



Applied nutritional investigation

Effects of nutrition factors on mortality and sepsis occurrence in a multicenter university-based surgical intensive care unit in Thailand (THAI-SICU study)



Supakrit Auiwattanakul M.D.^a, Kaweesak Chittawatanarat M.D., Ph.D.^{b,*}, Onuma Chaiwat M.D.^c, Sunthiti Morakul M.D.^d, Suneerat Kongsayreepong M.D.^c, Winai Ungpinitpong M.D.^e, Surakrant Yutthakasemsunt M.D., Ph.D.^f, Supawan Buranapin M.D.^g

^a Department of Surgery, Institute of Medicine, Suranaree University of Technology, Thailand

^b Department of Surgery, Faculty of Medicine, Chiang Mai University, Thailand

^c Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

^d Department of Anesthesiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

^e Department of Surgery, Surin Hospital, Surin Province, Thailand

^f Department of Surgery, Khon Kaen Hospital, Khon Kaen Province, Thailand

^g Department of Medicine, Faculty of Medicine, Chiang Mai University, Thailand

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ABSTRACT

Objectives: The aim of this study was to demonstrate the role of nutrition factors on a 28-d mortality outcome and sepsis occurrence in surgical intensive care unit.

Methods: The data was extracted from a THAI-SICU study that prospectively recruited participants (≥ 18 y of age) from three Thai surgical intensive care units (SICUs) of university-based hospitals. The demographic data and nutrition factors at SICU admission included energy delivery deficit, weight loss severity, route of energy delivery, and albumin and nutrition risk screening (NRS-2002). The outcomes were 28-d hospital mortality and sepsis occurrence. The statistical analysis was performed using Cox regression.

Results: The study included 1503 eligible patients with a predominantly male population. The 28-d mortality and sepsis occurrences were 211 (14%) and 452 (30%), respectively. Regarding multivariable analysis, for mortality outcome, the protective effects of nutrition variables were higher body mass index (BMI; hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.68–0.99; $P=0.039$), tube feeding (HR, 0.46; 95% CI, 0.26–0.83; $P=0.010$), and a combination of enteral and parenteral nutrition (HR, 0.24; 95% CI, 0.07–0.77; $P=0.016$). The harmful effects were severe weight loss (HR, 1.61; 95% CI, 1.16–2.22; $P=0.004$), albumin ≤ 2.5 (HR, 2.15; 95% CI, 1.20–3.84; $P=0.010$), and at risk according to NRS-2002 (HR, 1.34; 95% CI, 0.98–1.85; $P=0.071$). For the sepsis occurrence, only tube feeding had a protective effect (HR, 0.58; 95% CI, 0.39–0.88; $P=0.009$), and only albumin ≤ 2.5 had a harmful effect (HR, 1.71; 95% CI, 1.20–2.45; $P=0.003$).

Conclusion: Nutrition factors affecting the mortality or sepsis occurrence in this study were BMI, enteral feeding or combination with parenteral nutrition, severe weight loss, preadmission albumin ≤ 2.5 , and at risk according to NRS-2002.

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* Corresponding author: Tel.: +66 539 35533 Fax: +66 539 36139.

E-mail address: kchittaw@gmail.com (K. Chittawatanarat).

Introduction

Malnutrition leads to the worst outcome in hospital patients [1–3]. A large retrospective single-center study in the United States found the increase in 30-d mortality in critically ill patients with protein–energy malnutrition doubled [3]. In a previous large prospective cohort report in surgical critically ill patients in Thailand, malnourished patients were also at a significantly increased risk for intensive care unit (ICU), 28-d mortality, and sepsis

occurrence [2]. The consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition recommended diagnosis of adult malnutrition. The statement suggested that at least two factors of the following included insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation, and diminished functional status as measured by handgrip strength [4]. Serum albumin levels as a nutrition feature carry the highest weight in the prognostic nutrition index calculation and associated postoperative outcomes [5]. However, the effect size of these nutrition factors is still unknown, especially in surgical critically ill patients in Thailand. Therefore, the present study aimed to evaluate the effect of some of the nutrition factors, especially energy delivery deficit, weight loss, route of energy delivery before admission, and admission albumin and nutrition risk assessment on the mortality outcome and sepsis occurrence in multicenter surgical ICUs (SICUs) in Thailand.

Participants and Methods

Data source, participants, and study variables

The present data were retrieved from the multicenter study in SICUs (THAI-SICU study), which was run by two university-based hospitals in Bangkok and a third in Chiang Mai province. This was a prospective observational data collection study. The details of the methodology and unit characteristics were described previously [6].

The hospitals recruited all admission patients who were ≥ 18 y of age and had a length of stay or survived more than 24 h. At SICU admission, the demographic data, body mass index (BMI), diagnostic categories, and disease severity using the Acute Physiologic and Chronic Health Evaluation II (APACHE II) score were recorded. Additionally, nutrition indices including weight loss (Table 1), nutrition intake or energy delivery (Table 2), nutrition risk screening (NRS-2002), and admission albumin levels were also collected. For the nutrition or energy intake before SICU admission, oral intake was a retrospective self-report or an interview of the patient or caregiver by trained ICU nurses and a medical record review in those who had been in-hospital patient before SICU admission. Nutrition risk was defined as an NRS-2002 score of ≥ 3 [7].

Study outcomes of the mortality and the new sepsis occurrence were prospectively followed within the 28-d period after SICU admission. New sepsis occurrence was followed daily. Sepsis occurrence in this study used the Sepsis-II definition as a systemic inflammatory response and infection with or without organ failure or unstable hemodynamics, as well as patients with new onset of fever and suspected infection with or without an identified source (non-infectious patients were excluded) and starting antimicrobial agents. The detail of data collection protocol was defined in a previous methodology report [6]. The date of sepsis occurrence was the first date of culture or starting of antimicrobial agents. The office of Joint Research Ethic Committee approved this study before data collection [6].

Table 1
Weight loss criteria

Time period	Weight loss, %		
	Mild	Moderate	Severe
1 wk	<1	1–2	>2
2–3 wk	<2	2–3	>3
1 mo	<4	4–5	>5
3–5 mo	<7	7–8	>8
≥ 6 mo	<10	10	>10

Table 2
Energy or nutrition intake from normal requirement or usual intake criteria

Energy delivery, %	Period, d		
	≤ 7	8–14	>14
<10	Moderate	Severe	Severe
10–25	Mild	Moderate	Severe
25–50	No	Mild	Moderate
50–75	No	No	Mild
75–100	No	No	No

The definitions of weight loss severity and level of energy delivery deficit depend on their estimated or measured amount of weight or food intake history and the time frame of their alteration from the usual condition. In this study, we modified these definitions based on the nutrition triage tool (NT-2013), which is the most common nutrition assessment tool used in Thailand and is recommended by the Society of Parenteral and Enteral Nutrition of Thailand [8]. The original table scored the weight loss severity and energy deficit. We categorized these variables into four categories: no, mild, moderate, and severe. Details of the criteria are presented in Tables 1 and 2.

Statistical analysis and prediction models

The continuous or discrete data was described as median and interquartile range (IQR) or divided into two or more groups and was described by percentage. The categorical data was described as a percentage. We compared two samples of continuous or discrete data using the Wilcoxon rank-sum test and Fisher's exact test comparing two proportions of data. The significant factors were used as the adjusted variables on the multivariable Cox regression, which was performed on mortality and the first day of new sepsis occurrence within 28 d after SICU admission.

Results

In all, 1503 participants were eligible, after excluding 746 from 2249 based on nutrition data. The overall 28-d mortality rate was 14% ($n = 211$) and new sepsis occurrence was 30% ($n = 452$; Fig. 1).

Baseline data were comparable in the two groups: like age and sex except for BMI, APACHE II scores, and sepsis at admission. The APACHE II score was significantly higher on both sepsis occurrence and non-surviving patients ($P = 0.001$ and $P = 0.001$, respectively; Table 3). There were no differences in admission diagnosis between the 28-d mortality group and patients with sepsis occurrence, except sepsis at admission (Table 3). However, a patient with a diagnosis of respiratory, abdominal, and musculoskeletal–skin categories had a significantly higher proportion of sepsis occurrence in this cohort (Table 3).

In Table 4, significant differences in nutritional factors were seen in both outcomes of mortality and sepsis occurrence, including energy delivery deficit, weight loss, and route of energy delivery, but not duration of delivery. Both mortality and sepsis occurrence had a significant energy delivery deficit, more weight loss, and less tube feeding or combination of parenteral delivery. For energy delivery, most patients had a higher proportion in the group of >14 d of their self-report of nutrition delivery. For admitted albumin levels and NRS-2002 score, patients who were at risk for malnutrition or hypoalbuminemia strongly correlated with 28-d mortality and sepsis occurrence (median [IQR]: mortality: 2.3 [1.7–2.8] versus 2.9 [2.3–3.5] g/dL, $P < 0.001$; and sepsis occurrence: 2.4 [1.9–2.9] versus 3 [2.4–3.6] g/dL, $P < 0.001$, respectively; Table 4).

Severity of disease as measured by APACHE II and diagnostic categories was adjusted in multivariable analysis on interested outcomes (Table 5). Regarding mortality outcome, high BMI (median [IQR]: 0.82 [0.68–0.99], $P = 0.039$), previous tube feeding or receiving of enteral nutrition (median [IQR]: 0.46 [0.26–0.83], $P = 0.010$), or a combination of both enteral and parenteral nutrition (median [IQR]: 0.24 [0.07–0.77], $P = 0.016$) had a significant low probability of mortality. In contrast, severe weight loss, admission albumin levels of ≤ 2.5 g/dL (median [IQR]: 1.61 [1.16–2.22], $P = 0.004$ versus 2.15 [1.20–3.84] g/dL, $P = 0.010$, respectively) and nutrition risk (median [IQR]: 1.34 [0.98–1.85], $P = 0.071$) had a high probability of mortality. Regarding sepsis occurrence outcome, previous tube feeding ($P = 0.009$) had a significant low probability, and there was a low probability in the previous receipt of combined enteral and parenteral nutrition ($P = 0.086$). In contrast, only admission albumin levels of ≤ 2.5 g/dL ($P = 0.003$) had a high probability of sepsis occurrence (Table 5; Fig. 2).

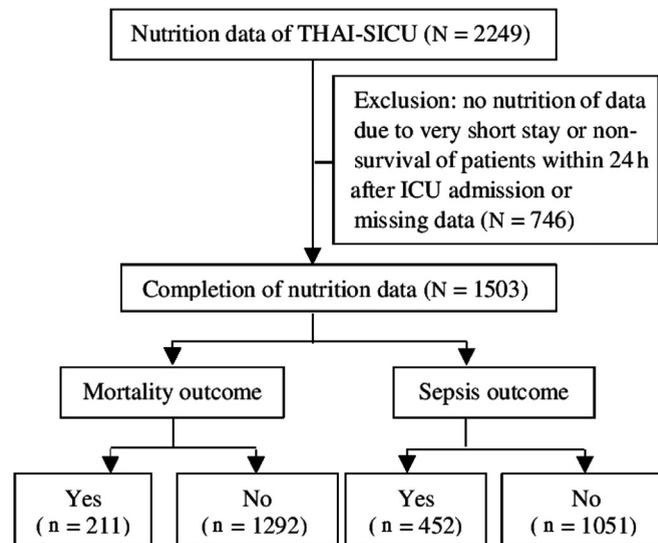


Fig. 1. Study flow. ICU, intensive care unit; SICU, surgical intensive care unit.

Table 3

Patient characteristics of non-survival (28-d mortality) vs survival and sepsis occurrence vs no sepsis occurrence (N = 1503)

Variables	Non-survival (n = 211)	Survival (n = 1,292)	P-value	Sepsis occurrence (n = 452)	No sepsis occurrence (n = 1,051)	P-Value
Age (y), median (IQR)	65 (54–77)	65 (52–76)	0.406	66 (53.5–77)	64 (52,–5)	0.121
Male, n (%)	115 (54.5)	745 (57.7)	0.409	269 (59.5)	591 (56.2)	0.256
BMI (kg/m ²), median (IQR)	22 (19–24.2)	22.6 (19.9–25.8)	0.012	22.3 (19.5–25.4)	22.5 (19.9–25.6)	0.578
APACHE II, median (IQR)	20 (16–27)	11 (8–15)	0.001	16 (12–22)	11 (7–15)	0.001
Diagnostic categories, n (%)			0.021			0.764
Cardiovascular	29 (13.7)	245 (19)	0.505	51 (11.3)	223 (21.2)	0.478
Respiratory	30 (14.2)	155 (12)	0.189	65 (14.4)	120 (11.4)	0.024
Abdominal (GI, HBP)	96 (45.5)	453 (35.1)	0.142	196 (43.4)	353 (33.6)	0.018
Neuro-Head-Neck	5 (2.4)	41 (3.2)	0.540	4 (0.9)	42 (4)	0.522
Sepsis at admission	13 (6.2)	24 (1.9)	0.012	32 (7.1)	5 (0.5)	0.001
Trauma	12 (5.7)	67 (5.2)	0.248	22 (4.9)	57 (5.4)	0.121
Metabolic	1 (0.5)	30 (2.3)	0.543	5 (1.1)	26 (2.5)	0.759
Renal-Genitourinary	8 (3.8)	114 (8.8)	0.983	23 (5.1)	99 (9.4)	0.481
Obstetric-Gynecologic	1 (0.5)	46 (3.6)	0.340	7 (1.6)	40 (3.8)	0.849
Musculoskeletal-Skin	13 (6.2)	89 (6.9)	0.365	43 (9.5)	59 (5.6)	0.007
Others	3 (1)	28 (2.2)	0.609	4 (0.9)	27 (2.5)	0.046

HBP, Hepato-biliary-pancreas; GI, gastrointestinal.

Bold values are the parameter that $p < 0.05$.

Discussion

In the present study, the crude 28-d mortality and new sepsis occurrence rate in SICU patients were 14% and 30%, respectively. On the univariable analysis, risk factors for mortality in this study were BMI, APACHE II score, diagnostic categories, weight loss severity, hypoalbuminemia, and being at nutritional risk according to the NRS assessment. Risk factors for sepsis occurrence were APACHE II score, diagnostic categories, hypoalbuminemia, and being at nutritional risk according to the NRS assessment.

Regarding BMI, a previous observation study reported by Lim et al. found that BMI did not affect the significant predictor of ICU mortality [9]. Severity of diseases and failure to remove an endotracheal tube had more influence on mortality in their study [9]. In the results of the present multivariable analysis, BMI was significantly associated with mortality, but was not significant in the occurrence of sepsis. The present results had the same direction as the recent systematic review and meta-analysis by Pepper et al., which found that overweight and obese patients had significantly lower adjusted mortality than sepsis patients admitted to the ICU [10]. Although the median and IQR of BMI in the present study were

within the normal range (Table 3), higher BMI had protective effects on probability for mortality. These phenomena might be referred to as the energy reserve play, an important role on the hypermetabolic state in critically ill patients.

Energy deficit from less food intake and malnourishment led to a lengthy hospital stay and mortality in a large observation by an Australasian nutrition day survey [11]. In the present results, moderate to severe energy delivery deficit was significantly associated with mortality, but was not significant after adjusted in multivariable analysis for both mortality and sepsis occurrence. These results might occur from the stronger effects of disease severity on a statistical model. Additionally, we found that the patient who previously received enteral or a combination had a lower risk for mortality and sepsis occurrence in the multivariable analysis.

Although there were no exact data on preadmission, there are two possible reasons for these effects. First, enteral nutrition in the functioning gut could be achieved or approached the target of energy requirement more than oral diet alone in sick patients. The more protective effect of mortality was shown in the patients with a combination of enteral and parenteral nutrition. Second, there was the physiologic effect of enteral nutrition on gut-barrier

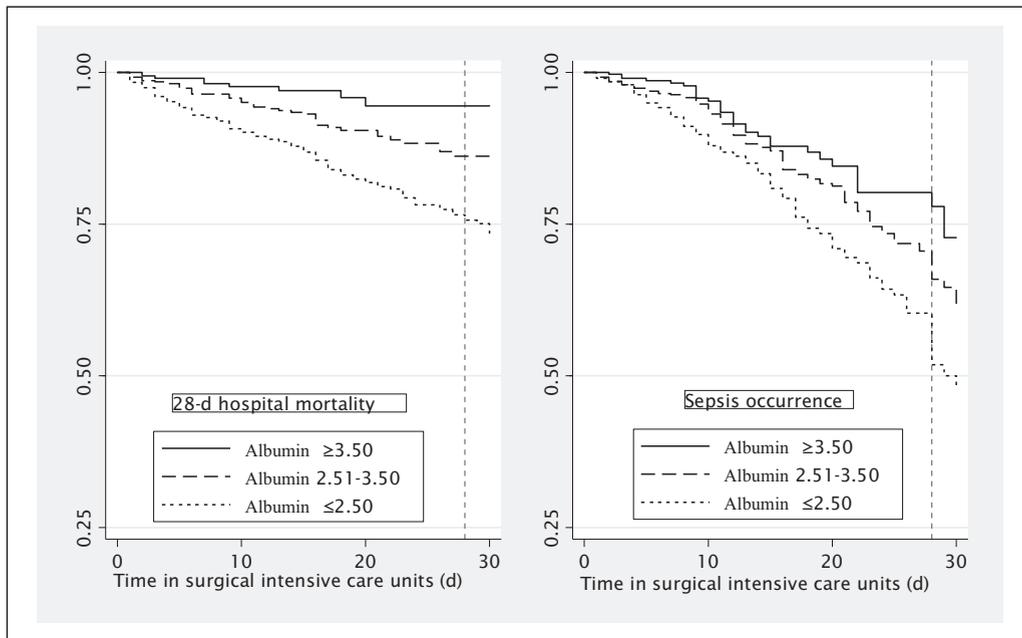


Fig. 2. Kaplan–Meier survival estimates of 28-d mortality and sepsis occurrence by albumin groups.

function [12]. The present results demonstrated that although there was no statistical significance on mortality in parenteral nutrition alone, the effect size of hazard was higher than oral nutrition, whereas enteral or combination nutrition had significant protective effects on mortality.

Weight loss is a characteristic of malnourishment (undernutrition). It is a parameter to evaluate and document on the nutrition status and is taken into account in screening and assessment tools [4]. Weight loss reflects the whole body reserve. However, acute weight gain in critically ill patients might be a sign of fluid accumulation or fluid overload and can lead to worsening outcomes [13]. We found that only severe weight loss in the definition of nutrition triage had a significant effect on mortality. Nevertheless, the accurate amount of weight change in a particular period is an estimation in some patients. Memory might affect the precision of the data.

In the multivariable analysis, albumin levels at admission, which were ≤ 2.5 g/dL, showed a strongly significant association with mortality. Likewise, a previous retrospective study by Seo et al. showed that albumin, base excess, and respiratory rate at admission could accurately predict 28-d mortality in severe sepsis with shock in the emergency department [14] and could predict mortality in an acute illness setting through the Herrmann et al. report [15].

Furthermore, nutrition risk (NRS 2002) at admission was significantly associated with mortality. This result was in line with previous studies [16,17]. The recent systematic review and meta-analysis of prospective cohort studies on NRS-2002 as a predictor of postoperative outcome in abdominal surgical patients demonstrated that the mortality risk in patients had a higher pooled odds ratio of 3.61 (95% CI, 1.38–9.47; $P = 0.009$) [18].

The strength of the present study was that it was a large cohort, multicenter observational study with an academic base and its comprehensive collaboration studies between specialties in Thailand. However, 33% (746 of 2,249) of short ICU stays, incomplete data, and missing data on nutrition variables were excluded owing to an observational study. The prehospital data in some patients,

especially on weight loss and amount of energy intake, were estimations; whereas weight loss was defined as the amount of the present weight decrease compared with the normal weight. If the present weight did not change or increase, it was classified as no weight loss. Additionally, the amount of energy intake was a proportion of the present intake and the normal intake. These might lead to recall bias if they missed the normal weight or the normal intake, respectively.

The limitations of the study were first that there was no specification of surgery types (elective/urgent/emergency) and no information on the variables of the nutrition intervention during ICU admission, which could modify the outcomes. Second, although there was a large number of SICU patients in Thailand, this study was conducted in three large tertiary university-based hospitals. The generalizability to other hospital levels might be limited. Third, although the duration and route of nutrition delivery might have a significant association, we could not demonstrate these associations because the exact delivery time (uncertain time) was 18.7% and a total of 73.5% of self-report duration of delivery accounted for the group of > 14 d. Additionally, 91.5% of self-report route provided was on oral nutrition route. A future study of comparison between prior admission of route and duration of nutrition support on SICU outcomes should be considered.

However, this study confirmed the knowledge gap of nutrition factors on the main outcomes in surgical critically ill patients. In addition to patient disease severity, the patients who had nutrition risk factors should be a concern and nutrition therapy should be undertaken as soon as possible. Although we found protective effects of enteral nutrition provision or its combination, the physiological effects and nutrition preparation with isocaloric enteral nutrition or oral supplement before SICU admission on elective high-risk surgical patients who need SICU admission might be initiated for future study. Additionally, nutrition assessment tools used in critically ill patients, such as the Bhumibol Nutrition Triage/Nutrition Triage, NRS-2002, Subjective Global Assessment, and NUTRIC score, might be initiated in a further study in multicenter studies in Thailand.

Table 4
Nutrition characteristics of non-survival (28-d mortality) and sepsis occurrence (N = 1503)

Nutrition factors	Non-survive (n = 211)	Survive (n = 1,292)	P- value	Sepsis occurrence (n = 452)	No sepsis occurrence (n = 1,051)	P-value
Energy delivery deficit, n (%)			<0.001			<0.001
No	108 (51.2)	863 (66.8)		251 (55.5)	720 (68.5)	
Mild	47 (22.3)	229 (17.7)		100 (22.1)	176 (16.8)	
Moderate	43 (20.4)	181 (14)		85 (18.8)	139 (13.2)	
Severe	13 (6.2)	19 (1.5)		16 (3.5)	16 (1.5)	
Weight loss severity, n (%)			<0.001			<0.001
No	97 (46)	812 (62.9)		239 (52.9)	670 (63.8)	
Mild	19 (9)	126 (9.8)		42 (9.3)	103 (9.8)	
Moderate	22 (10.4)	108 (8.4)		48 (10.6)	82 (7.8)	
Severe	73 (34.6)	246 (19)		123 (27.2)	196 (18.7)	
Route of delivery before admission, n (%)			<0.001			0.007
Oral	182 (86.3)	1,193 (92.3)		394 (87.2)	981 (93.3)	
Tube feed	16 (7.6)	37 (2.9)		29 (6.4)	24 (2.3)	
IV	6 (2.8)	11 (0.9)		7 (1.6)	10 (1)	
Combined	3 (1.4)	40 (3.1)		15 (3.3)	28 (2.7)	
None	4 (1.9)	11 (0.9)		7 (1.6)	8 (0.8)	
Duration of delivery (d), n (%)			0.121			0.139
≤7	13 (6.2)	45 (4.5)		23 (5.1)	35 (3.3)	
8–14	11 (5.2)	47 (3.6)		23 (5.1)	35 (3.3)	
>14	144 (68.2)	961 (74.4)		323 (71.4)	782 (74.4)	
Uncertain time	43 (20.4)	239 (18.5)		83 (18.4)	199 (18.9)	
Albumin level, median (IQR), g/dL	2.3 (1.7–2.8)	2.9 (2.3–3.5)	<0.001	2.4 (1.9–2.9)	3 (2.4–3.6)	<0.001
Albumin groups, n (%)			<0.001			<0.001
≥ 3.50	15 (7.1)	295 (22.8)		40 (8.9)	270 (25.7)	
2.51–50	58 (27.5)	543 (42)		139 (30.8)	462 (44)	
≤ 2.50	138 (65.4)	454 (35.1)		273 (60.4)	319 (30.4)	
Nutrition risk screening (NRS-2002)			<0.001			<0.001
At risk, n (%)	129 (70.9)	484 (43.1)		249 (63.9)	364 (39.8)	
No risk, n (%)	53 (29.1)	638 (56.9)		141 (36.2)	550 (60.2)	

IV, intravenous; NRS, nutrition risk screening.

Bold values are the parameter that $p < 0.05$.

Table 5
Multivariable Cox analysis of predictors of non-survival (28-d mortality) and sepsis occurrence

Variables	Non-survival*		Sepsis occurrence*	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Body mass index	0.82 (0.68–0.99)	0.039	1.01 (0.91–1.12)	0.828
Energy delivery deficit				
No	Reference		Reference	
Mild	1.16 (0.81–1.65)	0.412	0.90 (0.70–1.14)	0.367
Moderate	1.20 (0.83–1.73)	0.338	0.98 (0.76–1.27)	0.876
Severe	1.59 (0.89–2.87)	0.120	0.87 (0.52–1.46)	0.597
Weight loss severity				
No	Reference		Reference	
Mild	1.08 (0.64–1.82)	0.770	1.08 (0.77–1.51)	0.653
Moderate	1.05 (0.60–1.59)	0.890	0.93 (0.59–1.20)	0.320
Severe	1.61 (1.16–2.22)	0.004	1.02 (0.81–1.29)	0.863
Route of delivery before admission				
Oral	Reference		Reference	
Tube feed	0.46 (0.26–0.83)	0.010	0.58 (0.39–0.88)	0.009
IV	1.35 (0.58–3.10)	0.485	0.76 (0.36–1.62)	0.477
Combined	0.24 (0.07–0.77)	0.016	0.63 (0.37–1.07)	0.086
None	1.61 (0.58–4.44)	0.360	1.77 (0.79–3.99)	0.169
Admitted albumin, g/dL				
≥ 3.50	Reference	–	Reference	
2.51–3.50	1.11 (0.60–2.07)	0.734	1.21 (0.83–1.75)	0.318
≤ 2.50	2.15 (1.20–3.84)	0.010	1.71 (1.20–2.45)	0.003
NRS 2002				
No risk	Reference		Reference	
At Risk	1.34 (0.98–1.85)	0.071	1.08 (0.88–1.33)	0.480

IV, intravenous; NRS, nutrition risk screening.

Bold values are the parameter that $p < 0.05$.

*Include adjustment for APACHE II and diagnostic categories.

Conclusion

Nutrition factors having protective effects of mortality or sepsis occurrence are BMI, enteral feeding, parenteral nutrition, or a combination of both. In contrast, harmful factors of mortality or sepsis occurrence are severe weight loss, preadmission albumin levels of ≤ 2.5 , and nutrition at risk as assessed by the NRS-2002.

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