의학석사 학위논문

Relation between nutrition intake and 28-day mortality using modified NUTRIC score in patients with sepsis

패혈증 환자에서 modified NUTRIC score 를 이용한

영양공급과 28 일 사망률 사이의 관계

울 산 대 학 교 대 학 원

의 학 과

정 대 현

Relation between nutrition intake and 28-day mortality using modified NUTRIC score in patients with sepsis

지 도 교 수　　허 진 원

이 논문을 의학석사 학위 논문으로 제출함

2017 년 12 월

울 산 대 학 교 대 학 원

의　학　과

정 대 현

정대현의 의학석사학위 논문을 인준함

심사위원 홍상범 (인)

심사위원 허진원 (인)

심사위원 홍석경 (인)

울 산 대 학 교 대 학 원

2017 년 12 월

Abstract

Background & Aim: Appropriate nutrition intake is important for the outcome of critically ill patients. The NUTRIC (NUTrition RIsk in Critically ill) score and modified NUTRIC score are intensive care unit (ICU)-specific nutrition risk assessment tools that have been validated in many studies. The present study compared the accuracy of the NUTRIC score with the modified NUTRIC score for predicting 28-day mortality and investigated the relation between nutritional support and 28-day mortality using the modified NUTRIC score in patients with sepsis.

Methods: This was a retrospective cohort study in the medical ICU of a tertiary referral hospital. We included patients with sepsis admitted to Asan Medical Center between January 2011 and June 2017 who were at least 18 years old and stayed for more than 24 hours in the ICU. The NUTRIC or modified NUTRIC score was calculated using data within 24 hours of admission to the ICU. Nutritional support was categorized into <20, 20 to <25, and ≥25 kcal/kg energy intake and <0.8, 0.8 to <1.2, and ≥1.2 g/kg protein intake at day 7 after ICU admission. Multivariable logistic regression analysis was used for 28-day mortality as outcome.

Results: A total of 482 patients were analyzed. The area under the curve (AUC) of the NUTRIC score and modified NUTRIC score for predicting 28-day mortality was 0.762 (95% confidence interval [CI] 0.718–0.806) and 0.757 (95% CI 0.713–0.801), respectively. There was no significant difference between the two scores (P=0.45). In the group with high (≥5) modified NUTRIC scores, higher energy intake was significantly associated with lower mortality (20 to <25 kcal/kg: adjusted odds ratio [aOR] 0.373, 95% CI 0.169–0.740; ≥25 kcal/kg: aOR 0.367, 95% CI 0.182–0.740). Higher protein intake was significantly associated with lower mortality (0.8 to <1.2 g/kg: aOR 0.364, 95% CI 0.191–0.693; ≥1.2 g/kg: aOR 0.362, 95% CI 0.150–0.871). In patients with a low modified NUTRIC score (<5), higher energy intake (20 to <25 kcal/kg: aOR 0.185, 95% CI 0.046–0.744; ≥25 kcal/kg: aOR 0.111, 95% CI 0.032–0.384) and higher protein intake (0.8 to <1.2 g/kg: aOR 0.128, 95% CI 0.040–0.407; ≥1.2 g/kg: aOR 0.109, 95% CI 0.021–0.582) were significantly associated with

lower mortality.

Conclusions: The modified NUTRIC score was a good nutritional risk assessment tool for critically ill septic patients. High (≥5) modified NUTRIC scores were associated with high mortality. Adequate nutrition intake in the first week after ICU admission may improve 28-day mortality in patients with both high and low modified NUTRIC scores.

Keywords: nutrition, modified NUTRIC score, septic patients, mortality, intensive care unit

차 례

표 및 그림목차

Introduction

Malnutrition is very common among critically ill patients, with a prevalence of 20–50% [1-4]. Malnourished patients have increased morbidity and mortality [5-9]. Sepsis and septic shock are the leading causes of mortality in the intensive care unit (ICU). Hypermetabolism from excessive acute phase response and gastrointestinal dysfunction result in greater risk of malnutrition in patients with sepsis [10].

There have been many studies in recent decades on the importance of adequate nutrition support among critically ill patients, but the prevalence of hospital malnutrition has not changed much during the same period. It is important to assess nutrition status and provide adequate nutritional support in critically ill patients [11]. Adequate or aggressive nutritional support reduces hospital malnutrition and improves patient outcomes [12, 13]. Although many nutritional risk systems, such as the Nutritional Risk Screening 2002 (NRS 2002), Subjective Global Assessment (SGA), and Short Nutritional Assessment Questionnaire (SNAQ), have been developed for outpatients and inpatients, these systems are unsuitable for patients in the intensive care unit (ICU) [14-16]. Nutritional risk systems such as the NRS 2002, SGA, and SNAQ comprise factors that are difficult to obtain in critically ill patients, such as change of body weight, change of food intake in recent months, and gastrointestinal symptoms [17]. In addition, most ICU patients are classified as high-risk patients. Recently, Helyland et al. developed the Nutrition Risk in the Critically ill (NUTRIC) score as the first nutritional risk assessment tool for ICU patients, which consists of age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, number of comorbidities, days from hospital admission to ICU admission, and serum interleukin-6 (IL-6) level [18]. The NUTRIC score helps in identifying critically ill patients who may receive greater benefit from aggressive nutritional therapy. Although the NUTRIC score is based on variables including acute and chronic starvation, acute and chronic inflammation, and severity of underlying illness, measurement of IL-6 levels is not performed routinely in the critical care setting. Rahman et al. demonstrated the validity of the modified NUTRIC score, except for IL-6 [19]. Several studies have confirmed that the modified NUTRIC score is associated with clinical outcomes [20, 21]. However, the modified

NUTRIC score has not yet been validated in patients with sepsis.

There are insufficient studies on nutrition support for patients with sepsis. Most guidelines of nutritional support for septic patients are based on the results of studies among critically ill patients that include heterogenous groups [11, 22]. The effect of underfeeding in critically ill patients is controversial. Two randomized controlled trials (RCTs) comparing underfeeding with standard feeding in critically ill patients showed no difference in clinical outcomes [23, 24]. Arabi et al. showed that 90-day mortality in a subgroup of 292 patients with sepsis was not different between a hypocaloric feeding group and standard feeding group [24]. Another study showed that near-target caloric intake is associated with adverse outcomes such as increased hospital mortality and infectious complications [25]. Conversely, hypocaloric nutrition in critically ill patients is associated with more nosocomial infection [26]. Recently, many studies have shown the importance of the protein supply in nutrition support [27]. In the International Protein Summit, it was suggested that high doses of protein may be required in ICU settings, to optimize nutrition support and improve mortality rates [28]. Some guidelines recommend a protein intake of 1.2–2 g/kg/day for patients with sepsis [11]. An optimal protein supply may improve mortality among critically ill patients [29, 30]. A prospective observational study found that reaching both protein and energy targets is associated with decreased 28-day mortality, but only reaching the energy target is not associated with reduced mortality [29]. In an international, multicenter observational study, greater protein and energy intake was found to be associated with lower mortality and faster time to discharge alive in high-risk patients, using the modified NUTRIC score [31].

The present study was conducted to compare the accuracy of the NUTRIC score with the modified NUTRIC score for predicting 28-day mortality, and to investigate the relation between nutrition support and 28-day mortality using the modified NUTRIC score in patients with sepsis.

Materials and Methods

Study participants

This was a retrospective cohort study conducted in the medical ICU of Asan Medical Center, a tertiary referral hospital in Seoul, South Korea. From January 2011 to June 2017, a cohort of 518 patients with sepsis who were at least 18 years old and remained more than 24 hours in the ICU were included in the study. Patients who were discharged or died within 24 hours and those who were not evaluable for 28-day mortality were excluded. IL-6 was measured in blood samples from 482 patients included in the study. The study protocol was approved by the Institutional Review Board of Asan Medical Center. The requirement for informed consent was waived owing to the retrospective nature of the analysis.

Data collection

We reviewed patient data from electronic medical records of Asan Medical Center. We collected information of demographics, height, weight, comorbidities, diagnosis, length of stay (LOS) in the ICU, mechanical ventilation (MV), vasopressor drug use, and renal replacement therapy (RRT). Scores were calculated using data from the first 24 hours after ICU admission. We calculated the NUTRIC score (0–10) and modified NUTRIC score (0–9) using the available data. Scores ≥6 or ≥5 were considered high NUTRIC score and modified NUTRIC score, respectively [18, 19].

Energy (25–30 kcal/kg/day) and protein (1.2–1.5 g/kg/day) requirements were calculated using a simplistic weight-based equation [11]. The achieved daily energy and protein intakes were calculated by combining enteral nutrition (EN) and parenteral nutrition (PN) for 1, 3, and 7 days. Our nutrition support protocol was as follows: nutrition intake should reach 20–25 kcal/kg/day for energy and 0.8–1.2 g/kg/day for protein within one week. Nutritional adequacy was categorized into <20, 20 to <25, and ≥25 kcal/kg for energy and <0.8, 0.8 to <1.2, and ≥1.2 g/kg for protein at day 7 after ICU admission. This categorization was selected to ensure that nutritional intake was properly provided according to our nutrition protocol and to confirm 28-day mortality according to nutritional adequacy.

Statistical analysis

We compared high nutritional risk and low nutritional risk using the NUTRIC score and modified NUTRIC score, respectively. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Student's *t*-test or Wilcoxon–Mann–Whitney test. The model discrimination for predicting 28-day mortality was assessed by the area under the receiver operating characteristic (ROC) curve for both the NUTRIC score and modified NUTRIC score. The ROC curve of the two scores was compared using MedCalc (version 1.76; MedCalc Software bvba, Ostend, Belgium). We used logistic regression analysis in the univariable and adjusted multivariable analysis to compare variable differences in 28-day mortality with variable selection. We selected variables for the multivariable analysis if their P-value was 0.2 or lower in the univariable analysis. Multivariable logistic regression analysis with dummy variables for nutrition intake was used with 28-day mortality as outcome. All tests of significance were two sided; a P-value <0.05 was considered statistically significant. All statistical analyses were done using SPSS software (version 21.0; SPSS Inc., Chicago, IL).

Results

Characteristics of the 482 included patients are shown in Table 1, according to risk group in NUTRIC score and modified NUTRIC score. Overall, the median age of patients was 66 (56–74) years, the median BMI was 23 (20–25) kg/m^2, and 32% of patients were female. The median APACHE II score was 21 (16–28), the median SOFA score was 10 (7–14), and the median number of co-morbidities was 2 (1–3). There were 223 patients (46.3%) with neoplasm, and the median LOS in the ICU was 7 (4–14) days. MV was used in 312 (64.7%) patients, 417 patients (86.5%) received vasopressor drugs, and 152 patients (31.5%) received RRT. A total 255 (52.9%) and 316 patients (65.6%) had high NUTRIC score and modified NUTRIC score, respectively. Sixty-one patients with low score of NUTRIC score were changed to high score of modified NUTRIC score (Fig. 1). In these 61 patients, the median APACHE II score was 20 (17–23), the mean SOFA score was 9 (7–11), and 12 patients died within 28 days. The 28-day mortality increased with increased NUTRIC score and modified NUTRIC score (Fig. 2). The 28-day mortality for maximum NUTRIC score and modified NUTRIC score was 66.7% and 62.5% (Fig. 2), respectively. The area under the curve (AUC) of the NUTRIC score and modified NUTRIC score for predicting 28-day mortality was 0.762 (95% confidence interval [CI], 0.718–0.806) and 0.757 (95% CI, 0.713–0.801), respectively (Fig. 3). There was no significant difference in a comparison of ROC curves between the two scores (P=0.45). In the ROC curve of modified NUTRIC score, the best cutoff was found at 6 (sensitivity and specificity 75% and 65%, respectively), and the Youden index was 0.401 (Table 2). Nutrition profiles of patients, according to the modified NUTRIC score, are shown in Table 3. The mean energy target at week 1 was 1522 kcal/day and the mean achieved energy intake was 50.5%, 89.6%, and 99.8% of the energy target at 1, 3, and 7 days, respectively. The mean protein target at week 1 was 71.3 g/day and mean achieved protein intake was 31.5%, 70.2%, and 81.6% of the protein target at 1, 3, and 7 days, respectively. The rate of reaching the protein targets was relatively low compared with that of reaching the energy targets. In the low modified NUTRIC score group, enteral nutrition was started at day 3, on average, and 56.6% of patients received nutrition support as enteral nutrition on day 7. In the high modified NUTRIC score group, enteral nutrition was

started at day 4, on average, and 26.3% of patients received enteral nutrition support on day 7.

Relation between nutrition intake and 28-day mortality are shown in Table 4. The 28-day mortality was 32.8% (12.0% vs. 43.7% for low and high scores, respectively). The 28-day mortality decreased with increasing energy or protein intake. Univariable and multivariable logistic regression analysis for 28-day mortality in the total patients is shown in Table 5. Higher energy intake was significantly associated with lower mortality (20 to <25 kcal/kg: adjusted odds ratio (aOR) 0.346, 95% CI 0.172–0.694; ≥25 kcal/kg: aOR 0.303, 95% CI 0.164–0.557). Higher protein intake was significantly associated with lower mortality (0.8 to <1.2 g/kg: aOR 0.317, 95% CI 0.181–0.555; ≥1.2 g/kg: aOR 0.301, 95% CI 0.139–0.652). Results of univariable and multivariable logistic regression analyses for 28-day mortality in low modified NUTRIC score group are shown in Table 6. Among patients with low scores, higher energy intake was significantly associated with lower mortality (20 to <25 kcal/kg: aOR 0.185, 95% CI 0.046–0.744; ≥25 kcal/kg: aOR 0.111, 95% CI 0.032–0.384). Higher protein intake was significantly associated with lower mortality (0.8 to <1.2 g/kg: aOR 0.128, 95% CI 0.040–0.407; ≥1.2 g/kg: aOR 0.109, 95% CI 0.021–0.582). Results of univariable and multivariable logistic regression analyses for 28-day mortality in high modified NUTRIC score group are shown in Table 7. With high scores, higher energy intake was significantly associated with lower mortality (20 to <25 kcal/kg: aOR 0.373, 95% CI 0.169–0.826; ≥25 kcal/kg: aOR 0.367, 95% CI 0.182–0.740). Higher protein intake was significantly associated with lower mortality (0.8 to <1.2 g/kg: aOR 0.364, 95% CI 0.191–0.693; ≥1.2 g/kg: aOR 0.362, 95% CI 0.150–0.871).

Table 1. Patient characteristics according to NUTRIC score and modified NUTRIC score

	NUTRIC score (n = 482)			Modified NUTRIC score (n = 482)		
Variable	**Low score (n = 227)**	**High score (n = 255)**	**P-value**	**Low score (n = 166)**	**High score (n = 316)**	**P-value**
Age, years	63 (52–72)	68 (57–75)	<0.001	62 (48–71)	68 (57–75)	<0.001
Height, cm	163 (158–170)	163 (155–170)	0.175	163 (158–170)	163 (155–170)	0.456
Weight, kg	59 (52–66)	58 (51–67)	0.945	59 (52–67)	59 (52–66)	0.842
BMI, kg/m^2	23 (20–25)	23 (20–25)	0.456	23 (20–25)	22 (20–25)	0.827
Female, n (%)	68 (30)	86 (33.7)	0.376	52 (31.3)	102 (32.3)	0.831
APACHE II score	16 (13–20)	27 (22–32)	<0.001	15 (12–18)	25 (21–31)	<0.001
SOFA score	7 (5–10)	13 (11–16)	<0.001	6 (5–9)	12 (10–15)	<0.001
Days from hospital to ICU	0 (0–0)	0 (0–9)	<0.001	0 (0–0)	0 (0–8)	<0.001
Co-morbidities	1 (1–2)	2 (1–3)	<0.001	1 (1–2)	2 (1–3)	<0.001
IL-6, pg/ml	71 (21–169)	366 (54–1910)	<0.001	..	..	..
LOS in ICU, days	5 (3–9)	9 (4–17)	<0.001	5 (3–9)	8 (4–17)	<0.001
MV	102 (44.9)	210 (82.4)	<0.001	65 (20.8)	247 (78.2)	<0.001
Vasopressor use	172(75.8)	245 (96.1)	<0.001	123 (74.1)	294 (93.0)	<0.001
RRT	26 (11.5)	126 (49.4)	<0.001	17 (10.2)	135 (42.7)	<0.001
Diagnosis			0.693			0.465
Respiratory disease	103 (45.4)	118 (46.3)		69 (41.6)	152 (48.1)	
Liver/GI disease	60 (26.4)	63 (24.7)		48 (28.9)	75 (23.7)	
Cardiovascular disease	4 (1.8)	6 (2.4)		2 (1.2)	8 (2.5)	
Renal disease	22 (9.7)	18 (7.1)		17 (10.2)	23 (7.3)	
Febrile neutropenia	14 (6.2)	14 (5.5)		9 (5.4)	19 (6)	
SSTI	10 (4.4)	10 (3.9)		9 (5.4)	11 (3.5)	
Other	14 (6.2)	26 (10.2)		12 (7.2)	28 (8.9)	

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; TIA, transient ischemic attack; CRP, C-reactive protein; LOS, length of stay; ICU, intensive care unit; MV, mechanical ventilation; RRT, renal replacement therapy; GI, gastrointestinal; SSTI, skin and soft tissue infection.
Data are presented as number (%) or median (IQR).

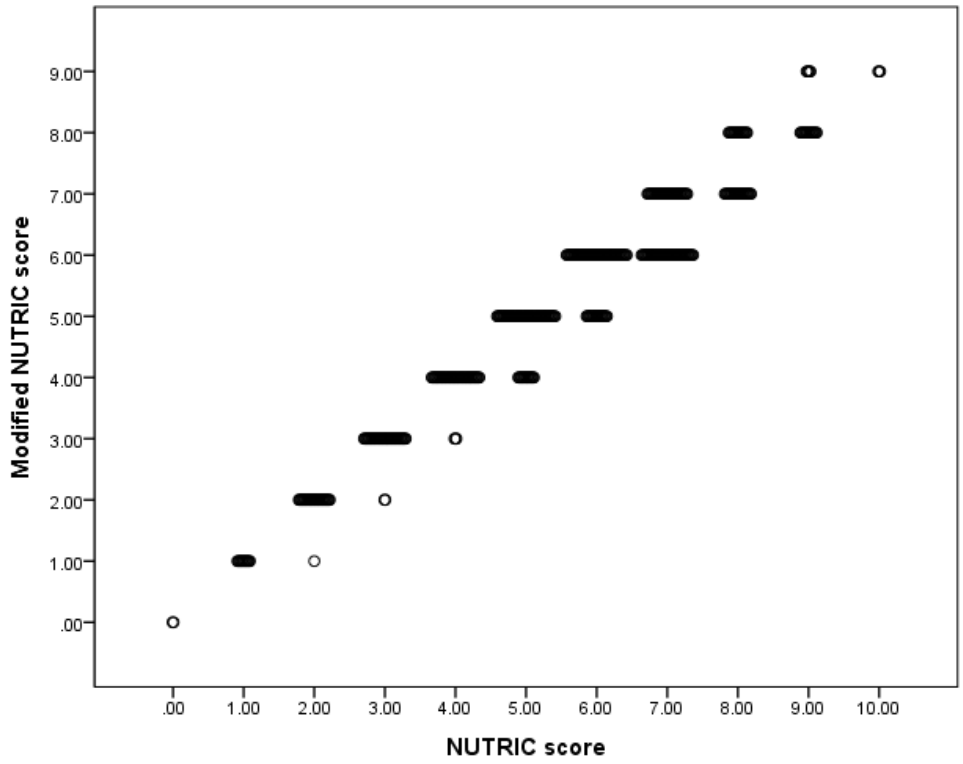
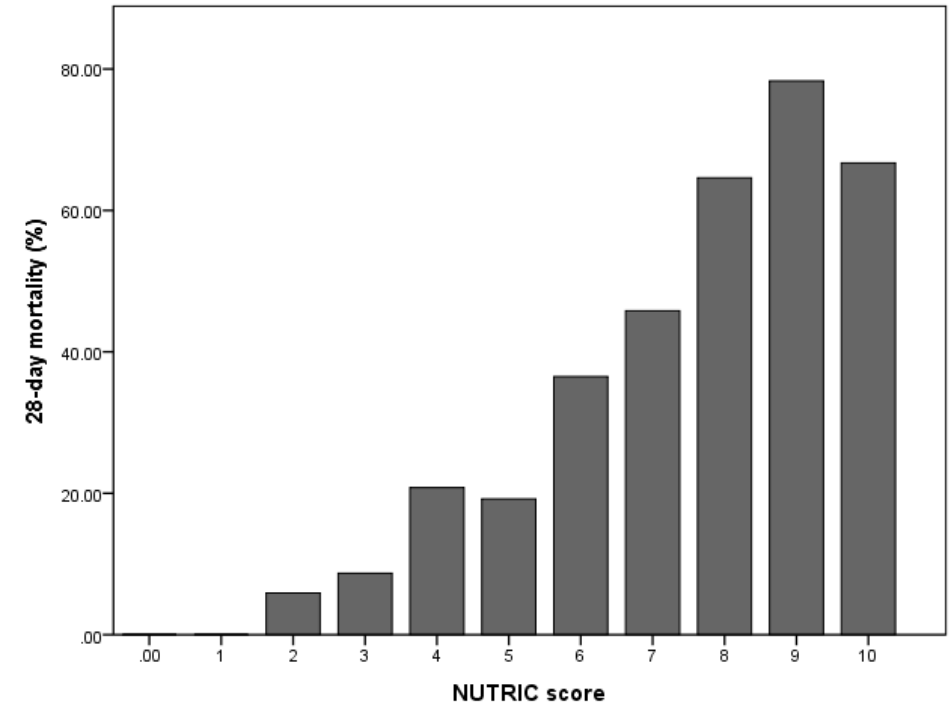
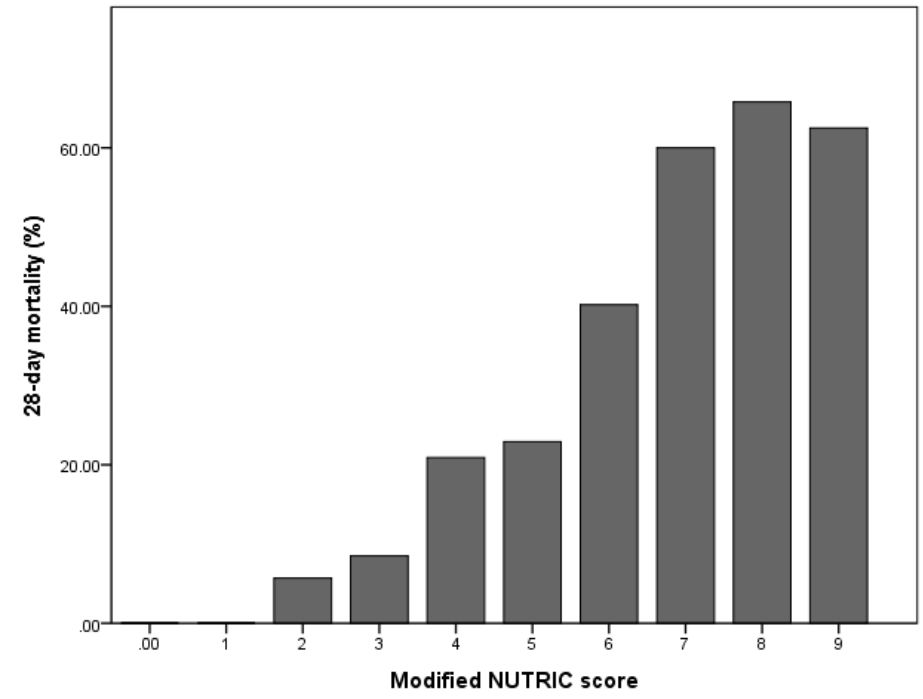


Fig 1. Changes between NUTRIC score and modified NUTRIC score



Patient No.	2	14	34	46	53	78	85	96	48	23	3
Mortality (%)	0	0	5.9	8.7	20.8	19.2	36.5	45.8	64.6	78.3	66.7

Fig 2A. The 28-day mortality according to NUTRIC score



Patient No.	2	15	35	47	67	83	117	70	38	8
Mortality (%)	0	0	5.7	8.5	20.9	22.9	40.2	60	65.8	62.5

Fig 2B. The 28-day mortality according to modified NUTRIC score

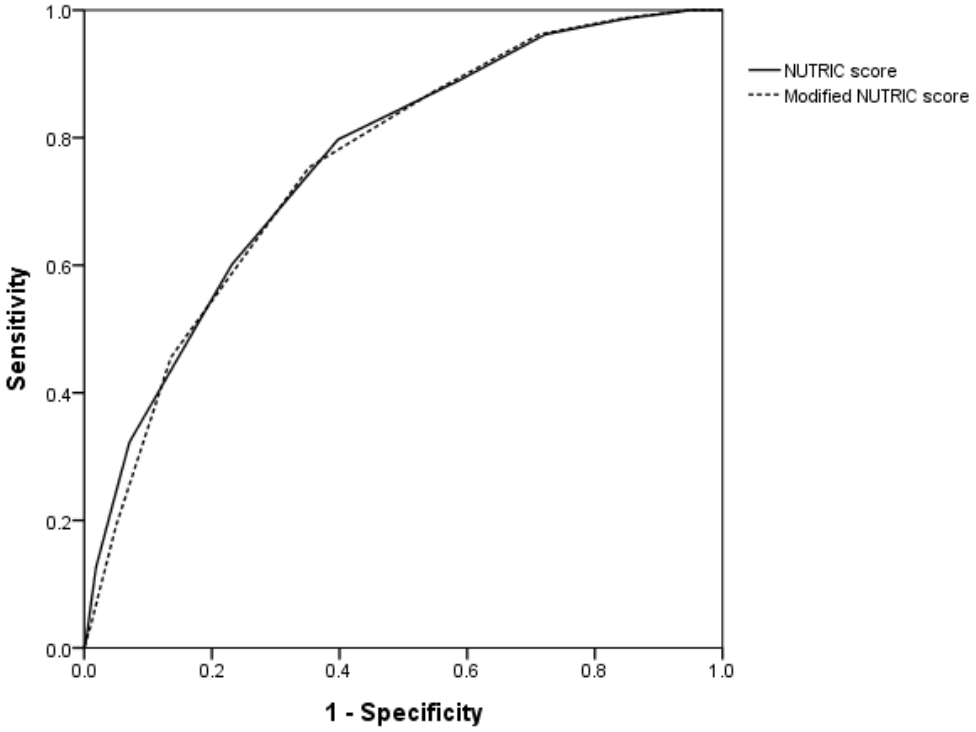


Fig 3. Performance of NUTRIC score and modified NUTRIC score in predicting 28-day mortality

NUTRIC score: AUC=0.763 (95% CI, 0.718–0.806); modified NUTRIC score: AUC=0.757 (95% CI, 0.713–0.801).

Table 2. Change in sensitivity and specificity according to cutoff

	NUTRIC score	mNUTRIC score (cutoff = 5)	P-value	mNUTRIC score (cutoff = 6)	P-value
Sensitivity	0.797	0.873	<0.001	0.753	0.016
Specificity	0.602	0.451	<0.001	0.648	<0.001
Youden index	0.399	0.324		0.401	

mNUTRIC score, modified NUTRIC score.

Table 3. Nutrition data profile of patients according to modified NUTRIC score

	Low score (n = 166)	**High score (n = 316)**	**P-value**
Energy target (kcal/d)	1503 (248)	1533 (242)	0.201
Energy intake (kcal/d)	D1: 761 (425)	D1: 746 (409)	0.713
	D3: 1405 (340)	D3: 1292 (384)	0.002
	D7: 1528 (299)	D7: 1458 (329)	0.024
Energy intake (% goal/d)	D1: 51.5 (29.4)	D1: 49.9 (29.3)	0.578
	D3: 95.5 (25.9)	D3: 86.3 (28.9)	0.001
	D7: 103.9 (23.9)	D7: 97.4 (25)	0.008
Protein target (g/d)	70.8 (11.4)	71.6 (12)	0.498
Protein intake (g/d)	D1: 22.8 (21.4)	D1: 21.4 (19.3)	0.464
	D3: 52.6 (17.9)	D3: 46.7 (18)	<0.001
	D7: 59.8 (13)	D7: 55 (14.2)	<0.001
Protein intake (% goal/d)	D1: 32.7 (31)	D1: 30.9 (28.9)	0.528
	D3: 75.5 (27.1)	D3: 67.2 (28)	0.001
	D7: 86.2 (20.8)	D7: 78.9 (23.3)	0.001

Nutrition data were unavailable for some patients on D3, D7; the number of patients with available data was as follows: D1: 482, D3: 466, D7: 428.
Data are presented as mean (SD).

Table 4. Relation between nutrition intake and 28-day mortality

	Low score (n = 159)			**P-value**	**High score (n = 269)**			**P-value**
Energy intake (kcal/kg)	<20	20 to <25	≥25		<20	20 to <25	≥25	
No. of patients	19 (11.9)	41 (25.8)	99 (62.3)		57 (21.2)	74 (27.5)	138 (51.3)	
Deaths	7 (36.8)	4 (9.8)	6 (6.1)	<0.001	30 (52.6)	21 (28.4)	41 (29.7)	0.007
Protein intake (g/kg)	<0.8	0.8 to <1.2	≥1.2		<0.8	0.8 to <1.2	≥1.2	
No. of patients	22 (13.8)	103 (64.8)	34 (21.4)		73 (27.1)	151 (56.1)	45 (16.7)	
Deaths	8 (36.4)	7(6.8)	2(5.9)	0.001	37 (50.7)	44 (29.1)	11 (24.4)	0.001

Data are presented as number (%).
P-values were calculated using chi-square test for trend.

Table 5. Univariable and multivariable logistic regression analysis for 28-day mortality

	Univariate analysis		Multivariate analysis*	
Variables	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Age	0.997 (0.983–1.010)	0.628	..	..
BMI	1.050 (0.999–1.104)	0.056	..	..
APACHE II score	1.203 (1.160–1.247)	<0.001	1.157 (1.111–1.204)	<0.001
SOFA score	1.274 (1.206–1.346)	<0.001	..	..
Days from hospital to ICU	1.023 (1.009–1.037)	0.001	1.014 (1.001–1.027)	0.041
Co-morbidities	1.150 (0.954–1.388)	0.143	..	..
Energy intake (kcal/kg)				
<20	Reference		Reference	
20 to <25	0.293 (0.156–0.551)	<0.001	0.346 (0.172–0.694)	0.003
≥25	0.261 (0.150–0.453)	<0.001	0.303 (0.164–0.557)	<0.001
Protein intake (g/kg)				
<0.8	Reference		Reference	
0.8 to <1.2	0.279 (0.168–0.463)	<0.001	0.317 (0.181–0.555)	<0.001
≥1.2	0.219 (0.107–0.449)	<0.001	0.301 (0.139–0.652)	0.002

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; OR, odds ratio; CI, confidence interval.
* Variables in the multivariable analysis were age, BMI, APACHE II score, SOFA score, days from hospital admission to the ICU, energy (or protein) intake.

Table 6. Univariable and multivariable logistic regression analysis for 28-day mortality in low modified NUTRIC score group

	Univariate analysis		Multivariate analysis*	
Variables	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Age	0.997 (0.966–1.029)	0.852	..	..
BMI	1.014 (0.893–1.153)	0.828	..	..
APACHE II score	1.155 (1.044–1.277)	0.005	..	..
SOFA score	1.155 (1.007–1.326)	0.039	..	..
Days from hospital to ICU	1.039 (0.984–1.096)	0.170	..	..
Co-morbidities	0.636 (0.355–1.141)	0.129	..	..
Energy intake (kcal/kg)				
<20	Reference		Reference	
20 to <25	0.185 (0.046–0.744)	0.017	0.185 (0.046–0.744)	0.017
≥25	0.111 (0.032–0.384)	0.001	0.111 (0.032–0.384)	0.001
Protein intake (g/kg)				
<0.8	Reference		Reference	
0.8 to<1.2	0.128 (0.040–0.407)	<0.001	0.128 (0.040–0.407)	<0.001
≥1.2	0.109 (0.021–0.582)	0.009	0.109 (0.021–0.582)	0.009

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; OR, odds ratio; CI, confidence interval.
*Variables in the multivariable analysis were APACHE II score, SOFA score, days from hospital admission to the ICU, co-morbidities, energy (or protein) intake.

Table 7. Univariable and multivariable logistic regression analysis for 28-day mortality in high modified NUTRIC score group

	Univariate analysis		Multivariate analysis*	
Variables	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Age	0.980 (0.963–0.997)	0.019	..	..
BMI	1.061 (1.001–1.125)	0.045	..	..
APACHE II score	1.218 (1.161–1.278)	<0.001	1.170 (1.110–1.235)	<0.001
SOFA score	1.248 (1.163–1.339)	<0.001	..	..
Days from hospitalto ICU	1.014 (1.001–1.027)	0.038	1.011 (0.998–1.024)	0.1
Co-morbidities	1.024 (0.822–1.275)	0.833	..	..
Energy intake (kcal/kg)				
<20	Reference		Reference	
20 to <25	0.357(0.173–0.736)	0.005	0.373 (0.169–0.826)	0.015
≥25	0.380 (0.202–0.718)	0.003	0.367 (0.182–0.740)	0.005
Protein intake (g/kg)				
<0.8	Reference		Reference	
0.8 to <1.2	0.400 (0.225–0.713)	0.002	0.364 (0.191–0.693)	0.002
≥1.2	0.315(0.139–0.715)	0.006	0.362 (0.150–0.871)	0.023

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment;
*Variables in the multivariable analysis were age, BMI, APACHE II score, SOFA score, days from hospital admission to the ICU, energy (or protein) intake.

Discussion

In this study, we found that the modified NUTRIC score was a good prognostic marker that could substitute the NUTRIC score in patients with sepsis. The baseline components of the two scores are similar, except for IL-6 level. We found no significant difference between the two tools in the ability to predict 28-day mortality. IL-6 level may not be a critical item in a nutritional risk scoring system. A cutoff score of 6 for the modified NUTRIC score (versus a cutoff of 5 for the NUTRIC score) was better in predicting 28-day mortality. In addition, although the modified NUTRIC score classified patients with sepsis into high-risk and low-risk groups, greater nutritional intake was associated with lower mortality regardless of risk group; these effects were more pronounced in the low-risk group. Rates of reaching energy or protein targets were higher in the low-risk group than in the high-risk group. This finding suggests that active monitoring of nutrition in high-risk patients is needed and reaching protein targets is important in critically ill patients.

Appropriate nutrition in critically ill patients is important. The prevalence of iatrogenic underfeeding is high among patients with critical illness worldwide. A prospective, multi-institutional study showed that patients received 61% of the prescribed energy and 58% of the prescribed protein; in addition, 74% of patients failed to reach at least 80% of the energy target [32]. That study reported that most critically ill patients, including those with high nutritional risk, fail to receive proper nutritional support. Adequate nutrition reduces hospital malnutrition and improves outcomes such as morbidity and mortality. Critical illness results in maintenance of a catabolic state, which leads to increased infection rates, multiple organ failure, and long-term hospital admission [5, 33]. The mechanisms by which malnutrition affect morbidity and mortality are diverse and include impaired immune function, delayed wound healing, delayed recovery from illness, and impaired functional status [34, 35]. Increased hospitalization period and ICU care are directly linked to increased health care costs. In some studies, adequate nutritional support has been shown to reduce length of stay and treatment costs [36, 37].

Some studies that include patients with sepsis have suggested that meeting energy targets may be associated with improved clinical outcomes, such as mortality, in critically ill

patients [38, 39]. In our study, greater energy and protein intakes were associated with lower mortality, regardless of risk group. Although guidelines suggest early initiation of EN in the first 7 days among critically ill septic patients [22], the fulfillment of EN was relatively low in the high-risk group. It is difficult to reach nutrition targets with enteral feeding alone. An RCT by Heidegger et al. showed that optimization of energy provision with supplemental parenteral nutrition could reduce nosocomial infection among patients with critical illness [40]. As mentioned above, greater nutrition intake could improve clinical outcomes including mortality, nosocomial infection, and quality of life.

Conversely, near-target caloric intake is associated with increased hospital mortality and ICU-acquired infections [25]. One RCT reported that permissive underfeeding may be associated with lower mortality than target feeding in critically ill patients [41]. However, several studies have showed that underfeeding may not differ with respect to clinical outcomes compared with standard feeding [23, 24, 42]. One trial reported that hypocaloric feeding in a subgroup of 292 patients with sepsis showed no difference in 90-day mortality compared with standard feeding [24]. In post hoc analysis of the PermiT Trial, in which 33% of patients had sepsis, permissive underfeeding had outcomes that were similar to standard feeding in both high- and low-risk patients [43]. In contrast, our study showed that underfeeding up to day 7 was associated with higher mortality in low- and high-risk patients. A multicenter cohort study showed that greater nutritional intake during the first week in the ICU was associated with longer survival time and faster physical recovery among critically ill patients requiring prolonged MV. That study suggested that current recommendations to underfeed critically ill patients may cause harm in some long-stay patients [44]. Although the effect of underfeeding in critically ill patients remains unclear, underfeeding in these patients should be considered carefully.

Recently, the importance of protein supply as well as energy intake has also emerged. Allingstrup et al. showed that increased protein intake was associated with lower mortality [30]; 10-day survival rates were 50%, 78%, and 87% in low (0.79 g/kg), medium (1.06 g/kg), and high (1.46 g/kg) protein groups. As in that study, we found a greater decline in mortality with increased protein intake than with increased energy intake. Nicolo et al. showed that achieving at least 80% of the protein target was associated with lower mortality and shorter

time to discharge alive in ICU patients (4-day sample: OR 0.68, 95% CI 0.50–0.91; 12-day sample; OR 0.60, 95% CI 0.39–0.93) [45]. Weijs et al. reported that early high protein intake was associated with lower mortality in non-septic critically ill patients; however, there was no beneficial effect on mortality among septic patients [46]. In that study, there were only 117 patients with sepsis and the mortality rate of septic patients was 48.6%. In our study, adequate protein intake had a beneficial effect on mortality in septic patients.

The response of nutritional intervention might be different depending on each patient's condition. Patients with sepsis who are malnourished or at risk of malnutrition might benefit most from nutritional support [47]. Some studies have showed that the beneficial effects of adequate nutrition support are more evident in high-risk patients [48, 49]. An international multicenter observational study conducted by Alberda et al. showed beneficial effects of greater energy and protein intakes according to pre-morbid nutritional status [48]. Greater energy or protein intake was associated with lower mortality in patients with BMI <25 and ≥35, with no benefit in patients with BMI 25 to <35. EN mainly reduces LOS in ICU and hospital mortality in the sickest patients, as defined by quartiles of severity of illness scores [49]. It is therefore important to assess the nutrition status of patients and to identify those who would benefit from aggressive nutritional support.

Greater nutrition intake is associated with lower mortality in patients with high NUTRIC score [18, 19, 21, 31]. A multicenter, multinational, observational study showed that greater protein intake was associated with lower mortality (4-day sample: OR 0.93; 95% CI 0.89–0.98; P=0.003 and 12-day sample: OR 0.90; 95% CI 0.84–0.96; P=0.003) and greater energy intake was associated with lower mortality (4-day sample: OR 0.93; 95% CI 0.89–0.97; P<0.001 and 12-day sample: OR 0.88; 95% CI, 0.83–0.94; P<0.001) in high-risk but not low-risk patients [31]. A study by Rahman et al. showed that greater nutritional adequacy is associated with lower mortality in patients with a high NUTRIC score [19]. In our study, however, greater nutrition intake was associated with lower mortality in patients with both low and high scores. A likely explanation of these beneficial effects in low-risk patients might be related to the relatively low BMI (22.6 kg/m^2) of the patients in our study compared with those of other studies. In most other studies, the mean patient BMI was more than 25 kg/m^2. In the present study, most patients (75.3%) had BMI less than 25 kg/m^2. Another

explanation for the beneficial effects of greater nutrition intake in low-risk patients is that we included patients with sepsis who had a catabolic stress state.

When comparing the NUTRIC score with the modified NUTRIC score, 28-day mortality according to increasing score was similar for each score. The 28-day mortality of the maximum score was 66.7% and 62.5% for the NUTRIC and modified NUTRIC score, respectively. No patients died who had either score of 0 or 1 (0/17 for NUTRIC score and 0/18 for modified NUTRIC score). These results were similar to the results of other validation studies [18, 19]. The AUC of the original development sample for predicting 28-day mortality was 0.783, which was similar to that of our study [18]. In the ROC curve of the modified NUTRIC score, the best cutoff was at 6 (sensitivity and specificity, 75% and 64%, respectively) and the Youden index was 0.391 in our study. However, the best cutoff was at 5 (sensitivity and specificity, 72% and 63%, respectively) and the Youden index was 0.34 in another study [21]. Further investigation is needed to find the best cutoff scores for the modified NUTRIC score in predicting 28-day mortality.

Our study has several limitations. First, this was a single center study with a retrospective design. Feeding compliance and cause of interruption to nutrition support might be not correct. Second, target energy or protein intakes were calculated based on actual body weight, not using indirect calorimetry. Third, the commercial enteral nutrition formulations used in the ICU have relatively low protein content (40–48 g/1000 ml); therefore, approaching the target protein intake was difficult.

Conclusion

In this study, the modified NUTRIC score was a good nutritional risk assessment tool in critically ill septic patients. In addition, adequate nutrition intake, including energy and protein intakes, in the initial 1 week may improve 28-day mortality in septic patients with both low and high nutrition scores. Rates of reaching caloric and protein targets were lower in the high nutrition score group than the low nutrition score group. Thus, nutrition monitoring is particularly important in high-risk patients.

References

1. Edington J, Boorman J, Durrant ER, Perkins A, Giffin CV, James R, et al. Prevalence of malnutrition on admission to four hospitals in England. The Malnutrition Prevalence Group. Clin Nutr 2000;19(3):191-5.
2. Kondrup J, Johansen N, Plum LM, Bak L, Larsen IH, Martinsen A, et al. Incidence of nutritional risk and causes of inadequate nutritional care in hospitals. Clin Nutr 2002;21(6):461-8.
3. Correia MI, Campos AC. Prevalence of hospital malnutrition in Latin America: the multicenter ELAN study. Nutrition 2003;19(10):823-5.
4. McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital. Bmj 1994;308(6934):945-8.
5. Villet S, Chiolero RL, Bollmann MD, Revelly JP, Cayeux RNM, Delarue J, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 2005;24(4):502-9.
6. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. Jama 2008;300(23):2731-41.
7. Schneider SM, Veyres P, Pivot X, Soummer AM, Jambou P, Filippi J, et al. Malnutrition is an independent factor associated with nosocomial infections. Br J Nutr 2004;92(1):105-11.
8. Kyle UG, Pirlich M, Schuetz T, Lochs H, Pichard C. Is nutritional depletion by Nutritional Risk Index associated with increased length of hospital stay? A population-based study. JPEN J Parenter Enteral Nutr 2004;28(2):99-104.
9. Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. Nutrition 1996;12(1):23-9.
10. Liu MJ, Bao S, Napolitano JR, Burris DL, Yu L, Tridandapani S, et al. Zinc regulates the acute phase response and serum amyloid A production in response to sepsis through JAK-STAT3 signaling. PLoS One 2014;9(4):e94934.
11. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40(2):159-211.
12. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr 2008;27(1):5-15.
13. Tappenden KA, Quatrara B, Parkhurst ML, Malone AM, Fanjiang G, Ziegler TR.

Critical role of nutrition in improving quality of care: an interdisciplinary call to action to address adult hospital malnutrition. JPEN J Parenter Enteral Nutr 2013;37(4):482-97.

14. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? 1987. Classical article. Nutr Hosp 2008;23(4):400-7.
15. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr 2003;22(3):321-36.
16. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). Clin Nutr 2005;24(1):75-82.
17. Anthony PS. Nutrition screening tools for hospitalized patients. Nutr Clin Pract 2008;23(4):373-82.
18. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care 2011;15(6):R268.
19. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr 2016;35(1):158-62.
20. Mendes R, Policarpo S, Fortuna P, Alves M, Virella D, Heyland DK. Nutritional risk assessment and cultural validation of the modified NUTRIC score in critically ill patients-A multicenter prospective cohort study. J Crit Care 2017;37:45-9.
21. Mukhopadhyay A, Henry J, Ong V, Leong CS, Teh AL, van Dam RM, et al. Association of modified NUTRIC score with 28-day mortality in critically ill patients. Clin Nutr 2016.
22. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43(3):304-77.
23. Charles EJ, Petroze RT, Metzger R, Hranjec T, Rosenberger LH, Riccio LM, et al. Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial. Am J Clin Nutr 2014;100(5):1337-43.
24. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med 2015;372(25):2398-408.

25. Arabi YM, Haddad SH, Tamim HM, Rishu AH, Sakkijha MH, Kahoul SH, et al. Near-target caloric intake in critically ill medical-surgical patients is associated with adverse outcomes. JPEN J Parenter Enteral Nutr 2010;34(3):280-8.
26. Petros S, Horbach M, Seidel F, Weidhase L. Hypocaloric vs Normocaloric Nutrition in Critically Ill Patients: A Prospective Randomized Pilot Trial. JPEN J Parenter Enteral Nutr 2016;40(2):242-9.
27. Weijs PJ, Cynober L, DeLegge M, Kreymann G, Wernerman J, Wolfe RR. Proteins and amino acids are fundamental to optimal nutrition support in critically ill patients. Crit Care 2014;18(6):591.
28. Hurt RT, McClave SA, Martindale RG, Ochoa Gautier JB, Coss-Bu JA, Dickerson RN, et al. Summary Points and Consensus Recommendations From the International Protein Summit. Nutr Clin Pract 2017;32(1_suppl):142s-51s.
29. Weijs PJ, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes AR, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr 2012;36(1):60-8.
30. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr 2012;31(4):462-8.
31. Compher C, Chittams J, Sammarco T, Nicolo M, Heyland DK. Greater Protein and Energy Intake May Be Associated With Improved Mortality in Higher Risk Critically Ill Patients: A Multicenter, Multinational Observational Study. Crit Care Med 2017;45(2):156-63.
32. Heyland DK, Dhaliwal R, Wang M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally 'at-risk' critically ill patient: Results of an international, multicenter, prospective study. Clin Nutr 2015;34(4):659-66.
33. McClave SA, Lowen CC, Kleber MJ, Nicholson JF, Jimmerson SC, McConnell JW, et al. Are patients fed appropriately according to their caloric requirements? JPEN J Parenter Enteral Nutr 1998;22(6):375-81.
34. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 2003;27(5):355-73.
35. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr 2009;28(4):387-400.
36. Kruizenga HM, Van Tulder MW, Seidell JC, Thijs A, Ader HJ, Van Bokhorst-de van der Schueren MA. Effectiveness and cost-effectiveness of early screening and treatment of malnourished patients. Am J Clin Nutr 2005;82(5):1082-9.
37. Pradelli L, Graf S, Pichard C, Berger MM. Supplemental parenteral nutrition in

intensive care patients: A cost saving strategy. Clin Nutr 2017.
38. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! Crit Care Med 2011;39(12):2619-26.
39. Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med 2011;37(4):601-9.
40. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381(9864):385-93.
41. Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr 2011;93(3):569-77.
42. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. Jama 2013;309(20):2130-8.
43. Arabi YM, Aldawood AS, Al-Dorzi HM, Tamim HM, Haddad SH, Jones G, et al. Permissive Underfeeding or Standard Enteral Feeding in High- and Low-Nutritional-Risk Critically Ill Adults. Post Hoc Analysis of the PermiT Trial. Am J Respir Crit Care Med 2017;195(5):652-62.
44. Wei X, Day AG, Ouellette-Kuntz H, Heyland DK. The Association Between Nutritional Adequacy and Long-Term Outcomes in Critically Ill Patients Requiring Prolonged Mechanical Ventilation: A Multicenter Cohort Study. Crit Care Med 2015;43(8):1569-79.
45. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study. JPEN J Parenter Enteral Nutr 2016;40(1):45-51.
46. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care 2014;18(6):701.
47. Perner A, Rhodes A, Venkatesh B, Angus DC, Martin-Loeches I, Preiser JC, et al. Sepsis: frontiers in supportive care, organisation and research. Intensive Care Med 2017;43(4):496-508.
48. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care

Med 2009;35(10):1728-37.
49. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 2006;129(4):960-7.

국문요약

배경: 적절한 영양지원은 중환자 예후에 중요하기 때문에 중환자를 위한 영양위험도 평가도구인 NUTRIC (NUTrition Risk in Critically ill) score 와 modified NUTRIC (except Interleukin 6) score 가 많은 연구에서 평가 되어왔다. 본 연구는 패혈증 환자에서 28 일 사망률 예측에 대한 NUTRIC score 와 modified NUTRIC score 의 정확성을 비교하고 modified NUTRIC score 를 이용하여 영양지원과 28 일 사망률 사이의 관계를 확인하고자 한다.

방법: 본 연구는 3 차 병원의 내과계 중환자실에서 시행한 후향적 코호트 연구이다. 2011 년 1 월부터 2017 년 6 월까지 아산병원에 입원한 18 세이상, 중환자실 재실기간이 24 시간 이상인 환자를 대상으로 하였다. NUTRIC score 혹은 modified NUTRIC score 는 중환자실 입실 후 24 시간 이내의 정보를 이용하여 계산되었다. 영양지원은 중환자실 입실 7 일째의 에너지 섭취량에 대해 <20, 20 to <25, ≥25 kcal/kg 군과 단백질 섭취량 <0.8, 0.8 to <1.2, ≥1.2 g/kg 군으로 분류되었다. 결과로써 28 일 사망률에 대해 다변형 회귀분석이 사용되었다.

결과: 총 482 명의 환자가 분석되었다. 28 일 사망 예측력에 대한 NUTRIC score 와 modified NUTRIC score 의 area under the curve (AUC)는 각각 0.762 (95% confidence interval [CI] 0.718-0.806), 0.757 (95% CI 0.713-0.801) 였다. 두 score 사이에 유의한 차이는 없었다. (p = 0.45). The modified NUTRIC score 의 high score(≥5) 군에서, 영양 섭취량이 더 많을수록 유의하게 더 낮은 사망률과 연관성이 있었다 (20 to <25 kcal/kg: adjusted odds ratio [aOR] 0.373, 95% CI 0.169-0.740; ≥25 kcal/kg: aOR 0.367, 95% CI 0.182-0.740). 또한 단백질 섭취량이 더 많을수록 유의하게 더 낮은 사망률과 연관성이 있었다 (0.8 to <1.2 g/kg: aOR 0.364, 95% CI 0.191-0.693; ≥1.2 g/kg: aOR 0.362, 95% CI 0.150-0.871). Low score (<5) 군에서도, 영양 섭취량이 더 많을수록 (20 to <25 kcal/kg: aOR 0.185, 95% CI 0.046-0.744; ≥25 kcal/kg: aOR 0.111, 95% CI 0.032-0.384) 그리고 단백질 섭취량이 더 많을수록(0.8 to <1.2 g/kg: aOR 0.128, 95% CI 0.040-0.407; ≥1.2 g/kg: aOR 0.109, 95% CI 0.021-0.582) 유의하게 더 낮은 사망률과 연관성이 있었다.

결론: The modified NUTIRC score 는 패혈증 중환자에서 좋은 영양위험도 평가도구이다. The modified NUTRIC score 의 high score (≥5) 군은 높은 사망률과 연관성이 있었다. 그리고 패혈증 환자에서 첫 1 주내에 충분한 영양지원은 28 일 사망률의 향상과 연관성을 보였다.

중심단어: 영양, modified NUTRIC score, 패혈증환자, 사망률, 중환자실