



UNIVERSITI PUTRA MALAYSIA

***FACTORS ASSOCIATED WITH FEEDING ADEQUACY AND
RELATIONSHIPS BETWEEN FEEDING ADEQUACY AND 60-DAY
MORTALITY IN THE INTENSIVE CARE UNIT IN A MALAYSIAN
HOSPITAL***

LEE ZHENG YII

FPSK(M) 2017 6



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By

LEE ZHENG YII

**Thesis Submitted to the School of Graduate Studies, Universiti Putra
Malaysia, in Fulfilment of the Requirements for the Degree of
Master of Science**

January 2017

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in
fulfilment of the requirement for the degree of Master of Science

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January 2017

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Faculty: Medicine and Health Sciences

Guidelines recommended to feed critically ill patients adequately to ensure optimum clinical outcomes. Nevertheless, underfeeding is commonly reported, but the factors associated with feeding adequacy are not clear. The contribution of feeding adequacy on clinical outcomes are also becoming controversial recently. This study was conducted to (1) investigate factors associated with feeding adequacy and (2) to determine the relationship between feeding adequacy and 60-day mortality among critically ill patients in the intensive care unit of Hospital Serdang. This study employed a prospective observational design. Adult patients (≥ 18 years old) who were mechanically ventilated within 48 hours of ICU admission and stayed in the ICU for at least three days were included. Demographic characteristics and nutrition risk (modified-NUTRIC) score were collected on day 1. Feeding characteristics were collected for a maximum of 12 evaluable nutrition days or until patients died or discharged. Clinical outcomes including the length of stay, duration of mechanical ventilation and mortality status were collected in hospital at day 60. Data were collected on a total of 154 patients with 1406 evaluable nutrition days. The mean 12-day energy and protein adequacy were $64.48 \pm 21.57\%$ and $56.42 \pm 20.68\%$, respectively. The top three categories of reasons for feeding interruption were due to procedures, potentially avoidable reasons and illness-related intolerances. Patient were divided into high (received $\geq 2/3$ of prescribed) or low (received $< 2/3$ of prescribed) energy and protein adequacy. Factors that significantly associated with higher energy adequacy were earlier feeding commencement, less enteral nutrition (EN) interruption, dietitian visits and the longer number of nutrition days. Factors that significantly associated with higher protein adequacy were earlier feeding commencement, less EN interruption, longer number of nutrition day, Chinese race and non-diabetic. At day-60, 44.8% of the patients died. Trend towards an increased in 60-day mortality was demonstrated for high energy and high protein adequacy after adjusted for potential confounders (Adjusted Odds Ratio: 1.99 and 1.93; $p=0.089$

and 0.116, respectively). When stratified by nutritional risk classification, patients with low nutritional risk (NUTRIC ≤ 5) had increased 60-day mortality if they were in the high energy and high protein group but the relationship was not observed among patients with high nutritional risk (NUTRIC >5). In conclusion, almost half of the energy and protein prescribed were not met. Independent predictors for both high energy and protein adequacy were earlier feeding commencement, less EN interruption and the longer number of nutrition days. However, energy and protein adequacy of $\geq 2/3$ of prescribed increased 60-day mortality among patients with low nutritional risk. Therefore, it is suggested to screen all patient admitted into the ICU for nutrition risk status.



Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains

**FAKTOR BERKAITAN DENGAN KECUKUPAN PEMAKANAN DAN
PERHUBUNGAN ANTARA KECUKUPAN PEMAKANAN DENGAN KADAR
KEMATIAN PADA HARI KE-60 DI UNIT RAWATAN RAPI DALAM SEBUAH
HOSPITAL DI MALAYSIA**

Oleh

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Januari 2017

Pengerusi: Profesor Madya Barakatun Nisak Binti Mohd Yusof, PhD
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Garis panduan terapi pemakanan sokongan mencadangkan untuk memberi tenaga dan protein yang secukupnya kepada pesakit kritikal bagi memastikan hasil klinikal yang optimum. Walaubagaimanapun, kajian sering menunjukkan bahawa pesakit kritikal tidak mendapati keperluan tenaga dan protein dengan secukupnya, tetapi faktor-faktor berkaitan dengan kecukupan pemakanan adalah tidak jelas. Selain itu, hubungan antara kecukupan pemakanan dan kesan klinikal juga menjadi isu yang kontroversi baru-baru ini. Kajian ini dijalankan untuk (1) menyiasat faktor-faktor berkaitan dengan kecukupan pemakanan dan (2) hubungan antara kecukupan pemakanan dan kematian pada hari ke-60 di unit rawatan rapi (ICU), Hospital Serdang. Satu kajian pemerhatian masa hadapan telah dijalankan. Kriteria kelayakan kajian adalah pesakit dewasa (umur ≥ 18) yang memerlukan pengudaraan mekanikal dalam masa 48 jam dimasukkan ke ICU dan tinggal di dalam ICU sekurang-kurangnya 3 hari. Ciri-ciri pada hari permulaan termasuk skor risiko pemakanan (modified-NUTRIC) telah dikumpulkan. Ciri-ciri pemberian pemakanan telah dikumpulkan untuk tempoh maksimum 12 hari (hari pemakanan) atau sehingga pesakit mati atau dipindahkan keluar daripada ICU. Hasil klinikal termasuk tempoh penginapan dan pengudaraan mekanikal serta status kematian dikumpulkan di dalam hospital pada hari ke-60. Seramai 154 pesakit dengan 1406 hari pemakanan telah dikumpulkan. Purata kecukupan pemakanan tenaga dan protein dalam tempoh 12 hari adalah $64.48 \pm 21.57\%$ dan $56.42 \pm 20.68\%$. Pesakit telah dibahagikan kepada tinggi (menerima $\geq 2/3$ daripada yang ditetapkan) atau rendah (menerima $< 2/3$ daripada yang ditetapkan) kecukupan tenaga dan protein. Regresi logistik multivariat telah mengenal pasti prediktor tidak bersandar bagi tinggi kecukupan tenaga adalah pemulaan pemakanan dengan lebih awal, kurang gangguan terhadap pemakanan enteral (EN), lawatan ahli diet dan hari pemakanan yang lebih panjang. Prediktor untuk tinggi kecukupan protein adalah pemulaan pemakanan dengan lebih awal, kurang gangguan terhadap EN, hari pemakanan yang lebih panjang, kaum Cina dan

pesakit yang tidak mengalami diabetes. Trend ke arah peningkatan kematian pada hari ke-60 adalah dalam kalangan kumpulan tinggi kecukupan tenaga dan protein, selepas diselaraskan dengan faktor pembaur yang berpotensi (Nisbah kemungkinan masing-masing yang telah diselaraskan: 1.99 and 1.93; $p=0.089$ and 0.116). Apabila dibahagikan oleh skor risiko pemakanan, pesakit yang mempunyai skor risiko pemakanan yang tinggi (NUTRIC >5) tidak terjejas oleh tahap kecukupan pemakanan manakala pesakit dengan skor risiko pemakanan yang rendah (NUTRIC ≤ 5) menghadapi kematian pada hari ke-60 yang lebih tinggi jika mereka adalah dalam kumpulan tinggi kecukupan tenaga dan protein. Secara keserluruhan, hampir separuh daripada tenaga dan protein tidak dipenuhi dengan tahap yang ditetapkan. Prediktor tidak bersandar untuk kedua-dua tinggi kecukupan tenaga dan protein adalah pemulaan pemakanan dengan lebih awal, kurang gangguan terhadap EN, dan hari pemakanan yang lebih panjang. Walaubagaimanapun, tinggi kecukupan tenaga dan protein meningkatkan kadar kematian pada hari ke-60 dalam kalangan pesakit yang mempunyai skor risiko pemakanan yang rendah. Oleh itu, pengenalpastian risiko pemakanan untuk semua pesakit ICU adalah dicadangkan.

ACKNOWLEDGEMENTS

First of all, I would like to thank God for His mercy and guidance throughout this journey. He has not only blessed me with His salvation but also granted me with health and wisdom for the completion of this degree.

Secondly, I would not be able to complete my degree without the guidance from my supervisors, Associate Professor Dr. Barakatun Nisak Mohd Yusof and Dr. Noor Airini Ibrahim. I appreciate the liberty given so that I have the greatest opportunity to explore and unleash my potential in this field. Their kindness, understanding and responsiveness are indeed very helpful. Their advice and guidance are never to be forgotten.

I am thankful to the Malaysia Ministry of Higher Education for sponsoring the entire tuition fee for my Master degree under the MyBrain scholarship. Their sponsorship had greatly lessened my financial burden.

Not to forget all the patients and staffs in ICU Hospital Serdang whom had been very helpful and cooperative during the data collection process. The journey of data collection will not be indeed fruitful without their participation.

I would also like to thank the Canadian Critical Care Nutrition Group for their International Nutrition Survey. Their effort over the years in conducting this international epidemiological research had enlighten me and given me the passion to pursue in this field and to join their effort in improving nutrition care among critically ill patients through research. I would like to especially thank Professor Daren Heyland for his guidance and willingness to be part of our review paper, which had greatly encouraged and motivated me.

I am also grateful to my friends, especially friends who are in the postgraduate room who are always available to listen, discuss and provide me ideas and thoughts which enlighten me during my research journey.

Finally, I would not be able to continue this journey without the love, patience, sacrifice and support by my family. I am especially indebted to my parents. Their encouragement and support are the sustaining factor for me in carrying out the work successfully.

Lee Zheng Yii
25th August 2016

I certify that a Thesis Examination Committee has met on 19 January 2017 to conduct the final examination of Lee Zheng Yii on his thesis entitled "Factors Associated with Feeding Adequacy and Relationships between Feeding Adequacy and 60-Day Mortality in the Intensive Care Unit in a Malaysian Hospital" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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LIST OF ABBREVIATIONS

| | |
|-----------|---|
| APACHE II | Acute Physiology & Chronic Health Evaluation II |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| EN | Enteral Nutrition |
| ETT | Endotracheal Tube |
| GICU | General Intensive Care Unit |
| GRV | Gastric Residual Volume |
| IC | Indirect Calorimetry |
| ICU | Intensive Care Unit |
| INS | International Nutrition Survey |
| IV | Intravenous |
| Kcal | Kilocalorie |
| kg | Kilogram |
| LOS | Length of Stay |
| MV | Mechanical Ventilation |
| NBM | Nil By Mouth |
| NUTRIC | Nutrition Risk in Critically Ill |
| OR | Odds Ratio |
| PN | Parenteral Nutrition |
| RCT | Randomised Controlled Trial |
| RDA | Recommended Dietary Allowance |
| REE | Resting Energy Expenditure |
| SOFA | Sequential Organ-Failure Assessment |
| SD | Standard Deviation |
| VFD | Ventilator-free Day |

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CHAPTER 1

INTRODUCTION

1.1 Background

The Intensive Care Unit (ICU) provides care for the critically ill patients (Vincent, 2013). The most severe type is those who are unconscious and unable to breathe adequately to maintain sufficient oxygen concentration in their blood. These patients are intubated and mechanically ventilated. As the patients are unconscious and/or mechanically ventilated, voluntarily food intake through the oral route is impossible, creating the needs to provide artificial nutrition (nutritional support) for their survival. (Casaer & Van den Berghe, 2014).

Critically ill patients are in a catabolic stress metabolic state to fight for disease, which is accompanied by increased energy and protein requirement (Preiser, Ichai, Orban, & Groeneveld, 2014). Energy is required to sustain body's various functions while protein is essential for maintaining structure and function of cells and tissues (Institute of Medicine, 2002). Therefore, energy and protein are the two most important indicators of nutritional adequacy (Ridley, Gantner, & Pellegrino, 2015). Other nutrients are also necessary, but if energy and protein are sufficient, they will theoretically be sufficient as well because they are given in a balanced proportion in a complete nutrition solution. However, if energy and protein are given in insufficient amount or malabsorption is suspected, micronutrients supplementation may be indicated (Preiser et al., 2015)

The importance of providing sufficient energy and/or protein are demonstrated by various observational studies. It has been shown to improve various clinical outcomes including reduced mortality, shortened length of hospital and ICU stay, reduced infectious complications rate, increased ventilator-free-day, and improved functional outcomes (Alberda et al., 2009; Elke, Wang, Weiler, Day, & Heyland, 2014; Heyland, Cahill, & Day, 2011; Heyland, Stephens, Day, & McClave, 2011; Nicolo, Heyland, Chittams, Sammarco & Compher, 2015; Wei, Day, Ouelette-Kuntz, & Heyland, 2015). On the other hand, inadequate energy and/or protein worsen clinical outcomes, even after adjusted for potential confounders such as disease severity (Dvir, Cohen, & Singer, 2006; Faisy et al., 2009; Rubinson, Diette, Song, Brower, & Krishnan, 2004; Villet et al., 2005).

Critically ill patients with high nutritional risk is harmed the most by inadequate provision of nutrition (Heyland, Dhaliwal, Jiang, & Day, 2011; Rahman et al., 2014). However, it has also been observed that providing full nutrition as early as 1 week in the ICU was associated with increased morbidity and mortality (Arabi et al., 2011; Casaer et al., 2013; Crosara, Mélot, & Preiser, 2015; Krishnan, Parce, Martinez, Diette, & Brower, 2003). Meta-analysis of

randomised controlled trial (RCT) showed moderate energy provision (1/3 to 2/3 of estimated energy requirement) was associated with the best survival as compared with lower or higher range of energy provision (Choi, Park, & Park, 2015; Tian et al., 2015). However, patients in these studies were mostly had normal baseline nutritional status and most probably at a low nutritional risk.

Clinical outcomes commonly reported in the literature including length of stay in the ICU and hospital, duration of mechanical ventilation (MV) and mortality in the ICU and hospital. In this study, 60-day mortality was used as the primary outcome for our analysis. The problem with length of stay (ICU or hospital) or duration of MV is that they are not entirely objective as such outcomes might also be affected on bed availability, machine availability, and family member request on patients' arrangement and so on. Although mortality is an objective outcome, but if patient's outcome is censored (no longer included in the analysis) by chance alone (during ICU/hospital death), the problem of informative censoring/competing risk ensued. An outcome with a landmark, for example at day 60, will avoid such problem (Schetz et al., 2013). In addition, primary outcome of 60-day mortality is used in many large international studies (Heyland et al., 2009, Elke et al, 2014, Nicolo et al., 2015). Therefore, the use of 60-day mortality as the main outcome in this study will also allow our analysis to be comparable with other international studies.

Although it is believed that energy and protein adequacy is associated with better clinical outcomes, the phenomenon of inadequate feeding is a never-ending problem. Observational studies have shown that achieving at least 80% of energy and protein requirement was associated with the best clinical outcomes (Heyland et al., 2011; Nicolo et al., 2015). However, the International Nutrition Survey (INS) in year 2013 documented that patients received about $61.2 \pm 29.4\%$ and $57.6 \pm 29.6\%$ of energy and protein prescribed, respectively (Heyland et al., 2014). In Asia, this level was lower, with energy and protein adequacy at about $53.5 \pm 28.0\%$ and $51.9 \pm 30.1\%$, respectively (Heyland et al., 2014).

Many factors contributed to feeding adequacy and can be categorised into two main factors i.e.: (i) Feeding interruption and (ii) Feeding-related management. Feeding can be interrupted due to various factors such a procedures, gastrointestinal intolerance or illness-related intolerance (Kozeniecki, Mcandrew, & Patel, 2015; O'Leary-Kelley et al., 2005; Reitnam Blaser et al., 2015). Such interruption leads to the stoppage of feeding and loss of volume that is supposed to be infused, causing less than optimal feeding adequacy. On the other hand, an evidence-based feeding management will lead to better feeding tolerance and troubleshooting, thereby ensuring better feeding adequacy.

1.2 Problem Statement

In Malaysia, two single-centre studies reported on feeding adequacy (Mageswary et al., 2013; Yip et al., 2014). Yip et al (2014) conducted a study in 77 mechanically-ventilated critically ill patients in a university-affiliated hospital. This study found that about 66% of the patients achieved 80% of energy requirement within three days of ICU admission. Reasons for feeding interruption were mainly due to procedures and high gastric residual volume.

In the second study, Mageswary et al (2013) conducted a study among 67 ICU patients in a government hospital. This study demonstrated that 69% of the patients achieved 70% of energy requirement by day-5 of feeding initiation. It was unsure whether all patients were mechanically ventilated in this study.

Both of these studies did not report the mean percentage of energy and/or protein adequacy for meaningful comparison with the INS (Heyland et al., 2014). In fact, neither Yip et al (2014) nor Mageswary et al (2013) reported on the patients' nutritional risk status as well as the protein adequacy. In addition, no analytical statistical analysis was done to investigate the factors associated with feeding adequacy. Furthermore, the association between feeding adequacy and clinical outcomes were not determined. Lastly, the sample sizes were relatively small with short period of follow-up, limiting the generalisability of the studies.

Given the scarcity of the data on nutritional adequacy among critically ill patients in Malaysia (Mageswary et al., 2013; Yip et al., 2014), there is a need for a proper study to reveal the current status in Malaysia and the contributing factors to feeding adequacy for quality improvement.

Furthermore, given the contradicting findings related to energy and protein adequacy and clinical outcomes (Arabi et al., 2015; Choi et al., 2015; Heyland et al., 2011), this study will explore such relationship in the Malaysia ICU setting by investigating the association between energy and protein adequacy with 60-day mortality.

1.3 Study Significance

This study provides data on feeding adequacy in a Malaysian ICU that is comparable to the international data. Besides, this study uncovers potential factors associated with feeding adequacy in a general ICU in Malaysia. In addition, the relationship between energy and protein adequacy with 60-day mortality are explored among critically ill patients in Malaysia, with a consideration of patients' nutritional risk status. These findings serve as a useful resource to better nutrition care for the critically ill patients in Malaysia.

Furthermore, data from this study may assist in developing critical care nutrition guidelines for Malaysian population that may contribute to improved patients' survival, reduced complications and cost. The data documented is important for practicing healthcare professionals including clinicians, dietitians and pharmacists as well as critical care nutrition guidelines development group in prioritizing nutritional intervention among the critically ill patients.

1.4 Research Questions

1. What are the proportion of patients who received high ($\geq 2/3$ of prescribed energy or protein) or low ($< 2/3$ of prescribed energy or protein) nutritional adequacy in mechanically ventilated patients in general ICU (GICU), Hospital Serdang?
2. What are the factors significantly associated with feeding adequacy (high or low) in mechanically ventilated patients in GICU, Hospital Serdang?
3. How feeding adequacy (high or low) predicts 60-day mortality?
4. Do nutritional risk classifications or length of stay in the ICU modified the relationship between feeding adequacy and 60-day mortality?

1.5 Objectives

The general objective of this study is to determine the factors associated with feeding adequacy and its relationship between feeding adequacy and 60-day mortality among mechanically ventilated patients in GICU, Hospital Serdang.

The specific objectives are:

1. To determine patients' characteristics (socio-demographic characteristics, clinical characteristics, nutritional status) and feeding practices (feeding interruption and management), feeding adequacy and clinical outcomes (including 60-day mortality) in mechanically ventilated patients in GICU, Hospital Serdang.
2. To compare patients' characteristics, feeding practices and clinical outcomes between low (received $< 2/3$ of prescribed) and high (received

≥2/3 of prescribed) energy and protein group in mechanically ventilated patients at GICU, Hospital Serdang

3. To determine factors (patients' characteristics and feeding practices) associated with feeding adequacy in mechanically ventilated patients at GICU, Hospital Serdang
4. To determine the contribution of feeding adequacy to predict 60-day mortality in mechanically ventilated patients at GICU, Hospital Serdang
5. To determine whether the nutritional risk classifications or length of stay in the ICU modified the relationship between feeding adequacy and 60-d mortality

1.6 Hypotheses

Specific objectives 3 to 5 involves hypothesis testing, and the hypotheses are:

1. There is a significant association between patients' characteristics and feeding practices with feeding adequacy in mechanically ventilated critically ill patients at GICU, Hospital Serdang.
2. There is a significant contribution of feeding adequacy on 60-day mortality
3. Nutritional risk classifications and length of stay in the ICU significantly modify the association between nutritional adequacy and 60-day mortality.

1.7 Conceptual Framework

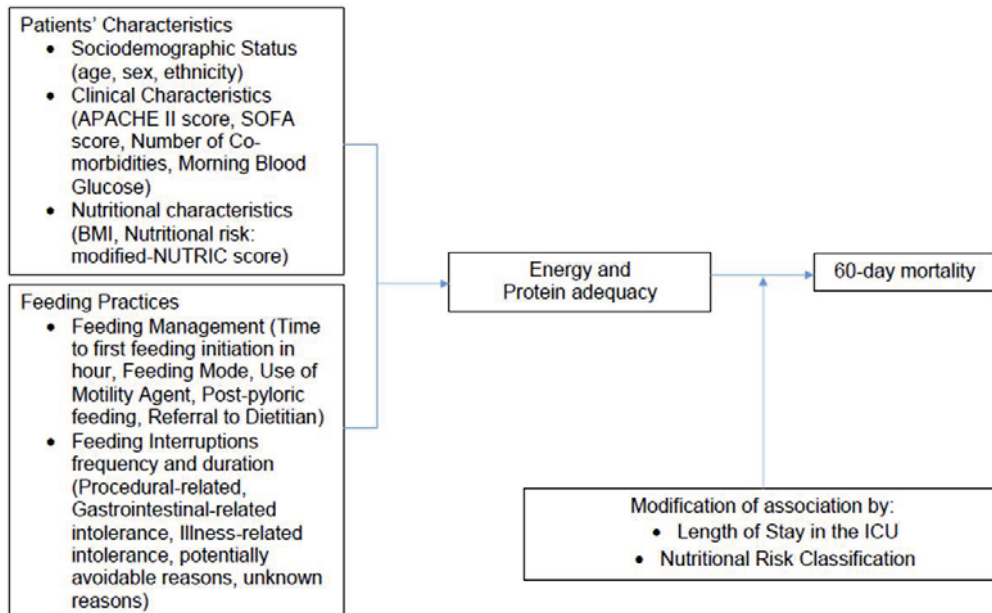


Figure 1.1: Conceptual Framework

ICU: Intensive Care Unit, APACHE II: Acute Physiology & Chronic Health Evaluation II, SOFA: Sequential Organ-Failure Assessment, NUTRIC: Nutrition Risk in Critically Ill, BMI: Body Mass Index, EN: Enteral Nutrition

Figure 1.1 shows the conceptual framework of the study. Patients' characteristics includes sociodemographic status, clinical characteristics and nutritional characteristics. Sociodemographic status recorded were age, sex and ethnicity (Malay, Chinese, Indian and Others). Clinical characteristics recorded were acute physiology and chronic health evaluation II (APACHE II), sequential organ-failure assessment (SOFA), number of co-morbidities, and morning blood glucose level. While nutritional characteristics includes body mass index (BMI) and nutritional risk status as measured by the modified-NUTRIC score.

Feeding practices includes feeding management and feeding interruptions. Feeding management includes time to first feeding initiation recorded in hour, feeding mode for EN (bolus or intermittent pump feeding), use of motility agent or post-pyloric feeding and whether patients were referred to a dietitian.

Feeding adequacy was measured by the proportion of energy or protein prescribed received over the number of evaluable nutrition day (maximum 12 days). Adequate or high energy or protein was defined as receiving $\geq 2/3$ of prescribed energy or protein. In the calculation of feeding adequacy. Days after patients progressed to permanent oral intake was not counted as one evaluable

nutrition day and therefore was excluded in the calculation of feeding adequacy. At day-60, medical record was examined to determine the mortality status. This study will determine the factors associated with energy or protein adequacy where the plausible factors will be obtained from the variables under patients' characteristics and feeding practices. Secondly, the association between energy or protein adequacy with 60-day mortality was determined and whether such association will be modified by length of stay in the ICU (≥ 7 days or < 7 days) or nutritional risk classification as measured by the modified-NUTRIC score (low risk [0-5], high risk [6-9]).



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