal temperature and minute ventilation will also be recorded

4. **When will I receive the trial product and how should it be kept?**

You will receive no trial product as no intervention done.

5. **What are my responsibilities when taking part in this study?**

It is important that you answer all of the questions asked by the study staff honestly and completely. If your condition or circumstances change during the study, you must tell the study doctor.

It is very important that your study doctor be informed very rapidly of any eventual changes to your health during your participation in the study. For your own security, it is important that you follow your study doctor's instructions throughout the entire duration of the study.

6. **What kind of treatment will I receive after my participation in the trial?**

No study product will be given to you at the end of your participation in the study as no intervention needed for this study. Whether you complete the study or withdraw early, your doctor will discuss the best alternatives for your future treatment with you.

7. **What are the potential risks and side effects of being in this study?**

No potential risks and side effects involve in this study as no intervention done. Only data are collected throughout your stay in ICU.

8. **What are the benefits of being in this study?**

There may or may not be any benefits to you. Information obtained from this study will help improve the treatment or management of other participants with the same disease or condition.

9. What if I am injured during this study?

If you are injured as a result of being in this study, you should contact your study doctor You do not lose any of your legal rights to seek compensation by signing this form.

10. **What are my alternatives if I do not participate in this study?**

You do not have to participate in this study to get treatment for your disease or condition. No data will be collected from you.

11. **Who is funding the research?**

This study is sponsored by International Islamic University of Malaysia Medical Center. All drugs and procedures that are not required by the study but are part of your routine medical care will have to be paid by you or your insurance.

12. **Can the research or my participation be terminated early?**

The study doctor or the sponsor may due to concerns for your safety, stop the study or your participation at any time. If the study is stopped early for any reason you will be informed and arrangements made for your future care. You may be asked to attend a final follow-up visit.

13. **Will my medical information be kept private?**

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, your identity will not be revealed without your expressed consent. Individuals involved in this study and in your medical care, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities may inspect and copy your medical records, where appropriate and necessary.

Data from the study will be archived and may be transmitted outside the country for the purpose of analysis, but your identity will not be revealed at any time.

With your permission your family doctor will be informed of your participation in the study.

14. **Who should I call if I have questions?**

If you have any questions about the study or if you think you have a study related injury and you want information about treatment, please contact the study doctor, Dr Khairul Anam Bin Mansor at telephone number 0133217894.

If you have any questions about your rights as a participant in this study, please contact: The Secretary, Medical Research & Ethics Committee, Ministry of Health Malaysia, at telephone number 03-2287 4032.

INFORMED CONSENT FORM

Title of Study: Determination of the best predictive equations for resting energy expenditure among mechanically ventilated patients in an intensive care unit

By signing below I confirm the following:

- I have been given oral and written information for the above study and have read and understood the information given.
- I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my participation is voluntary and I can at anytime free withdraw from the study without giving a reason and this will in no way affect my future treatment. I am not taking part in any other research study at this time. I understand the risks and benefits, and I freely give my informed consent to participate under the conditions stated. I understand that I must follow the study doctor's (investigator's) instructions related to my participation in the study.
- I understand that study staff, qualified monitors and auditors, the sponsor or its affiliates, and governmental or regulatory authorities, have direct access to my medical record in order to make sure that the study is conducted correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL
- I will receive a copy of this subject information/informed consent form signed and dated to bring home.
- I agree/disagree* for my family doctor to be informed of my participation in this study. *(*delete which is not applicable)*

Subject:

Signature:	I/C number:
Name:	Date:

Investigator conducting informed consent:

Signature:	I/C number:
Name:	Date:

Impartial witness:

Signature:	I/C number:
Name:	Date:

APPENDIX B: CASE REPORT FORM

Version : 1
Date : 20/2/20

Case Report Form

Group ☐ Indirect Calorimetry ☐ Standard Care Patient ID: ☐☐☐

Date of hospital admission _____ Date of hospital discharge _____
Date of ICU admission _____ Date of ICU discharge _____

Patient Baseline Characteristics

Date of Birth ☐☐☐☐☐☐ Age (Years): _____

Gender ☐ Male ☐ Female

Ethnicity ☐ Malay ☐ Chinese ☐ Indian ☐ Others: Please specify _____

Actual Body weight (kg): _____ Height (cm): _____ Body Mass Index (kg/m^2) _____

Admission Category ☐ Medical ☐ Surgical
Admission Diagnosis: Co-morbidities:

	Cardiovascular	
	Respiratory	
	Gastrointestinal	
	Endocrine/Metabolic	
	Neurological	
	Infective	
	Renal	
	Liver	
	Trauma	
	Maternity/Gynecological	
	Malignancy	

	Diabetes Mellitus
	Hypertension
	Chronic CV Disease
	Chronic Kidney Disease
	Chronic Liver Disease
	Chronic Lung Disease
	Malignancy
	Hematologic
	Immunosuppression/HIV
	Other Disabling Conditions

APACHE II SCORING SYSTEM

A – Acute Physiology Score (APS)

Parameters	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal Temperature[◦C]	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
MAP [mmHg]	≥ 160	130-59	110-129		70-109		50-69		≤ 49
Heart rate [min^{-1}]	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
Ventilation rate [min^{-1}]*	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
Oxygenation [mmHg] $FiO_2 \geq 0.5$ A-aDO_2 $FiO_2<0.5$ PaO_2	≥ 500	350-499	200-349		<200 >70	61-70		55-60	<55
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
Serum Sodium [mmol/l]	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
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
Serum Creatinine [µmol/l]	≥ 310	177-309	133-176		53-132		< 52		
Hematocrit [%]	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WBC [t/mm³]	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		<1
HCO_3^- [mmol/l]	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
Glascow Coma Scale	Score = 15 minutes actual Glascow-Coma-scale								

*non-ventilated or ventilated

B – Age Points

Age	Points
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

APACHE II SCORE Sum of	
A + B + C	
APS Score	A
Age points	B
Chronic points	C
Total Score	

C – Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immune-commpromised
Assign points as follows

a)	Non-operative or emergency postoperative patients points	5
b)	Elective postoperative patients points	5

Definition of severe organic and immune deficiency

Liver	-	Biopsy proven cirrhosis and documented portal hypertension
	-	Episodes of past upper GI bleeding at attributed to portal hypertension
	-	Prior episodes of hepatic failure/ encephalopathy/ hepatic coma
Cardiovascular	-	Chronic heart failure NYHA IV
Respiratory	-	Chronic restrictive, obstructive or vascular disease
	-	Documented chronic hypoxia, hypercapnia, secondary polycythemia
	-	Severe pulmonary hypertension (>40mmHg)
	-	Respirator dependency
Kidney	-	Receiving chronic dialysis
Immuno-Compromised	-	Therapeutic immune suppression
	-	Chemotherapy, radiation
	-	Long-term or recent high dose steroids
	-	Leukemia, lymphoma, AIDS

SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE (SOFA)

Reference: Vincent JL. et al. Intensive care Medicine (1996) 22:707-701, Vincent JL. et al. Crit Care Med, Vol 26(11). No 1998, 1793-1800

SOFA Score	0	1	2	3	4
Respiration PaO_2/F_1O2	>400	301-400	201-300	101-200 with respiratory support	0-100 with respiratory support
Hematological Platelets ($x10^3/mm^3$)	>150	101-150	51-100	21-50	0-20
Hepatic Bilirubin (mmol/L)	0-19	20-23	33-101	102-204	>204
Cardiovascular Hypotension*	MAP > 70mmHg	MAP 0-70mmHg	Dopamine 1-5µg/kg/min* Or Dobutamine (any dose)*	Dopamine 6-15µg/kg/min* Or Adrenaline ≤ 0.1µg/kg/min* Or Noradrenaline ≤ 0.1µg/kg/min*	Dopamine >15µg/kg/min* Or Adrenaline > 0.1µg/kg/min* Or Noradrenaline > 0.1µg/kg/min*
Central Nervous System Glasgow Coma Score	15	13-14	10-12	6-9	3-5
Renal Creatinine (µmol/L) Or Urine Output (ml/day)	0-110	110-170	171-299	300-440 Or 200-499	>440 Or <200
TOTAL					

*Adrenergic agents administered for at least 1 hour

NAME OF PATIENT: ..... TOTAL SOFA SCORE: .....

NUTRIC SCORE COMORBIDITIES

NUTRIC Score variables

Parameters	Range	Points
Age	< 50	0
	50 - <75	1
	≥ 75	2
APACHE II	< 15	0
	15 - < 20	1
	20-28	2
	≥ 28	3
SOFA	< 6	0
	6 - < 10	1
	≥ 10	2
Number of Co-morbidities	0 – 1	0
	≥ 2	1
Days from hospital to ICU admission	0 - < 1	0
	≥ 1	1

The NUTRIC Score is designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy. For co-morbidities score, refer to page 2.

NUTRIC Score scoring system:

Sum of Points	Category	Explanation
5-9	High Score	• Associated with worse clinical outcomes (mortality, ventilation). • These patients are the most likely to benefit from aggressive nutrition therapy
0-4	Low Score	• These patients have low malnutrition risk

Determining the best predictive equation for resting energy expenditure among mechanically ventilated critically ill patients in a Malaysian tertiary hospital

Parameters	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day11	Day12
Date												
Position (supine/left lateral/right lateral/prone)												
Feeding intermittent/continuous												
Time of last feeding												
Renal replacement therapy HD/CVVH												
Time of last HD												
Tidal volume (mls)												
Minute ventilation (L/min)												
PEEP (cmH2O)												
FIO2												
Respiratory rate (breath/min)												
Maximum body temperature (C)												
Sedation												
Rikers score												
VO2 variation (%)												
VCO2 variation (%)												
Respiratory quotient												
Time of IC measurement												
IC measurement (kcal/day)												
Standard weight based (kcal/day)												
Harris-Benedict (kcal/day)												
Harris-Benedict w adj weight (kcal/day)												
Mifflin-St. Jeor (kcal/day)												
Penn-State (kcal/day)												
Penn-State modified (kcal/day)												
Ireton-Jones (kcal/day)												
Ireton-Jones for obesity (kcal/day)												
Faisy (kcal/day)												
Jolliet (kcal/day)												
Fusco (kcal/day)												
Owen (kcal/day)												
FAO/WHO/UNU (kcal/day)												
Liu (kcal/day)												
Ismail (kcal/day)												
Schofield (kcal/day)												
Schofield w height (kcal/day)												
IMNA (kcal/day)												
Henry (kcal/day)												
Henry w height (kcal/day)												

APPENDIX C: KULIYYAH RESEARCH COMMITTEE APPROVAL

KULLIYYAH OF MEDICINE

Our Ref. : IIUM/305/20/4/1/7
Date : 18th February 2020

Assoc. Prof. Dato' Dr. Mohd Basri B. Mat Nor
Department of Anaesthesiology
Kulliyyah of Medicine
International Islamic University Malaysia

Dear Assoc. Prof. Dato' Dr. Mohd Basri B. Mat Nor السلام عليكم ورحمة الله وبركاته

APPROVAL OF DISSERTION PROPOSAL
Title: Determination of the Best Predictive Equations for Resting Energy Expenditure among Mechanically Ventilated Patients in an Intensive Care Unit
Research ID: 418

I am pleased to inform you that the above research proposal has been reviewed again on **18th February 2020** and has been **approved**. Any changes to the proposal must be reported back to the committee. Significant changes to the protocol may require resubmission.

Thank you. والسلام

LEADING THE WAY

PROF. DR. AZMI MD NOR
Chairman, Kulliyyah of Medicine Research Committee (KRC), *and*
Dean, Kulliyyah of Medicine

cc Head of Research,
Kulliyyah of Medicine

Garden of Knowledge and Virtue
Kulliyyah of Medicine, International Islamic University Malaysia, Bandar Indera Mahkota,25200 Kuantan, Pahang Darul Makmur, Malaysia.
Tel: +609 571 6400 Fax: +609 571 6770 E-mail : medic@iiumedic.edu.my Website: http://www.iiumedic.edu.my

APPENDIX D: IREC APPROVAL

الجامعة الإسلامية العالمية ماليزيا
INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA
يونيورسيتي إسلام انتارابغسا ملسيا
(Company No 101067-P)

RESEARCH MANAGEMENT CENTRE

Our Ref. : IIUM/504/14/11/2/ IREC 2020-042
Date : 9 Mar 2020

Assoc. Prof. Dato' Dr. Mohd Basri Mat Nor (Principal Investigator)
Kulliyyah of Medicine
25200 Kuantan, Pahang

Dear Assoc. Prof. Dato' Dr.,

The IIUM Research Ethics Committee (IREC) has reviewed your study protocol as mentioned below:-

ID NO.	:	**IREC 2020-042**
TITLE	:	**Determination of the best predictive equations for resting energy expenditure among mechanically ventilated patients in an intensive care unit**
REGISTRATION DATE	:	**24 February 2020**
STUDENT	:	**Dr. Khairul Anam Bin Mansor (Postgraduate Student)**
NAME OF SITE	:	**General ICU, IIUM Medical Center**
SAMPLE SIZE	:	**30**
ETHICAL EXPIRY DATE	:	**6 Mar 2021**

The IIUM Research Ethics Committee (IREC) operates in accordance to the Declaration of Helsinki, International Conference of Harmonization Good Clinical Practice Guidelines (ICH-GCP), Malaysia Good Clinical Practice Guidelines and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

The following documents have been received and reviewed to the above study:-

1. Study Proposal/Protocol: Version 1, dated 20 Feb 2020
2. Informed Consent Form (ICF) :-
   i. Information Sheet (English) – Version 1, dated 20 Feb 2020
   ii. Consent Form (English) – Version 1, dated 20 Feb 2020
3. Case Report Form – Version 1, dated 20 Feb 2020
4. Approval Letter from Kulliyyah of Medicine, IIUM
5. Principal Investigator's CV

QUALITY SYSTEM
SIRIM
CERTIFIED TO MS ISO 9001:2008
Registration No. AR 3492

Garden of Knowledge and Virtue

Office Address: Research Management Centre, Level 1, Block 2, Office of The Campus Director, IIUM Kuantan Campus, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan Pahang.
Tel: +609 570 4220 / 4223 **Fax:** +609 571 6741 **E-mail:** rmcKuantan@iium.edu.my **Website:** www.iium.edu.my/research

Decision by IIUM Research Ethics Committee (IREC):

(√) Approved
( ) Disapproved

Date of Approval: 6 Mar 2020

The investigator(s) are required to:

a) submit the 'Continuing Review Form' 30 days before **EXPIRY DATE** to renew Ethical Approval.
b) notify IREC of any change in protocol and obtaining further ethical approval as appropriate.
c) report any adverse incident during the course of a study to IREC even if the incident is not directly related to the study.
d) report to the IREC within 72 hours for all internal SAEs (occurring in IIUM PI site).
e) report in a prompt manner if the information impacts the continued ethical acceptability of the trial for external SAEs (occurring in participants at other sites).
f) provide information of minor protocol deviation in Progress Report or End Report whichever necessary.
g) report any major protocol deviation occurs within 5 working days.
h) submit Progress Report Form before the end of six (6) month given by IREC.
i) complete and submit the End of Project Report Form to the IREC Secretariat's Office.
j) All records and data subjects are **CONFIDENTIAL** and used only for the purposes of this study and all issues and procedures on data confidentiality must be observed.

Thank you.

Yours sincerely,

PROF. DR. NASSER MUHAMMAD AMJAD
Chairman,
IIUM Research Ethics Committee (IREC)

Copy : File –IREC 2020-042

DISCLAIMER: The approval letter only covers the ethical aspect of your study only. Any other permission/approval to use any facilities, data or human resource should fall under applicant's responsibility.