Original article

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First-week energy deficit and mortality in critically ill Covid-19 patients

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Abstract

***Introduction*: Risk factors for mortality of critically ill Coronavirus disease 2019 (Covid-19) were older age, use of a mechanical ventilator, high modified nutrition risk in critically ill (mNUTRIC) score, presence of comorbidities, lower body mass index (BMI), acute respiratory distress syndrome (ARDS), and energy deficit in an intensive care unit (ICU).**

***Methods*: A retrospective cohort study was conducted in the ICU of Dr. Kariadi Central Hospital, Semarang, Indonesia from March to December 2020. Subjects were adult, confirmed Covid-19 patients, stayed in the ICU for 3 days or more. Secondary data collected were demographic and anthropometric data, respiratory support, comorbidity, partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) ratio, mortality, body mass index (BMI), mNUTRIC score, route of nutrition delivery, and energy deficit. Cut-off points for energy deficit at days 3, 5, and 7 were determined by the receiver operating characteristic (ROC) curve. The calculation for relative risk followed by multiple logistic regression analysis measured risk for mortality.**

***Result*: A total of 112 patient data were analyzed. Most subjects were male, aged <60 years old, had at least 1 comorbidity, had moderate or severe ARDS. The mortality rate was 50.9%. An energy deficit of 2000 kcal at day 3, 2975 kcal at day 5, and 3750 kcal at day 7 yielded a relative risk of 8.2, 6.6, and 2.5, respectively. The degree of ARDS, the use of mechanical ventilator, mNUTRIC score, and comorbidity were also significantly associated with mortality.**

***Conclusion*: Energy deficit at the first week of ICU stay was a significant risk factor for mortality in critically ill Covid-19 patients.**

Key words: Energy deficit, ICU mortality, critically ill Covid-19.

Introduction

Critically ill Coronavirus disease 2019 (Covid-19) poses a higher risk for poor outcomes in the intensive care unit (ICU). Several studies reported a mortality rate of 26-71%. (1,2) Previous studies reported factors involved in mortality of critically ill Covid-19 patients such as older age and invasive mechanical ventilation requirement, (3) higher modified nutrition risk in critically ill (mNUTRIC) score, (4), and a presence of comorbidities. (5) Another study listed factors which also associated with mortality in ICU patients with Covid-19 included lower body mass index (BMI), chronic kidney disease (CKD) or received renal replacement therapy, lower partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) ratio, and receiving vasopressors. (6)

Energy deficit was reported as an independent predictor for mortality in critically ill patients. A study in Brazil calculated energy deficit during ICU stay and determined a critical energy deficit of more than 480 kcal/day. Patients who were not in the critical energy deficit group (<480 kcal/day) had a lower mortality rate. (7) Another study in postoperative subjects found a similar result. It reported that energy intake less than 70% in subjects with a high mNUTRIC score was associated with a higher risk for mortality. (8) This finding was also applicable in patients with Covid-19. A study in Italian ICU con-

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ducted during the first wave of Covid-19 found that early energy deficit in the first 4 days of ICU stay was associated with higher mortality. (9)

The energy target for critically ill Covid-19 patients during the early acute phase is determined to be 20-25 kcal/kg body weight, which can be steeply administered based on patients' condition and tolerance. (10,11) Unfortunately, during the first week of stay, most critically ill Covid-19 patients experience hemodynamic instability due to the inflammation phase of the disease course. As a consequence, feeding intolerance frequently occurs and parenteral nutrition is not possible to be given due to fluid and electrolyte imbalance, limited vascular access, and availability. This results in energy deficit during ICU stay and the following adverse effects. Since studies that reported the association of energy deficit and mortality in the critically ill Covid-19 patients are limited, this study was aimed to seek the association of energy deficit and mortality in the first week of ICU stay.

Methods

A retrospective cohort study was conducted in the isolation ICU of Dr. Kariadi Central Hospital in Semarang, Indonesia. Population study were critically ill patients admitted to the ICU from March to December 2020. Subjects were those with age >18 years old, confirmed Covid-19 based on the positive result of reverse transcription polymerase chain reaction assay (RT-PCR) of the nasopharyngeal swab, stayed in ICU for 3 days or more, and had complete observed data. Ethical clearance has been obtained from the Health Research Ethics Committee of Dr. Kariadi Central Hospital Semarang No. 531/EC/KEPK-RSDK/2020. Informed consent was not performed as this was a retrospective study using secondary data from the electronic medical record.

Data collection

Data were collected from the electronic medical record including demographic data, weight, height, respiratory support, presence of comorbidity, PaO2/FiO2 ratio (PFR), and ICU mortality. Body mass index (BMI) was calculated using the Quetelet index and categorized based on the Asia-Pacific classification. (12) mNUTRIC score was calculated in the first 24 hours of admission. Nutrition support included the route of nutrition delivery, energy intake, energy targets based on the European Society of Nutrition and Metabolism (ESPEN) Guideline (25-30 kcal/kg/day), (10) which were calculated from actual body weight for patients with underweight, and normal weight, or ideal body weight for obese patients. Energy deficits were calculated with the formula:

(Accumulation of energy target since ICU admission to day-x) - (accumulation of energy intake since ICU admission to day-x). Day-x referred to the measurement days (day 3, day 5, and day 7).

Statistical analysis

SPSS for Windows was used to analyze data. Mean and standard deviation was used to present continuous data with normal distribution, while median and 25th and 75th percentile were used to present continuous data with non-normal distribution. These continuous data were then categorized into two groups based on the international standard for each data. Categorical data were presented using frequency tables. Cut-off points for energy deficit at days 3, 5, and 7, which were associated with mortality, were determined by the receiver operating characteristic (ROC) curve. Chi-square analysis was performed to seek associations between independent variables and mortality as a dependent variable, followed by calculation for relative risk for those with significant associations. Multiple logistic regression analysis was conducted to measure the risk for mortality of dependent variables and possible confounders.

Result

A total number of 112 patients who met the inclusion criteria were included in the analysis. Demographic data and characteristics of subjects are presented in **Table 1**.

Table 1 shows that most subjects were male, aged <60 years old. The presence of comorbidity was frequently found in our subjects. More than 60% of subjects had at least 1 comorbidity such as type 2 diabetes mellitus, hypertension, heart disease, renal disease, or a combination of them. Almost 70% of subjects were admitted to the ICU due to moderate or severe acute respiratory distress syndrome (ARDS), in whom mechanical ventilator support was needed, and the rest needed either high-flow nasal cannula (HFNC) or non-rebreathing mask (NRM). Most of those who initially used NRM later required HFNC while in the ICU. The median ventilator day length was 7 days and the median length of ICU stay was 9 days. As much as 50.9% of subjects died in the ICU.

Body mass index (BMI), which was categorized based on classification for the Asia Pacific population, revealed that more than 75% of subjects were overweight or obese. mNUTRIC score found that only 16% of subjects had a score of more than 5, which was associated with a higher risk of malnutrition and needed intensive nutritional therapy while in the ICU. Most subjects (62.2%) received exclusive enteral nutrition while the rest received supplemented parenteral nutrition due to inadequate enteral intake. Energy deficit within the first week of ICU stay was determined on days 3, 5, and 7. In terms of energy deficit, **Table 1** shows that the longer ICU stay, the more energy deficit. It ranged from more than 2000 kcal on day 3 and increased to more than 4000 kcal on day 7. ROC analysis was then performed to seek a cut-off point for energy deficit on each measured day.

The best cut-off for energy deficit at the first week in ICU was determined based on ROCs (**Figure 1**). Cut-offs for energy deficit of 2000 kcal at day 3, 2975 kcal at day 5, and 3750 at day 7 were chosen based on their sensitivity and specificity values.

Association between variables and mortality in the ICU

The bivariate analysis found that several variables were associated with mortality. **Table 2** shows that age, BMI, and feeding route were not the risk factors for mortality in the ICU, while mNUTRIC score, comorbidity, ARDS, use of a mechanical ventilator, and energy deficit on days 3, 5, and 7 were significant risk factors.

The risk for mortality of subjects with mNUTRIC score ≥ 5 was 1.86 higher than those with lower mNUTRIC scores. Most subjects (70.9%) who were admitted to ICU had at least 1 comorbidity (**Table 1**). These subjects were 1.62 times more likely to die in the ICU compared to those without comorbidity. The most frequent comorbidity found was diabetes. ARDS was also the main factor of the patient being referred to the ICU. When categorized to the degree of ARDS, those with moderate to severe ARDS had mortality risk as high as 1.74 compared to those with mild ARDS. When these patients were on a mechanical ventilator, they were 8.57 times more likely to die in the ICU compared to those who were on HFNC or NRM.

Energy deficit, which was calculated on days 3, 5, and 7 of ICU stay, was categorized using ROC. It was found that the cut-offs were 2000 kcal, 2975 kcal, and 3750 kcal, respectively. Patients with an energy deficit of more than 2000 kcal on day 3, 2975 kcal on day 5, and 3750 kcal on day 7 were 3.32, 2.75, and 2.23 times more likely to pass away in the ICU.

Table 3 shows three multivariate analysis models on subjects who were still in the ICU on days 3, 5, and 7. These multiple logistic regression models depicted that interaction of PFR and use of a mechanical ventilator, and energy deficit at any measurement day remained as risk factors for mortality. The difference pattern was observed only on day 3 when mNUTRIC score was found to be a significant covariate, but not on the next two measurement days, when the presence of comorbidity replaced mNUTRIC score as a risk factor for mortality.

Apart from other variables, energy deficit on days 3, 5, and 7 yielded a relative risk of 8.2, 6.6, and 2.5, respectively, indicating subjects with energy deficit above the cut-off on those days had a higher risk to die in the ICU compared to those with less energy deficit. The trend was lower as the ICU length of stay was longer.

Across three models, the interaction between PFR and the use of a mechanical ventilator was found to be a strong risk factor. Most patients have been admitted to the ICU due to ARDS and 69.2% of those with moderate to severe ARDS needed mechanical ventilators in the ICU, of whom 77.9% died in the ICU.

Discussion

The proportion of male patients, who were admitted to ICU in this study, was more than 75%, however, the bivariate analysis did not observe its association with mortality. Most studies found that male patients had a higher risk of having severe or critically ill Covid-19 and thus, a higher mortality rate. (13,14) Conversely, another study that measured 28-day mortality found no difference in mortality between males and females although the proportion of males was much higher than females. (15) The difference between our study findings and previous studies may due to characteristics of our patients at that period when more female patients were admitted to the ICU with severe conditions or being pregnant. As has been published in a previous study, pregnancy was associated with a higher risk for intensive care unit admission and mortality. (16,17)

Our study found different results from previous studies which reported a higher proportion and mortality among ICU patients with Covid-19. The proportion of subjects aged 60 years old or more in this study was only 30% and age was not associated with mortality. It was generally accepted that older age was another significant contributing factor for ICU admission and mortality in Covid-19 infection due to poor immune systems in the elderly. Analysis of data from 32 European countries found that the mortality rate increased with age. (18,19) The difference between the results of our study with other studies may be due to the high mortality rate in our patients, regardless of age group. A retrospective study of more than 4000 subjects in Indonesia reported that increasing age and presence of comorbidity were associated with mortality. The mortality rate in Covid-19 patients without comorbidity was much less than those with one or more comorbidity. This finding was consistent across age groups. (20) Our study also found a similar result. Those who did not have any comorbidity were less likely to die in the ICU compared to those with at least one comorbidity.

Obesity was reported as a significant risk factor for ICU admission and mortality in some studies. Based on the Asian Pacific classification for obesity, (12) our study found that more than half of the subjects (58.1%) were obese. However, there was no association between BMI≥30 kg/m^2 and mortality. This finding may be because most of our obese subjects had BMI 30 to 39.4 kg/m^2, a range where the lower mortality rate was observed in the study of obese population with Covid-19 which reported a lower mortality rate in subjects with BMI 30.0 to 39.9 kg/m^2 compared to those with BMI≥40 kg/m^2 or <30.0 kg/m^2. (21)

mNUTRIC score has been proposed as a nutrition screening tool that is able to determine patients who were at risk for malnutrition and need nutrition support while in the ICU. It has been widely reported to be a significant predictor of mortality in ICU patients. (22) The use of mNUTRIC score in Covid-19 patients was confirmed in a previous study in Mexico, Mexico, and Wuhan, China. (4,23) However, there was a study in Italy that reported low discriminative ability to determine nutritional risk in Covid-19 patients. (24) In concordance with previous studies, our study found a similar result. Patients with mNUTRIC score of 5 or more had a higher mortality risk than their counterparts with a score of 4 or less. In a multivariate model, mNUTRIC score was also observed as a risk factor for mortality, but only at day 3 measurement. This may be because mNUTRIC score in our study was obtained at the first 24-hour of ICU admission, therefore, it only predicted mortality at day 3 and not the days after, when the severity of disease and the presence of comorbidity became important determinants for mortality regardless of nutritional status.

The majority of our subjects were referred to the ICU due to moderate to severe ARDS, where 60.7% of them needed a mechanical ventilator for respiratory support. The chance to discharge alive from the ICU dramatically drop when patients were on a mechanical ventilator due to worsening respiratory distress. In our study, patients who needed a mechanical ventilator were 8.57 times more likely to pass away in the ICU. Only 25.4% of those with mechanical ventilators were able to be weaned and discharged alive from the ICU. Interaction of ARDS and the use of mechanical ventilator as a risk factor for mortality, which was consistently observed in three models of multiple logistic regression, suggested the role of these variables as potential causes of death in critically ill Covid-19 patients. Not exclusively for Covid-19 patients, ARDS has been well recognized as an important predictor for ICU and hospital mortality. The previous study reported a mortality rate of 34.9%, 40.3%, and 46.1% for those with mild, moderate, and severe ARDS, respectively. (25) Meanwhile, a systematic review of 177 papers reported ICU mortality of 38%. (26) In critically ill Covid-19 patients, ARDS was also significantly associated with mortality. A systematic review of several reports across the world found various mortality rates ranging from 13% in Germany to 69% in China and 73% in Poland, with pooled mortality estimate of 39% worldwide. (27) Mechanical ventilator support was also of interest in critically ill Covid-19. Regardless of the controversy about the initiation of intubation and raising discussion of whether mechanical ventilator should be avoided for Covid-19 patients, the mortality rate of Covid-19 patients who were on mechanical ventilators were overwhelming. It was reported to be more than 50% and even reached 97%. (2,6)

The route of nutrition delivery was not associated with mortality in this study. Although enteral nutrition was highly recommended in critically ill patients, (28) the use of supplemented parenteral nutrition in Covid-19 patients in ICU was considered safe. (29) This study confirmed that neither early enteral nutrition nor supplemented parenteral nutrition was associated with mortality.

Previous studies found that energy and protein deficit in patients who stayed in the ICU was risk factors for mortality. (7,8) This study found a similar result. Energy deficits on days 3, 5, and 7 of ICU stay were significant risk factors for mortality. There was a decreasing trend of energy deficit for mortality as ICU stay longer although the amount of deficit was larger. These results may be due to the severity of the disease. Those with severe disease deceased earlier while patients who managed to stay in the ICU longer had less severe disease. Other explanations were that our patients who remained in the ICU after day 5 or 7 had less comorbidity. If they passed away, the cause of death was due to worsening hemodynamic conditions and not merely a consequence of energy target fulfillment. In a study of critically ill Covid-19 patients who stayed in ICU≥4 days, patients who achieved energy intake of ≥80% targets had lower mortality. (9) This study used total energy deficit instead of the proportion of energy intake. Nevertheless, the findings of our study confirmed that energy deficit during the first week of ICU stay was a risk factor for mortality in critically ill Covid-19 patients.

Conclusion

Energy deficits at days 3, 5, and 7 were associated with mortality in critically ill Covid-19 patients in ICU. The degree of ARDS and the use of mechanical ventilators remained as other risk factors for mortality during the first week of ICU stay. Modified NUTRIC score was a risk factor for mortality at early days while comorbidity was a risk factor at day 5 or more.

Disclosure

The authors declare that there was no conflict of interest.

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Table 1. Demographic data and characteristics of subjects

Variables	
Male	74 (66.1)
Age (years) - ≥60 years	53.5±13.44 36 (32.1)
BMI (kg/m^2) (12) - <18.5 (underweight) - 18.5-22.9 (normo weight) - 23.0-24.9 (overweight) - 25.0-29.9 (obese I) - ≥30.0 (obese II)	26.2±4.89 3 (2.7) 23 (20.5) 21 (18.8) 43 (38.4) 22 (19.7)
mNUTRIC score ≥5	18 (16.1)
Presence of at least 1 comorbidity	71 (63.4)
Route of nutrition delivery - Enteral nutrition - Enteral+parenteral nutrition - Parenteral nutrition	 69 (61.6) 42 (37.5) 1 (0.9)
Energy deficit day 3 (kcal)	2261.4±1059.95
Energy deficit day 5 (kcal)	3262.8±1653.56
Energy deficit day 7 (kcal)	4197.7±2383.20
PaO2/FiO2 ratio - Mild ARDS - Moderate ARDS - Severe ARDS	 33 (29.5) 33 (29.5) 46 (41.0)
Respiratory support - Mechanical ventilation - High-flow nasal cannula - Non-rebreathing mask	 68 (60.7) 20 (17.9) 24 (21.4)
MV day length (days)	7 (4.11)
ICU length of stay (days)	9 (6.12)
ICU mortality	57 (50.9)

Legend: BMI=body mass index; mNUTRIC=modified nutrition risk in critically ill; PaO2=partial pressure of oxygen; FiO2=fraction of inspired oxygen; ARDS=acute respiratory distress syndrome; MV=mechanical ventilation; HFNC=high-flow nasal cannula; NRM=non-rebreathing mask; ICU=intensive care unit.
Data are presented as n (%), mean±standard deviation, and median (25th, 75th percentiles).

Table 2. Bivariate analysis of risk factors for mortality in ICU

Variables	RR (95% CI)	p
Male	0.80 (0.56-1.16)	0.26
Age >60 years old	1.14 (0.78-1.66)	0.49
Presence of at least 1 comorbidity*	1.62 (1.03-2.53)	0.02
BMI≥30 kg/m^2	0.77 (0.45-1.31)	0.29
mNUTRIC score≥5*	1.86 (1.37-2.53)	0.003
ARDS moderate to severe*	1.74 (1.04-2.93)	0.02
Using mechanical ventilator*	8.57 (3.34-22.0)	0.000
Feeding route: exclusive EN	1.01 (0.69-1.48)	0.94
Energy deficit on day 3 (≥2000 kcal)*	3.32 (1.82-6.07)	0.000
Energy deficit on day 5 (≥2975 kcal)*	2.75 (1.46-5.15)	0.000
Energy deficit on day 7 (≥3750 kcal)*	2.23 (1.31-3.78)	0.001

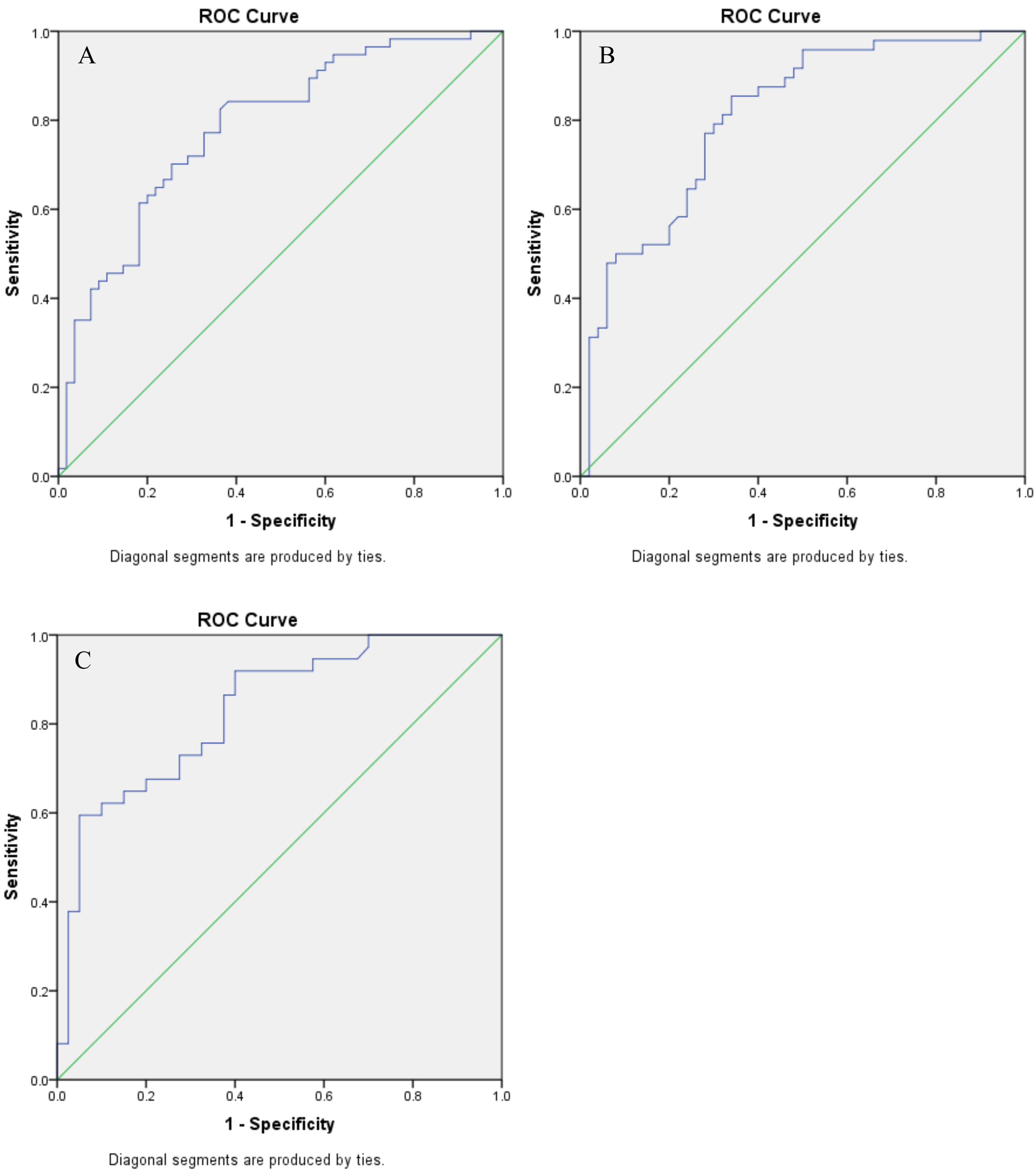
Legend: ICU=intensive care unit; BMI=body mass index; mNUTRIC=modified nutrition risk in critically ill; ARDS=acute respiratory distress syndrome; EN=enteral nutrition; RR=relative risk; CI=confidence interval. *=the p-value of this variable was significant.

Table 3. Multivariate analysis

	Risk	95% CI	p
Model 1			
- mNUTRIC score	8.1	1.62-40.31	0.01
- PFR*MV	12.2	2.18-68.56	0.04
- Energy deficit on day 3	8.2	2.97-22.39	0.00
Model 2			
- Comorbidity	2.9	1.07-8.07	0.03
- PFR*MV	7.1	1.32-27.36	0.02
- Energy deficit on day 5	6.6	2.44-17.97	0.00
Model 3			
- Comorbidity	2.9	1.04-8.01	0.04
- PFR*MV	6.3	1.17-32.85	0.03
- Energy deficit on day 7	2.5	1.27-9.61	0.02

Legend: mNUTRIC=modified nutrition risk in critically ill; PFR=partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) ratio; MV=mechanical ventilation; PFR*MV means that the interaction between PFR and the use of MV was closely associated.

Figure 1. ROC for energy deficit at first week in ICU



Legend:
A=ROC for energy deficit on day 3. AUC 0.78 (95% CI-0.69-0.89), sensitivity=0.84, specificity=0.62
B=ROC for energy deficit on day 5. AUC 0.81 (95% CI=0.72-0.89), sensitivity=0.83, specificity=0.66
C=ROC for energy deficit on day 7. AUC 0.83 (95% CI=0.74-0.92), sensitivity=0.86, specificity=0.63
ROC=receiver operating characteristic; ICU=intensive care unit; AUC=area under the curve; CI=confidence interval.

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