Original Article

Lower body mass indices and near-target early energy nutrition therapy may increase intensive care unit-associated infections: A retrospective study in Guangzhou, China

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Background and Objectives: The optimal energy intake for early nutrition therapy in critically ill patients is unknown, especially in Chinese patients with a lower BMI. This study investigated the relationship between energy intake and clinical outcomes in this patient population. **Methods and Study Design:** A retrospective study was carried out at a tertiary hospital. Critically ill patients were recruited and divided into 3 tertiles according to the ratio of actual/target energy intake during the first week of hospitalization in the intensive care unit (ICU) (tertile I, <33.4%; tertile II, 33.4%–66.7%; and tertile III, >66.7%). 60-day mortality and other clinical outcomes were compared. To adjust for potentially confounding factors, multivariate and sensitivity analyses were performed exclusively in patients who stayed in the ICU for ≥7 days. **Results:** A total of 325 patients with a mean BMI of 22.5±4.7 kg/m^2 were recruited. 60-day mortality was similar between the 3 tertiles. In the unadjusted analysis, tertile III had a longer length of stay in the ICU and at the hospital, longer duration of mechanical ventilation, and higher rate of ICU-associated infections, but only the latter showed a significant difference between the 3 tertiles in the multivariate and sensitivity analyses. Logistic regression analysis showed that energy groups was an independent risk factor for ICU-associated infections. **Conclusions:** Energy intake in early nutrition therapy influences risk of ICU-associated infections in Chinese critically ill patients with lower BMI. Furthermore, patients with near-target energy intake have more frequent ICU-associated infections.

Key Words: nutrition, energy intake, intensive care unit, BMI, clinical outcome

INTRODUCTION

Patients admitted to intensive care unit (ICU) usually suffer from severe illness or injury, which are associated with increased energy expenditure and protein catabolism that can lead to a state of metabolic stress.[1] Meanwhile, nutrient intake is reduced by anorexia and loss of appetite. Thus, malnutrition is inevitable during ICU stays regardless of prior nutrition status.[1] Loss of muscle mass and disability are increased with length of stay (LOS) in the ICU.[2] Nutrition therapy is an essential aspect of the management of critically ill patients, especially during the first week in the ICU, which is the critical period of disease progression, inflammation, and insulin resistance[3] and represents a window of opportunity for achieving nutritional and non-nutritional benefits.[4] However, the level of dietary energy intake in critically ill patients during this period is unknown, with most research focusing on European and American patients. Meanwhile, variations in height and body shape across countries result in differences in body mass index (BMI)-related criteria. For example, a BMI ≥28 kg/m^2 is defined as obese in China but is considered overweight in the United States. As such, the implementation of early nutrition therapy for Chinese ICU patients must take into consideration their lower BMI values.

Optimal energy intake in early nutrition therapy is debated, with several studies reporting contradictory findings. An aggressive nutrition strategy was previously recommended to counter malnutrition and prevent catabolism, but this has been challenged by other studies demonstrating that permissive underfeeding (40%–70% of target energy intake) improved clinical outcomes[5-7] and that target feeding (84.7% of target energy intake) sig-

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nificantly increased mortality.[8] Other researchers later argued that methodological flaws confounded these results.[3] However, several well-designed randomized controlled trials (RCTs)[9-12] and meta-analyses[13-15] showed that permissive underfeeding/trophic feeding (15%–25% of target energy intake) and full feeding had similarly clinical outcomes. The RCTs enrolled younger (average age of 50–54 years) critically ill patients with higher BMI (average of 28–30 kg/m^2) and excluded subjects with preexisting malnutrition. There has been concern regarding the safety of permissive underfeeding/trophic feeding, and full feeding is still recommended for patients requiring prolonged mechanical ventilation[16] or who have an elevated risk of nutritional deficiency.[17] However, the validity of the Nutrition Risk in the Critically Ill score, which is used to identify such patients, has been questioned as it only reflects a disease state without considering baseline nutritional status.[18] Some researchers have proposed that forced mandatory feeding of critically ill patients should be avoided in the first week after admission to the ICU to preserve autophagy and thus maximize the response to oxidative stress, maintain organ function, and improve outcome,[1] but support for this argument is questionable.[19]

To address the above mentioned controversies, the present study investigated the relationship between energy intake and clinical outcomes in Chinese ICU patients with lower BMI to determine the optimal energy intake of early nutrition therapy in clinical practice.

METHODS

Study design

This retrospective study was conducted in the medical and surgical ICU of a tertiary hospital in Southern China from January 2015 to August 2017. The study was approved by the university and affiliated hospital. We divided patients into 3 tertiles (tertile I, <33.4%; tertile II, 33.4%–66.7%; and tertile III, >66.7%) according to the ratio of actual energy intake/target energy intake in early nutrition therapy. Actual energy intake included daily energy intake through enteral nutrition (EN), parental nutrition (PN), intravenous dextrose, and propofol. Clinical outcomes of the 3 tertiles were compared.

Patients

A total of 325 critically ill patients were recruited. All patients were adults (≥18 years of age), stayed in the ICU for ≥72 h, and received nutrition therapy in the first week. Exclusion criteria were as follows: pregnant or lactating mothers; and patients who were re-admitted to the same ICU, for whom BMI and 60-day survival data were unavailable, or who had incomplete medical records. The patient selection process is shown in Figure 1.

Data collection

All data were collected through medical records and telephone follow-up using a self-designed questionnaire. The following information was collected from each participant: demographic information (i.e., age, sex, height, and weight); disease category; ICU category; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; Nutrition Risk Screening 2002 (NRS2002) score; diabetes history; chronic renal failure; mechanical ventilation; gastrointestinal integrity; craniocerebral trauma; sepsis; blood glucose level at the time of ICU admission; vasopressor/analgesia and sedation use within the 24 h after ICU admission.

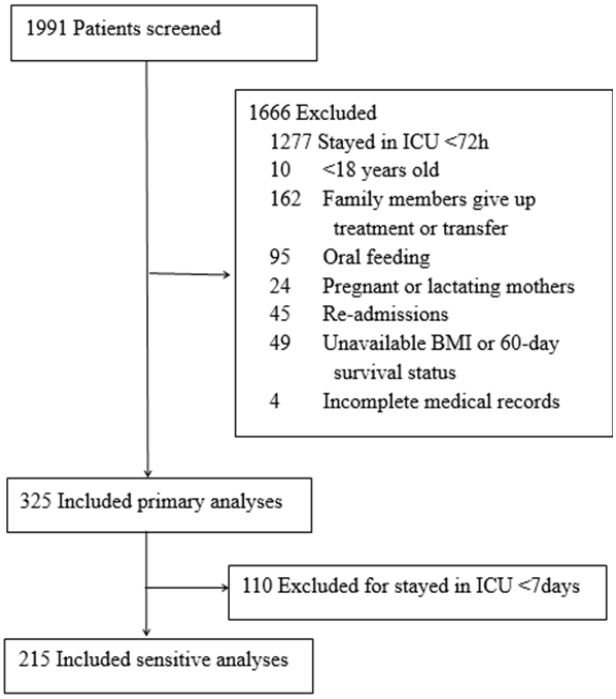

Figure 1. Flow diagram of study subject recruitment

We recorded and calculated patients' actual energy and protein intake through EN, PN, and other modalities every day in the first week. We considered protein intake as an important confounder and adjusted our results accordingly when analyzing the effect of energy intake on clinical outcome. Energy intake from PN was calculated with the following formula: total energy (kcal) = (glucose [g] × 4) + (amino acids [g] × 4) + (fat emulsion [g] × 9). Target energy intake, which depends on BMI, was calculated as 25 kcal/kg/day × (actual weight) for BMI <30 kg/m^2; 12.5 kcal/kg/day × (actual weight) for a BMI of 30–50 kg/m^2; and 25 kcal/kg/day × (ideal weight) for BMI >50 kg/m^2.[20] Target protein intake was calculated as 1.5 g/kg/day × (actual weight) for BMI <30 kg/m^2; 2.0 g/kg/day × (ideal weight) for a BMI of 30–40 kg/m^2; and 2.5 g/kg/day × (ideal weight) for BMI ≥40 kg/m^2.[20]

The patients were followed up for 60 days after ICU admission. The primary outcome was 60-day mortality, and secondary outcomes were ICU mortality, hospital mortality, duration of mechanical ventilation, ICU LOS, hospital LOS, days free of mechanical ventilation, ICU-free days, hospital-free days, and ICU-associated infections. Mean glucose, insulin dosage, feeding intolerance, and use of prokinetics were also assessed and compared.

Statistical analysis

Statistical analyses were performed with SPSS v21.0 (SPSS Inc., Chicago, IL, USA) and Excel 2016 (Microsoft, Redmond, WA, USA). Demographic information, disease- and nutrition therapy-related information, and clinical outcomes were recorded and analyzed according to variable type, with continuous variables presented as

mean and standard deviations. Differences between the 3 tertiles were assessed by analysis of variance or the Kruskal-Wallis test. Categorical variables are reported as a number and percentage, and the chi-squared test or Fisher's exact test was used to assess differences between tertiles. Survival probability from ICU admission to 60 days post-admission was compared between the 3 tertiles with Kaplan-Meier curves and the log-rank test. Given the retrospective nature of the study, there were confounding factors that influenced our results. We therefore performed multivariate linear and logistic regression analyses using clinical outcomes as dependent variables and the energy group and other confounding factors such as sex, BMI, APACHE II score, NRS2002, admission category (medical or surgical ICU), mechanical ventilation, ratio of actual/target protein intake, mode of nutrition therapy, and ICU LOS as independent variables.[5] As shorter ICU stays are associated with lower energy intake and better clinical outcome, we performed a sensitivity analysis using the above procedure exclusively in patients with ICU LOS ≥7 days.

RESULTS

Baseline characteristics of the study population and nutrition therapy

A total of 325 patients were recruited for this retrospective analyses. The average age was 60.2±17.7 years, and 56.9% of patients were >60 years of age. Only 8.3% of patients had a BMI ≥28.0 kg/m^2, and mean BMI was 22.5±4.7 kg/m^2. Mean APACHE II score was 22.0±7.3, and all patients were at moderate or high nutritional risk. Other baseline characteristics as well as results of nutrition therapy during the first 7 days in the ICU are shown in Table 1. There were significant differences in sex ratio, BMI, NRS2002 score, and ICU category between the 3 tertiles because physicians administered nutrition therapy according to these factors. We adjusted for these confounds when comparing clinical outcomes.

Clinical outcomes

We initially analyzed clinical outcomes without considering confounding factors and found that tertile III had a higher rate of ICU-associated infections and longer ICU LOS, hospital LOS, and duration of mechanical ventilation than the other two groups (p<0.05; Table 2). Other clinical outcomes including 60-day mortality were similar across tertiles. We also found no difference between the 3 tertiles with respect to feeding intolerance and prokinetics use in patients receiving EN. Overall survival did not differ significantly between the 3 tertiles (Figure 2).

We performed multivariate linear and logistic regression analyses after adjusting for 9 potentially confounding variables (i.e., sex, BMI, APACHE II score, NRS2002 score, ICU category, mechanical ventilation, ratio of actual/target protein intake, mode of nutrition therapy, and ICU LOS) and found that energy group no longer affected ICU LOS, hospital LOS, or duration of mechanical ventilation. Energy group entered the regression equation when ICU-associated infection was taken as the dependent variable (OR=1.617, 95% CI=1.085–2.410; Table 3).

We performed a sensitivity analysis with patients who stayed in the ICU for ≥7 days and found that overall clinical outcomes did not differ significantly (Table 4). Patients in tertiles II and III had higher rates of ICU-associated infections than those in tertile I, but the difference was not statistically significant. The results of the multivariate linear and logistic regression analyses were similar to those obtained in the unadjusted analysis (Tables 3 and 5). The risk of ICU-associated infection increased 1.746-fold for every 33% increase in energy intake (OR=1.746, 95% CI=1.064–2.865). The results of the survival analyses are shown in Figure 3.

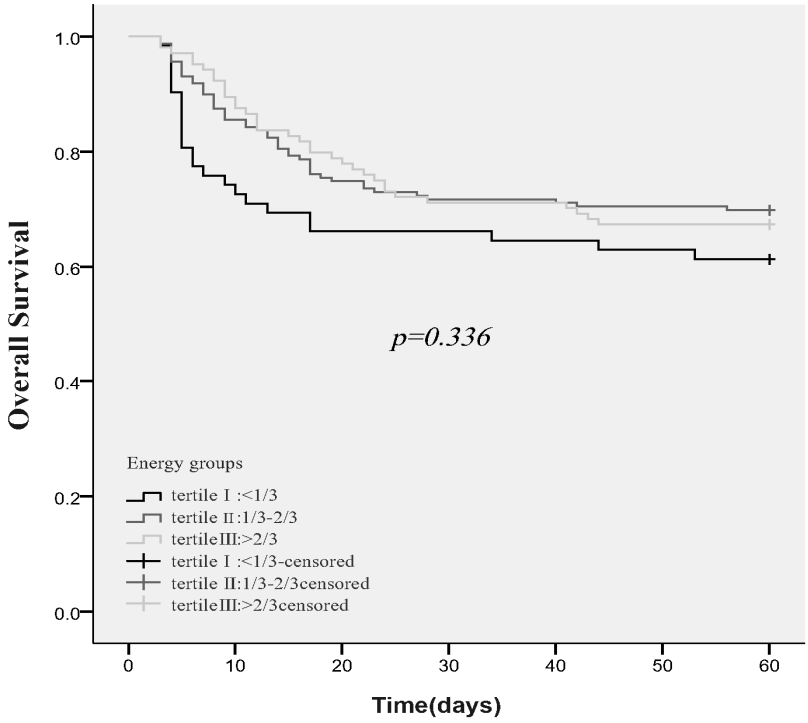

Figure 2. Survival time after ICU admission in 3 tertiles of 325 patients determined by Kaplan-Meier and log-rank analyses.

Table 1. Baseline characteristics and nutrition therapy (n=325)

Variable	Overall (n=325)	Tertile I† (n=62)	Tertile II† (n=159)	Tertile III† (n=104)	*p* value
Age	60.2±17.7	55.9±15.6	60.6±18.4	62.1±17.4	0.084
Sex (women)	102 (31.4)	17 (27.4)	38 (23.9)	47 (45.2)	0.001*
BMI (kg/m^2)	22.5±4.7	23.9±3.6	23.4±4.8	20.2±4.2	<0.001*
Disease category					
Nonoperated	201 (61.8)	34 (54.8)	91 (57.2)	76 (73.0)	0.111
Operated	124 (38.2)	28 (45.2)	68 (42.8)	28 (27.0)	
ICU category					
Medical	163 (50.2)	23 (37.1)	75 (47.2)	65 (62.5)	0.004*
Surgical	162 (49.8)	39 (62.9)	84 (52.8)	39 (37.5)	
APACHE II score	22.0±7.3	21.2±7.7	21.8±7.1	22.7±7.4	0.409
NRS 2002 score	4.6 200	4.3 200	4.4 200	4.9 200	0.008*
Diabetes history (n [%])	60 (18.5)	11 (17.7)	29 (18.2)	20 (19.2)	0.967
Chronic renal failure (n [%])	12 (3.7)	0 (0.0)	8 (5.0)	4 (3.8)	0.293
Gastrointestinal integrity (n [%])	288 (88.6)	51 (82.3)	143 (89.9)	94 (90.4)	0.214
Craniocerebral trauma (n [%])	23 (7.1)	8 (12.9)	10 (6.3)	5 (4.8)	0.125
Sepsis [n (%)]	16 (4.9)	3 (4.8)	10 (6.3)	3 (2.9)	0.459
Vasopressor within 24 h (n [%])	120 (36.9)	22 (35.5)	56 (35.2)	42 (40.4)	0.767
Analgesia/sedation within 24 h (n [%])	185 (56.9)	38 (61.3)	96 (60.4)	51 (49.0)	0.300
Mechanical ventilation (n [%])	251 (77.3)	48 (77.4)	121 (76.1)	82 (78.8)	0.873
Glucose at ICU admission (mmol/L)	9.4±3.5	9.9±4.1	9.3±3.3	9.4±3.4	0.461
Energy target (kcal/day)	1473±307	1636±290	1555±262	1250±256	<0.001*
Energy intake (kcal/day)	1032±348	666±244	1026±260	1259±330	<0.001*
EN energy (kcal/day)	508±348	176±183	534±303	665±356	<0.001*
PN energy (kcal/day)	291±330	158±115	258±287	419±423	<0.001*
Intravenous dextrose energy (kcal/day)	229±157	308±153	233±165	176±125	<0.001*
Propofol‡ energy (kcal/day)	6.8±15.5	7.4±16.2	7.4±15.6	5.4±15.0	0.545
Energy intake/target (%)	57.0±28.1	20.0±8.7	51.1±9.1	88.0±21.9	<0.001*
Protein intake (g/day)	66.0±27.1	55.4±22.5	65.6±26.6	72.9±28.3	<0.001*
Protein target (g/day)	96.7±20.4	105.5±19.0	102.0±17.9	83.3±18.1	<0.001*
Protein intake/target (%)	51.1±23.4	39.1±19.2	51.2±22.4	57.9±24.5	<0.001*

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index; EN: enteral nutrition; ICU: intensive care unit; NRS 2002: Nutrition Risk Screening 2002; PN: parental nutrition.
†The ratio of actual energy intake/target energy intake: tertile I, <33.4%; tertile II, 33.4%–66.7%; and tertile III, >66.7%.
‡Propofol is a fatty sedative drug and used in some of the participants; its energy value was included in the energy intake calculation.
*Statistically significant difference.

Table 2. Clinical outcomes (n=325)

Variable	Overall (n=325)	Tertile I† (n=62)	Tertile II† (n 159)	Tertile III† (n=104)	*p* value
ICU mortality (n [%])	81 (24.9)	17 (27.4)	36 (22.6)	28 (26.9)	0.637
Hospital mortality (n [%])	89 (27.4)	18 (29.0)	41 (25.8)	30 (28.8)	0.844
60-day mortality (n [%])	102 (31.4)	22 (35.5)	46 (28.9)	34 (32.7)	0.609
ICU-associated infection (n [%])	84 (25.8)	7 (11.3)	43 (27.2)	34 (32.7)	0.008*
ICU LOS (days)	13.2±15.1	8.0±7.0	13.5±16.4	15.7±15.8	<0.001*
Hospital LOS (days)	35.6±31.8	27.0±21.6	36.5±31.9	39.5±35.7	0.049*
Duration of mechanical ventilation (days)	6.0±10.2	3.3±4.4	5.8±9.3	8.0±9.3	0.016*
ICU-free days‡ (days)	32.7±23.9	33.3±25.4	33.4±23.8	31.1±23.5	0.729
Hospital-free days‡ (days)	18.1±19.7	19.5±19.5	18.0±19.6	17.3±20.0	0.788
Days free of mechanical ventilation‡ (days)	38.1±25.7	37.3±27.2	38.7±25.7	37.8±25.1	0.925
Insulin dosage	16.2±24.7	14.6±21.5	17.8±27.2	14.7±22.5	0.532
Mean glucose (mmol/L)	9.6±2.2	9.5±2.2	9.6±2.2	9.6±2.3	0.879
EN patients (n)	262	38	136	88	
Feeding intolerance (n [%])	105 (40.1)	11 (28.9)	55 (40.4)	39 (44.3)	0.278
Prokinetics use (n [%])	43 (16.4)	5 (13.2)	18 (13.2)	20 (22.7)	0.143

EN: enteral nutrition; ICU: intensive care unit; LOS: length of stay.
†The ratio of actual energy intake/target energy intake: tertile I, <33.4%; tertile II, 33.4%–66.7%; and tertile III, >66.7%.
‡Intensive care unit (ICU)-free days, hospital-free days, and days free of mechanical ventilation were the number of days since patients had left the ICU or hospital or had not used mechanical ventilation in the first 60 days after ICU admission, respectively; if a patient died on or before day 60, the value was recorded as 0.
*Statistically significant difference.

Table 3. Logistic regression analysis of ICU-associated infections (n=325)

Independent variable	β	SE	Wald	*p* value	OR	95% CI
Constant	−2.481	0.481	26.565	<0.001	0.084	–
Energy groups	0.481	0.204	5.570	0.018	1.617	1.085–2.410
ICU category	−0.653	0.293	4.987	0.026	0.520	0.293–0.932
ICU LOS	0.049	0.012	18.085	<0.001	1.050	1.027–1.074

CI: Confidence interval; ICU: intensive care unit; LOS: length of stay; SE: standard error; OR: odds ratio.

DISCUSSION

The results of this retrospective study showed that energy intake had no effect on mortality rate in critically ill patients with lower BMI, consistent with the results of 3 recent, well-designed RCTs.[9,10,12] Our findings regarding ICU LOS, hospital LOS, and duration of mechanical ventilation were also in agreement with those of observational studies[5,6] (although these did not exclude days on an oral diet[3]) based on the unadjusted analysis. When we adjusted for potentially confounding factors, the differences between the 3 tertiles disappeared; however, a higher energy intake was still associated with increased risk of ICU-associated infections.

Three large RCTs[9,10,12] and meta-analyses[13-15] have shown that trophic feeding or permissive underfeeding produced the same clinical outcomes as full feeding. There has been concern regarding the safety and benefit of hypocaloric feeding in critically ill patients who are at high nutritional risk. Based on the large difference in BMI between Americans/Europeans and Asians, our aim was to assess the effects of energy intake in patients with a lower BMI. Excessive nutrition may increase ICU-associated infection rates and medical costs; thus, a low energy intake may be beneficial in early nutrition therapy. Our study included 155 (47.7%) patients at high nutritional risk, which was determined based on NRS2002 score. Others have reported an association between protein and energy intake and improved mortality in higher risk critically ill patients,[17] which was not supported by our data or by post hoc analysis in the PermiT trial.[21] Additional tools and strategies are needed to identify critically ill patients at high nutritional risk.[22]

We observed significant differences in intertertile comparisons of ICU LOS, hospital LOS, and duration of mechanical ventilation in the unadjusted analysis but not in the multivariate analysis. A possible explanation for this discrepancy is that patients with good prognosis may have had a shorter stay in the ICU and consumed fewer energy, and were more likely to be allocated to tertile I, which comprised patients with shorter ICU LOS, hospital LOS, and duration of mechanical ventilation. When we performed the sensitivity analysis only in patients with an ICU LOS ≥7 days, the difference disappeared. Patients with extremely poor prognosis who are more likely to die in the first 7 days of hospitalization and consume fewer energy may have been assigned to tertile I despite having a shorter ICU LOS, hospital LOS, and duration of mechanical ventilation than patients with a better prognosis. We therefore selected an appropriate time point to calculate ICU-free days, hospital-free days, and days free of mechanical ventilation to better represent actual prognosis. Accordingly, ICU-free days, hospital-free days, and days free of mechanical ventilation at 60 days yielded consistent results in the unadjusted, multivariate, and sensitivity analyses. Previous observational studies[5,6] reported findings similar to those of our unadjusted analysis because they disregarded the aforementioned confounding factors and did not exclude the duration of oral

Table 4. Clinical outcomes (ICU LOS ≥7 days, n=215)

Variable	Overall (n=215)	Tertile I† (n=23)	Tertile II† (n=111)	Tertile III† (n=81)	*p* value
ICU-associated infection (n [%])	72 (33.5)	3 (13.0)	37 (33.3)	32 (39.5)	0.060
ICU length of stay (days)	17.6±16.9	14.1±8.6	17.4±18.3	18.8±16.7	0.493
Hospital LOS (days)	39.4±32.3	32.7±16.1	39.8±32.7	40.8±35.0	0.563
Duration of mechanical ventilation (days)	8.2±12.0	5.7±6.3	7.5±10.7	9.8±14.5	0.255

ICU: intensive care unit; LOS: length of stay.
†The ratio of actual energy intake/target energy intake: tertile I, <33.4%; tertile II, 33.4%–66.7%; and tertile III, >66.7%.

Table 5. Logistic regression analysis of ICU-associated infection (ICU LOS ≥7 days, n=215)

Independent variable	β	SE	Wald	*p* value	OR	95% CI
Constant	−2.147	0.622	11.906	0.001	0.117	–
ICU category	−0.875	0.329	7.098	0.008	0.417	0.219–0.793
ICU LOS	0.037	0.012	10.284	0.001	1.038	1.015–1.062
Energy groups	0.557	0.253	4.863	0.027	1.746	1.064–2.865

CI: confidence interval; ICU: intensive care unit; LOS: length of stay; SE: standard error; OR: odds ratio.

feeding.[3]

ICU-associated infection rates differed significantly between the unadjusted and multivariate analyses; however, when we included only patients with ICU stays ≥7 days and performed a sensitivity analysis, the *p* value was 0.060. A possible explanation for this result is that the sensitivity analysis did not include a sufficient number of patients, which reduced analytical power. In contrast to the findings of 2 recent large RCTs,[10,12] we found that increased energy intake was associated with a higher rate of ICU-associated infections. Tertile III received more energy from PN, which increases the risk of intestinal bacterial translocation, and the allocation and infusion processes has been linked to an elevated risk of bacterial infection.[23,24] The increased infection rates may be attributable to the fact that early administration of PN suppresses autophagy, resulting in inadequate clearance of damaged cells and microorganisms.[25] Thus, the natural physiologic response of appetite loss and anorexia in the acute phase of critical illness may be beneficial.[8] Additional studies are needed to clarify the mechanistic basis for this observation.

Hypocaloric feeding can reduce glucose levels and decrease insulin dosages;[10,26] however, we did not observe

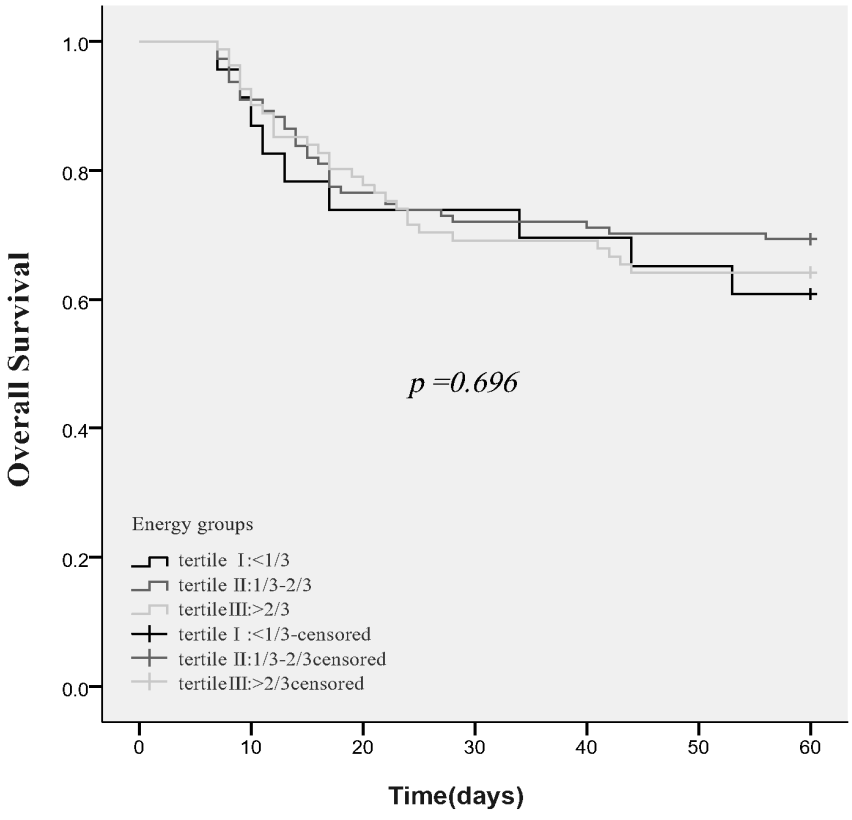

Figure 3. Survival time after ICU admission in 3 tertiles of 215 patients determined by Kaplan-Meier and log-rank analyses (ICU LOS ≥7days).

any differences in these parameters. We speculate that tertile I received more dextrose energy through intravenous feeding, despite a lower total energy intake.

Patients in tertile III had higher rates of gastrointestinal intolerance and prokinetics usage than those in tertile I but the difference was nonsignificant, consistent with an earlier report.[12] Previous studies have shown that patients receiving full feeding experienced greater gastrointestinal intolerance and used more prokinetics.[9,10] The possible reason for different results maybe we calculated energy intake from PN, and clinicians at our research center routinely prescribe prokinetics. Several gastrointestinal intolerance symptoms such as gastric retention and bowel sound weakening or disappearance were not noted in the medical records.

Our study had some limitations. Firstly, this was a retrospective study and although we employed various measures to eliminate the effects of potential confounders, some factors may have influenced our results. Secondly, because our study was carried out at a single hospital, the conclusions may not be generalizable to all ICU patients. Finally, because of the restricted sample sizes, we could not perform subgroup analyses by age, BMI, nutrition risk, and APACHE II score, which may have prevented the detection of significant differences.

Conclusion

The results of this study demonstrate that energy intake in early nutrition therapy influences the risk of ICU-associated infections in Chinese ICU patients with a lower BMI and that patients with near-target energy intake have a higher frequency of ICU-associated infections. These findings provide a basis for managing nutritional intake in ICU patients in order to ensure a good clinical outcome.

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AUTHOR DISCLOSURES

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