# THE IMPACT OF INDIRECT CALORIMETRY GUIDED MEDICAL FEEDING PROTOCOL ON CLINICAL OUTCOMES IN MECHANICALLY VENTILATED CRITICALLY ILL PATIENTS

BY

SAMIULLAH SAEED

A thesis submitted in fulfilment of the requirement for the degree of Master in Medical Sciences

Kulliyyah of Medicine
International Islamic University Malaysia

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# ABSTRACT

The international guidelines recommend using indirect calorimetry (IC) to measure energy requirements in critically ill patients than the currently used weight-based equations. This single-centre randomised controlled trial aimed to assess the effects of IC-guided nutrition versus the standard nutrition care on clinical outcomes in critically ill patients. Sixty mechanically ventilated patients that were expected to stay in an intensive care unit (ICU) for more than three days were randomised into a group in which energy needs were determined by the IC (IC group) and a group prescribed with 25kcal/kg/day reflecting the standard care (SC group). The primary outcome was the ICU length of stay (LOS). Secondary outcomes included the change in quadriceps muscle layer thickness (QMLT, ultrasound) during the first ten days of ICU admission, hospital LOS, duration of mechanical ventilation, ICU mortality and 28-day-in hospital mortality. The mean energy requirement was similar in both groups (1216±222 vs 1304±211, $p = 0.124$). The IC group received 85.63% of the IC-based energy goal, whereas the SC group received 76.83% of the formula based energy goal ($p = 0.002$), although the mean energy intakes were similar in both groups. The protein intake goal was better met in the IC group (89.58 %) than in the SC group (77.66 %) ($p = 0.007$). Both groups had a median of 8.0 days ICU-LOS ($p = 0.424$). QMLT was decreased progressively in both IC and SC groups by 21.9% vs 25.3% from day 1 to day 10 ($p < 0.001$), respectively. There were no significant differences observed in the muscle mass changes and other secondary clinical outcomes between the groups. IC-guided nutrition groups received more energy and protein, with higher feeding adequacy than the standard care group. However, there was no difference in term of clinical outcome and muscle layer thickness between both groups. This study is registered with Clinicaltrials.gov, identifier no. NCT04479254.

# خلاصة البحث


توصي الدلائل الإرشادية الدولية باستخدام مقياس السعرات الحرارية غير المباشر (IC) لقياس متطلبات الطاقة لدى المرضى ذوي الحالات الحرجة أكثر من المعادلات القائمة على الوزن المستخدمة حاليًا. هدفت هذه التجربة المعشاة ذات الشواهد وحيدة المركز إلى تقييم آثار التغذية الموجهة بال IC مقابل الرعاية التغذوية القياسية على النتائج السريرية في المرضى المصابين بأمراض خطيرة.تم اختيار ستين مريضًا خضعوا للتهوية الميكانيكية ومن المتوقع أن يبقوا في وحدة العناية المركزة (ICU) لأكثر من 3 أيام بشكل عشوائي في مجموعة تم فيها تحديد احتياجات الطاقة بواسطة IC (مجموعة IC)ومجموعة موصوفة بـ 25 كيلو كالوري / كجم / يوم تعكس الرعاية القياسية (مجموعة SC). كانت النتيجة الأولية هي(ICU) مدة الإقامة في وحدة العناية المركزة (LOS) .تضمنت النتائج الثانوية التغيير في سماكة الطبقة العضلية للعضلات الرباعية الرؤوس (QMLT ، الموجات فوق الصوتية) خلال الأيام العشرة الأولى من دخول وحدة العناية المركزة ، وفقدان المناعة في المستشفى ، ومدة التهوية الميكانيكية ، ومعدل الوفيات في وحدة العناية المركزة ، ووفيات المستشفى لمدة 28 يومًا. كان متوسط متطلباتا الطاقة متشابهًا في كلا المجموعتين (1216 ± 222 مقابل 1304 ± 211 ، 0.124 = $p$). تلقت مجموعة IC 85.63 % من هدف الطاقة المستند إلى IC ، بينما تلقت مجموعة SC 76.83 % من هدف الطاقة المعتمد على الصيغة = $p$) 0.002)، على الرغم من أن متوسط مآخذ الطاقة كانت متشابهة فيكلا المجموعتين. تم تحقيق هدف تناول البروتين بشكل أفضل في مجموعة( 89.58 ٪ ) IC من مجموعة (77.66 %) SC = $p$) 0.007) .كان لدى كلتا المجموعتين متوسط 8.0 أيام ICU-LOS (0.424 = $p$). انخفض QMLTبشكل تدريجي في كل من مجموعات IC و SC بنسبة 21.9 % مقابل 25.3 % من يوم 1 إلى يوم 10 ($p<0.001$)، على التوالي. ومع ذلك ، لم تكن هناك فروق ذات دلالة إحصائية لوحظت في تغيرات كتلة العضلات والنتائج السريرية الثانوية الأخرى بين المجموعات. تلقت مجموعة التغذية الموجهة بال IC مزيدًا من الطاقة والبروتين مع قدرة تغذية أعلى من مجموعة الرعاية القياسية. ومع ذلك لم يكن هناك فرق من حيث النتيجة السريرية وسمك طبقة العضلات بين المجموعتين. هذه الدراسة مسجلة في Clinicaltrials.gov ، رقم NCT04479254 .

# APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Medical Sciences.

…………………………………..
Mohammad Basri Mat Nor
Supervisor

…………………………………..
Azrina MD Ralib
Co-Supervisor

…………………………………..
Edre Mohammad Aidid
Co-Supervisor

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Medical Sciences.

…………………………………..
Nizamuddin Ismail
Internal Examiner

…………………………………..
Azarina Binti Azaham
External Examiner

This thesis was submitted to the Department of Anaesthesiology and Intensive Care and is accepted as a fulfilment of the requirement for the degree of Master of Medical Sciences.

…………………………………..
Abdul Hadi Bin Mohamad
Head, Department of
Anaesthesiology and Intensive Care

This thesis was submitted to the Kulliyyah of Medicine and is accepted as a fulfilment of the requirement for the degree of Master of Medical Sciences.

…………………………………..
Jamalludin Bin Ab. Rahman
Dean, Kulliyyah of Medicine

# DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Samiullah Saeed

Signature ........................................................... Date .........................................

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*To My Parents*

*The Source of Kindness and Strength*

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| | |
|---|---|
| APACHE II | Acute Physiology & Chronic Health Evaluation |
| BMI | Body Mass Index |
| EI | Energy Intake |
| EN | Enteral Nutrition |
| ER | Energy Requirement |
| GICU | General Intensive Care Unit |
| GRV | Gastric Residual Volume |
| IBW | Ideal Body Weight |
| IC | Indirect Calorimetry |
| ICU | Intensive Care Unit |
| Kcal | Kilocalories |
| LOS | Length of Stay |
| MV | Mechanical Ventilation |
| NUTRIC | Nutrition Risk in Critically ill |
| PEs | Predictive Equations |
| PI | Protein Intake |
| PN | Parenteral Nutrition |
| PR | Protein Requirement |
| QMLT | Quadriceps Muscle Layer Thickness |
| RCT | Randomized Control Trial |
| REE | Resting Energy Expenditure |
| RQ | Respiratory Quotient |
| SOFA | Sequential Organ Failure Assessment |

| | |
|---|---|
| SPN | Supplemental Parenteral Nutrition |
| VAP | Ventilator Associated Pneumonia |

# CHAPTER ONE

# INTRODUCTION

## 1.1 BACKGROUND OF THE STUDY

Malnutrition is a global issue in intensive care units (ICU) (Lew et al., 2018; Oshima et al., 2019). Critically ill patients are at significant risk for malnutrition. The prevalence of malnutrition at hospital admission is estimated to be as high as 30%-50% (Yeh et al., 2015), where this prevalence is higher among ICU patients, which is approximately 40 to 80% (Article, 2011; Lew et al., 2017; Wang et al., 2017).

Several recent studies have shown that malnutrition in critical illness patients is significantly associated with poorer clinical outcomes, such as increased complications, hospital costs, and mortality (Investigations, 2011; Sioson et al., 2017; Yeh et al., 2015). Furthermore, hypercatabolism associated with critical illness may further increase the risk of adverse clinical outcomes among ICU patients who receive inadequate nutrition (Oshima et al., 2017; Delsoglio, Achamrah, Berger & Pichard, 2019 ).

The role of nutritional therapy in critical illness has been the focus of great interest in recent years, which is recognized as an essential component in the management of critically ill patients (De Waele et al., 2019; Lambell, Tatucu-Babet, Chapple, Gantner & Ridley, 2020). Adequate nutritional support plays an important role to improve outcomes associated with malnutrition in critically ill patients (Singer et al., 2019). However, critically ill patients generally receive insufficient feeding, with data reporting around 50-70% of energy and protein targets are received (Alberda et al., 2009; Nicolo, Heyland, Chittams, Sammarco & Compher, 2016). In addition, stress responses experienced during critical illness, and inadequate intake of healthy nutrients, stimulate several mechanisms that enhance prolonged catabolism. Therefore, adequate nutritional therapy is required for critically ill patients to help them meet their metabolic needs (Singer & Singer, 2016; Wang et al., 2017). Nutritional adequacy, is often defined as the percentage of nutritional intake over the nutritional requirement. It is calculated as the amount of energy and protein received divided by the amount prescribed and multiply by 100 (Cahill, Dhaliwal, Day, Jiang & Heyland, 2010). The percentage to define feeding adequacy is varied. Energy administration below 70% of the defined target is defined as underfeeding (Heyland et al., 2015), while overfeeding is usually defined as receiving >110% of prescribed energy (Lichtenberg, Guay-Berry, Pipitone, Bondy & Rotello, 2010; Singer et al., 2019). Both underfeeding and overfeeding are associated with poor clinical outcome in critically ill patients (Cohen et al., 2016; Schlein & Coulter, 2014). Therefore, adequate nutritional support is essential to achieve favourable clinical outcomes during the management of critical illness (Ndahimana & Kim, 2018).

The provision of energy and protein is considered an integral part of adequate nutritional therapy (Ridley, Gantner & Pellegrino, 2015). However, critically ill patients' optimal amount of energy and protein to reduce morbidity and mortality is controversial. Some observational studies have found that underfeeding or caloric debt in critically ill patients is correlated with poor clinical outcomes (Alberda et al., 2009; Heyland, Cahill & Day, 2011; Nicolo et al., 2015; Wei, Day, Ouellette-Kuntz & Heyland, 2015). In contrast, other studies have suggested better short-term outcomes in patients receiving low caloric intake (Arabi et al., 2010; Krishnan et al., 2003).

In a meta-analysis of randomised controlled trials (RCTs) to compare the impact of initial underfeeding and full feeding in critically ill patients, there was no considerable difference between the underfeeding and full-feeding groups in overall mortality and other secondary clinical outcomes (Choi, Park & Park, 2015).

In another meta-analysis of RCTs, it was shown that an initial moderate intake of nutrients (33.3 to 66.6 % of target energy) compared to high energy might decrease mortality, and a higher intake of proteins combined with high energy (≥0.85 g / kg per day) may decrease infection rate. However, energy versus protein intake contribution to outcomes remains unknown (Tian et al., 2015). Moreover, the meta-analysis performed by Marik and Hooper (2016) found no difference in the risk of acquired infections, hospital mortality, ICU length of stay (LOS) or ventilator-free days between patients receiving intentional hypocaloric (< 50 per cent of energy expenditure) compared to usual caloric (70%-100% of EE) nutritional targets (Marik & Hooper, 2016).

However, It was proposed that 'trophic feeds and permissive underfeeding cannot be considered safe or indicated in older, higher risk ICU patients as it appears to increase mortality and negatively influence the long-term quality of life' (Ridley, Gantner & Pellegrino, 2015).

In addition, the findings of the study by Zusman et al. (2016) suggest that both underfeeding and overfeeding appear to be harmful to critically ill patients, such that achieving an Adcal/REE (the per cent of administered calories divided by resting energy expenditure) of 70 % had a survival advantage. An AdCal/REE of >70 % was associated with an increased LOS and length of ventilation. increasing protein intake was also related to reduced mortality. These findings revealed that the optimum way to define calorie targets requires a precise estimation, ideally performed using indirect calorimetry (Zusman et al., 2016).

As a result, the success of nutritional support depends on how well energy and protein needs are estimated and matched by prescribing and delivering the required nutrients. Therefore, determining energy requirements is vital as prescribed targets are used to guide nutrition delivery (Stapel, Weijs, Girbes & Oudemans-van Straaten, 2018; Tatucu-Babet, Ridley & Tierney, 2016). However, it is difficult to accurately determine energy needs in critically ill patients because the effects of illness, injury and stress on REE are often varied and unpredictable (De Waele et al., 2019; Singer & Singer, 2016).

In clinical practices, caloric requirements of critically ill patients can be calculated either by Predictive equations (PEs) or by indirect calorimetry (IC) measurements (De Waele et al., 2013; Wichansawakun, Meddings, Alberda, Robbins & Gramlich, 2014). PEs estimating EE are the most commonly used method due to their simplicity of use; however, these equations have been repeatedly proven inaccurate and unacceptable for clinical use compared to measured EE using IC ( Tatucu-Babet, Ridley & Tierney, 2016; De Waele, Honore & Spapen, 2016). Most importantly, these commonly used equations are not generally validated in those with higher nutritional risk and its inaccuracies increase in the extreme of weight (obese), elderly, most severely unwell and malnourished populations (Reeves & Capra, 2003; Tatucu-Babet, Ridley & Tierney, 2016) as well as can lead to underfeeding or overfeeding (Ladd, Skillman, Haemer & Mourani, 2018). Achieving energy balance as guided by IC measurements compared to PEs may lead to more appropriate nutrition intake as recent RCTs showed that higher mean intake of energy and protein was provided in the IC-directed protocol compared with controls whose nutrition therapy directed by PEs (Lange et al., 2017; Lev et al., 2011).

Therefore, to feed critically ill patients adequately, an accurate assessment of energy needs is needed (Gonzalez-granda, Schollenberger, Haap, Riessen & Bischoff, 2018; Oshima et al., 2019). To improve the accuracy of the variable energy requirements in ICU patients, both the European and North American guidelines suggest the use of IC to determine EE (McClave et al., 2016; Mehta et al., 2017; Picolo et al., 2016; Singer et al., 2019). However, these recommendations have been poorly implemented in practice (Lev, Cohen & Singer, 2010), and many ICU clinicians still use the simplistic weight-based formula (25-30 kcal/kg) to calculate EE when IC is not available. In contrast, IC is used in patients in whom altered EE is suspected or conventional nutritional support fails to respond (De Waele et al., 2019; Singer & Singer, 2016).

IC is currently the gold standard for measuring REE in critically ill patients as recommended by guidelines (Gonzalez-granda et al., 2018; Oshima et al., 2017; Sioson et al., 2018). IC measures REE by measuring the volume of O2 ($VO_2$) consumed and the volume of CO2 ($VCO_2$) produced (Das Gupta et al., 2017; Oshima et al., 2017; Stapel et al., 2018). Then, by using the Weir equation, REE is calculated as follows:

$$REE\ (kcal/day) = [(3.9 \times VO_2) + (1.1 \times VCO_2) - 61] \times 1440$$

It is hypothesized that nutrition therapy guided by IC may improve clinical outcomes in critically ill patients.

Meanwhile, muscle wasting is common in severe critical illness (Casaer, 2015). ICU-acquired weakness is a long-term consequence after critical illness, where it has been related to muscle atrophy and can be considered as one of the leading nutritional support challenges at the intensive care unit. Measuring muscle mass by image techniques has become a new area in research for the nutritional support field (Alfredo et al., 2017).

Critically ill patients exhibit a dramatic loss of lean body mass, particularly skeletal muscle, irrespective of adequate nutritional support. Muscle wasting is one of the many common problems that have to be dealt with by patients in ICU (Gruther et al., 2008).

From a nutritional perspective, one of the main challenges of providing nutritional support to critically ill patients are to stop or slow lean mass losses. Therefore, dietitians need to measure and evaluate muscle wasting during critical illness using a simple and accessible technique (Alfredo et al., 2017). Ultrasonography has been increasingly involved in the daily management of ICU patients over the past decade and has recently been suggested to measure muscle volume and architecture (Parry et al., 2015; Puthucheary et al., 2015). Thus, the ultrasound has become a commonly used non-invasive bedside tool to measure muscle thickness and quantify muscle mass wasting with remarkable accuracy and reliability (Pardo et al., 2018). The quadriceps muscle groups are generally regarded as the site to be imaged as it is commonly associated with muscle atrophy in various disease states and among critically ill patients. Thigh muscles also have excellent associations with measures of the whole body muscle mass in healthy populations. The quadriceps muscle is an accessible landmark in immobile patients and has well defined facial borders for identification during analysis. The quadriceps group may also have greater implications compared to other muscle groups in clinical and functional outcomes for patients, such as ICU-LOS and physical function at ICU discharge. The thickness of the quadriceps was chosen over the cross-section area (CSA) in this study because of the ease in measurement on the ultrasound screen. As, the structure of muscle begins to deteriorate, the thickness may be more readily identifiable in comparison to the CSA.

## 1.2 PROBLEM STATEMENT AND JUSTIFICATION OF THE STUDY

Despite the current therapeutic advances, malnutrition and the severity of critical illness are associated with high mortality rate and poor clinical outcome in intensive care units.

According to the Malaysian Registry of Intensive Care (MRIC) Report 2016, overall ICU and hospital mortality rates for MOH hospitals and university of Malaya medical centre (UMMC) were 18.6% and 26.2%, respectively. The severity of illness and malnutrition may be part of significant factors contributing to 20% of ICU death annually in Malaysia.

Providing optimal nutrition support is an essential component in managing ICU patients with nutritional risk, which requires an accurate estimation of energy and protein requirements in the clinical setting (De Waele et al., 2019; Rattanachaiwong & Singer, 2018). PEs have been widely used in critical care settings to estimate energy requirements among critically ill patients. However, the prescription of nutrition by the existing PEs have been proven inaccurate (Tatucu-Babet, Ridley & Tierney, 2016), and their accuracy is still questioned. The PEs may not be suited for all patients because most of them were validated for healthy, young and adult population.

On the other hand, with the increase of life expectancy, the growing number of older people admitted to intensive care units made the effectiveness of these equations limited for estimating the REE of critically ill elderly patients (Espinoza et al., 2016). Furthermore, most of the equations for critically ill patients were developed and validated among western countries and not among the Asian population. Hence, their accuracy in predicting energy requirement is questionable in Malaysian critically ill patients. Currently, IC is the gold standard for determining REE in critically ill patients, as recommended by guidelines (Oshima et al., 2017).

Several studies have shown that IC guided nutrition therapy can improve clinical outcomes in critically ill patients ( Heidegger et al., 2013; Lev et al., 2011; Petros, Horbach, Seidel & Weidhase, 2016). However, all the studies were conducted in the western population. Therefore, questions arise whether the results apply to our local ICU setting. In addition, there is a lack of conclusive data to evaluate the impact of IC guided nutrition therapy on clinical outcomes in Malaysian critically ill patients.

This was the first RCT to evaluate the effectiveness of IC guided nutrition therapy on clinical outcomes in Malaysian critical care settings. The information we get from this study will help us to improve energy prescription and provide the highest quality of nutrition care to critically ill patients in our local ICU setting. Furthermore, to the best of our knowledge, no study related to IC has been done among critically ill patients in IIUM Medical Centre. Knowledge gained from these data will further refine clinical practice and increase the positive impact of clinical nutrition support, and it will be the first published study for IIUM Medical Centre Kuantan Pahang.

Furthermore, the use of IC among Malaysian dietitians is limited to the information from this study, which will convince clinicians to increase the utilization of IC in their daily feeding practice. Increased use of IC would facilitate individualized patient care and should lead to improved treatment outcomes.