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Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study

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Title:

Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study

Running title:

Nutritional risks in critical care

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Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study

ABSTRACT

Objectives The aims of this study were to explore the predictive value of single and multiple risk factors for the clinical outcome of critically ill patients with enteral nutrition, and to establish an effective evaluation model.

Design Retrospective cohort study.

Setting Retrospective cohort study.Data from the 2020-2021 period were collected from the electronic records of the First Affiliated Hospital, Nanjing Medical University.

Participants 459 critically ill patients with enteral nutrition in the geriatric intensive care unit were included in the study.

Primary outcome 28-day mortality.

Results Prealbumin, procalcitonin (PCT), acute physiology and chronic health evaluation II score (APACHE II) and nutritional risk screening (NRS) 2002 were found to be independently related with 28-day mortality of the critically ill. Moreover, both prealbumin/PCT ratio and the combination model of PCT, prealbumin and NRS2002 were identified to have higher predictive value for patients' clinical outcome. Subgroup analysis also identified that higher inflammatory state (PCT > 0.5 ng/mL) and major nutritional risk (NRS2002 > 3) led to worse clinical outcome. In addition, patients on whole protein formulae beard less nutritional risk than those on short peptide formulae.

Conclusions PCT, prealbumin, APACHE II and NRS2002 were independent nutritional risk factors for 28-day mortality of critically ill patients. Both prealbumin/PCT ratio and the combination model of PCT, prealbumin and NRS2002, as composite models of inflammation and nutrition, could better predict the prognosis of critically ill patients.

Keywords: Critically ill patients, Enteral nutrition, Procalcitonin, NRS2002, Prognosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study investigated the nutritional risk factors in critical scenario
- This study produced a convenient prediction model for the outcomes of the critically ill
- The study was a retrospective and data were relatively abundant
- Since clinical data cannot be obtained from other centers, no external validation was performed.

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INTRODUCTION

In critically ill patients, due to severe stress or trauma, the metabolic rate is significantly increased, and metabolic disorders and malnutrition are very common, and the incidence of malnutrition can be as high as 30-50% [1]. Malnutrition would prolong patients' hospital stay in the intensive care units (ICU), increase the incidence of infection and other complications, thus increase mortality [2]. Studies have shown that early enteral nutritional support could reduce the severity of disease in critically ill patients, reduce the risk of complications, shorten the length of ICU stay, and improve the prognosis of patients [3]. Nutrition practice guidelines in Europe, Canada and the United States all suggested early implementation of enteral nutrition for critically ill patients with stable hemodynamics [4-7].

Nutrition therapy includes nutritional risk assessment, nutritional plan formulation and implementation. Timely and accurately assessing the nutritional risk of patients is a prerequisite for providing reasonable nutrition therapy. At present, there are a wide variety of nutritional screening and evaluation tools. Single indicators include hemoglobin, albumin, prealbumin, creatinine, urea, body mass index (BMI), skinfold thickness, middle arm circumference, indirect calorimetry [8] and phase angle [9]. Composite indicators include Nutrition Risk Screening 2002 (NRS2002) score [10], Critical Care Nutrition Risk Score [11], and so on. Each nutritional risk assessment tool has its pros and cons. Up to date, there is no gold standard for nutritional risk assessment in critically ill patients.

Critically ill patients are often accompanied with infection. And procalcitonin (PCT) as an inflammatory marker, can usually reflect the status of infection [12-13]. Studies have shown that PCT has predictive values for prognosis of critically ill patients [14]. Therefore, in this study, we aimed to screen the risk factors for the outcomes of critically ill patients, and to establish a composite model of inflammatory and nutritional factors to predict the prognosis.

We present the following article in accordance with the STROBE reporting checklist.

METHODS

Study design and participants

A retrospective study was conducted in the critically ill patients in the geriatric Intensive Care Unit of the First Affiliated Hospital of Nanjing Medical University from January 2020 to January 2021. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (approval number: 2020-SR-055). All patients enrolled in this study received enteral nutrition. The data of all patients were reviewed and analyzed anonymously, so informed consent was exempted.

Inclusion criteria: (1) admitted to ICU; (2) enteral nutrition received; (3) age > 18 years. Exclusion criteria: (1) ICU stay or death < 24 hours; (2) incomplete medical record; (3) patients received parenteral nutrition; (4) patients received oral nutrition.

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The goal of nutritional support was 25-30 kcal/kg/d calories and 1.2-2.0 g/kg/d protein [7] for each patient, via nasogastric or naso-intestinal tube. According to patient's disease and nutritional status, corresponding nutrition formula were applied.

Outcomes and risk factors

All enrolled medical records were subjectively reviewed. Lab testing results were recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II), NRS2002 and BMI were withdrawn for 2 weeks after admission. Other clinical data including age, gender, length of stay in ICU and 28-day clinical outcome were also collected. In this study, we analyzed the risk factors for patients' 28-day clinical outcome, and evaluated the predictive values of single and composite indexes. Subgroup analysis was also conducted according to nutritional scores and inflammatory status.

Statistical analysis

GraphPad Prism 8.0 was used for statistical analysis. All continuous variables were tested for normal distribution. Normally distributed variables were expressed as mean ± standard deviation, and unpaired t test was used for comparison between two groups. Non-normally distributed variables were expressed as the median and interquartile range, and Mann-Whitney test was used for comparison between groups. The count data was expressed as percentages, and chi-square test was used for comparison.

Univariate and multivariate logistic regression were used to screen the risk factors for 28-day clinical outcomes. Receiver operating characteristic (ROC) curves were drawn to analyze the predictive power of single and composite indexes. According to inflammatory and nutritional status, subgroup analysis was carried out based on PCT and NRS2002 levels. Survival curves were drawn for subgroups. $P < 0.05$ was considered to be statistically significant.

Patients and public involvement

No patients or members of the public were involved in the design, conduct or reporting of this study. The study results were not disseminated to study participants.

RESULTS

Clinical and demographic characteristics of the studied patients

A total of 459 patients were enrolled in this study. Among the total enrolled population, 158 patients were excluded from the analysis because they met one or more exclusion criteria (Fig. 1). Finally, 301 patients data were analyzed, including 214 males and 87 females, 183 survivals and 118 non-survivals.

Compared with the survival group, the non-survivals had higher APACHE II and NRS2002 scores, higher serum creatinine, urea, aspartate aminotransferase (AST) and PCT levels, lower prealbumin and transferrin, and shorter ICU stay. For above mentioned comparison, the P values were all less than 0.05 (Table 1).

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Table 1 Clinical characteristics of study population

Variables	Survivors (n = 183)	Non-survivors (n = 118)	P-value
	n (%) / mean ± SD / median (IQR)	n (%) / mean ± SD / median (IQR)	
Age (years)	70.0 (56.0,83.0)	74.0 (58.0,85.0)	0.13
Male	134 (73.2%)	81 (68.6%)	0.43
ICU stay (days)	13.0 (6.0,28.0)	8.9 (4.0,14.6)	**<0.01**
NRS2002	4.0 (3.0,4.0)	4.0 (4.0,6.0)	**<0.01**
APACHE II	18.9 ± 5.3	23.3 ± 5.5	**<0.01**
BMI (kg/m^2)	22.5 (20.5,25.3)	21.8 (19.1,25.2)	0.14
Lab testing results			
Albumin (g/L)	34.8 ± 4.7	34.0 ± 5.3	0.17
Globulin (g/L)	26.0 (22.7,28.3)	26.4 (23.2,29.1)	0.68
Total protein (g/L)	59.6 ± 8.7	58.9 ± 9.2	0.48
Retinol-binding protein (mg/L)	27.7 (19.2,39.0)	25.3 (16.5,36.6)	0.17
Prealbumin (g/L)	0.15 (0.10,0.20)	0.12 (0.08,0.17)	**<0.01**
Transferrin (g/L)	1.20 (0.97,1.65)	1.09 (0.83,1.46)	**0.01**
Hemoglobin (g/L)	100.8 (87.0,115.0)	96.3 (82.8,117.0)	0.31
Serum creatinine (μmol/L)	69.1 (51.9,105.6)	107.4 (72.5,176.3)	**<0.01**
Urea (mmol/L)	9.2 (6.9,13.9)	13.6 (8.5,18.6)	**<0.01**
ALT (U/L)	36.7 (24.5,63.5)	36.4 (23.6,71.8)	0.98
AST (U/L)	41.5 (29.2,64.5)	56.1 (31.6,85.4)	**<0.01**
Procalcitonin (ng/mL)	0.30 (0.13,0.94)	1.43 (0.37,3.64)	**<0.01**
Infective comorbidities			
Pneumonia	101 (55.19%)	96 (81.36%)	**<0.01**
Septic shock	14 (7.65%)	30 (25.42%)	**<0.01**
Blood stream infection	4 (2.19%)	8 (6.78%)	0.09
Urinary infection	11 (6.01%)	8 (6.78%)	0.79
Infections of the central nervous system	3 (1.64%)	4 (3.39%)	0.55
Intra-abdominal infection	3 (1.64%)	4 (3.39%)	0.55
Surgical disease			
Cerebral hemorrhage	45 (24.59%)	33 (27.97%)	0.51
Abdominal surgery	23 (12.57%)	7 (5.93%)	0.06

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Multiple injuries	18 (9.84%)	5 (4.24%)	0.07
Complications			
Heart failure	51 (27.87%)	59 (50.00%)	**<0.01**
Renal insufficiency	25 (13.66%)	57 (48.31%)	**<0.01**
Liver insufficiency	13 (7.10%)	18 (15.25%)	**0.02**
Hypertension	79 (43.17%)	75 (63.56%)	**<0.01**
Diabetes mellitus	30 (16.39%)	43 (36.44%)	**<0.01**
Hypoproteinemia	12 (6.56%)	9 (7.63%)	0.72
Cerebral ischemic stroke	49 (26.78%)	33 (27.97%)	0.82

APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; NRS, Nutrition Risk Screening; SD, standard error.

Screening of risk factors for clinical outcome

In this study, univariate and multivariate logistic regression was used to screen out risk factors for clinical outcomes of critically ill patients. Univariate regression showed that APACHE II, NRS2002, prealbumin, serum creatinine, urea, AST and PCT all affected 28-day clinical outcome of critically ill patients with enteral nutrition. Multivariate regression showed that APACHE II, gender, globulin and AST were risk factors for the 28-day clinical outcome in critically ill patients. In the other hand, prealbumin was proved to be a protective factor for patients' 28-day clinical outcome (Table 2).

Table 2 Univariate and multivariate regression analysis for critically ill patients with enteral nutrition

Variables	Univariable models		Multivariable model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.01 (1.00,1.02)	0.14	0.99 (0.96,1.01)	0.17
Gender	1.25 (0.75,2.08)	0.39	2.60 (1.33,5.23)	**<0.01**
NRS2002	1.24 (1.05,1.47)	**0.01**	0.92 (0.71,1.18)	0.51
APACHE II	1.17 (1.11,1.23)	**<0.01**	1.18 (1.11,1.26)	**<0.01**
BMI (kg/m^2)	0.95 (0.90,1.01)	0.08	0.93 (0.86,1.00)	0.08
Albumin (g/L)	0.97 (0.92,1.01)	0.17	1.04 (0.94,1.15)	0.43
Globulin (g/L)	1.01 (0.96,1.05)	0.83	1.12 (1.02,1.23)	**0.02**
Total protein (g/L)	0.99 (0.96,1.02)	0.48	0.99 (0.93,1.05)	0.65
Retinol-binding protein (mg/L)	0.99 (0.98,1.00)	0.16	1.00 (0.97,1.03)	0.85

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Prealbumin (g/L)	0.00 (0.00,0.02)	**<0.01**	0.00 (0.00,0.02)	**<0.01**
Transferrin (g/L)	0.80 (0.45,1.27)	0.39	2.26 (1.07,6.50)	0.09
Hemoglobin (g/L)	0.99 (0.98,1.00)	0.38	1.01 (0.99,1.03)	0.17
Serum creatinine (μmoI/L)	1.00 (1.00,1.01)	**0.00**	1.00 (1.00,1.01)	0.09
Urea (mmol/L)	1.04 (1.01,1.07)	**0.01**	1.02 (0.97,1.07)	0.51
ALT (U/L)	1.00 (1.00,1.00)	0.18	0.99 (0.99,1.00)	0.21
AST (U/L)	1.00 (1.00,1.00)	**0.04**	1.01 (1.00,1.01)	**0.04**
Procalcitonin (ng/mL)	1.03 (1.01,1.07)	**0.03**	1.01 (0.98,1.05)	0.56

APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; NRS, Nutrition Risk Screening; OR, odds ratios.

Predictive values of each model on 28-day outcome

ROC curves were drawn based on the 28-day clinical outcome for each index. PCT and APACHE II had higher predictive value, with area under ROC curves (AUROC) at 0.71 and 0.72 respectively. In addition, NRS2002, prealbumin, serum creatinine and urea also had good predictive values for the 28-day clinical outcome of critically ill patients with enteral nutrition. The AUROCs were 0.60, 0.63, 0.68 and 0.63 respectively, and all P values < 0.01 (Fig. 2A).

According to inflammatory status, we analyzed the predictive values of PCT-based composite model for patients' 28-day outcome. Results showed that PCT + AST had higher predictive value, with its AUROC at 0.70. In addition, PCT + prealbumin, PCT + NRS2002, PCT + transferrin, PCT + serum creatinine, and PCT + urea also performed well in predicting 28-day outcomes of studied patients, with AUROCs at 0.63, 0.67, 0.65, 0.65 and 0.69 respectively, and all P values < 0.01 (Fig. 2B).

According to nutritional risk, we analyzed the predictive values of NRS2002 based composite model for patients' 28-day outcome. Results showed that NRS2002 + prealbumin, NRS2002 + transferrin, NRS2002 + serum creatinine, NRS2002 + urea and NRS2002 + AST all had good predictive value for 28-day outcome. The AUROCs were 0.64, 0.61, 0.68, 0.66 and 0.63, respectively, and all P values < 0.01 (Fig. 2C).

Importantly, we combined the inflammatory and nutritional risks together, to establish a more effective model to predict patients' 28-day outcome. The results showed that triple indicator (PCT + NRS2002 + prealbumin) and double indicator (PCT + prealbumin) performed best on predicting 28-day outcomes, with AUROCs at 0.73 and 0.71 respectively, and both P values < 0.01 (Fig. 2D).

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In addition, we presented the heat map of all indices' correlation in supplementary figure S1. And the predictive value of the prealbumin-based composite index for patients' 28-day outcome were less powerful and presented in supplementary figure S2.

Survival analysis based on inflammatory and nutritional risks

In this study, patients were divided into groups based on whether the patients' NRS2002 score was at a high nutritional risk (> 3 or cut-off value 3.5), and whether the PCT level was in a severe inflammatory state (> 0.5 or cut-off value 1.02). The differences in 28-day outcome of each group were compared. Survival curves were drawn, and the results showed that the overall survival rate of patients in each group was significantly different at 28 days ($P < 0.01$). For patients at higher inflammatory and nutritional risk, if PCT > 0.5 and NRS2002 > 3, the survival rate would be significantly lower than that of other groups (Fig. 3).

Influences of different enteral nutritional formulae

According to nutritional formulae, patients were divided into three groups: peptide-based formulae group (PB), peptide step to whole protein formulae group (PW) and whole protein formulae group (WP). Results showed that after 3 days of enteral nutrition, the improvement of AST and alanine aminotransferase (ALT) in PB group was higher than that of other groups ($P < 0.05$). After 7 days of enteral nutrition, the improvement of NRS2002 score in PB group was higher than that of other groups ($P < 0.01$) (Fig. 4).

APACHE II, NRS2002, serum creatinine, ALT and AST levels in the PB group were significantly higher than other groups, meanwhile, globulin level was lower than the WP group at admission, P values were all < 0.05 (Fig. 5).

DISCUSSION

The mortality rate of critically ill patients is generally very high. In this retrospective study, we observed enterally fed patients in ICU on their APACHE II score, NRS2002 score, serum creatinine, urea, AST, procalcitonin, and prealbumin, to identify independent risk factors for their clinical outcomes. Univariate analysis have shown that patients in the non-survival group had more severe inflammation and nutritional deficiency, with worse multi-organ dysfunction. Logistic regression also proved that APACHE II was a risk factor for 28-day survival in critically ill patients with enteral nutrition. Meanwhile, prealbumin was a protective factor for 28-day outcome. These results are in consistent with previous studies [15-17]. Researches have shown that APACHE II score could be applied to assess severity and predict prognosis of disease [15]. Multiple studies have shown that prealbumin was an independent protective factor for patient and had very good predictive value for outcomes [16-17].

Guidelines issued by the American Society of Parenteral and Enteral Nutrition in 2016 recommended the use of NRS2002 and NUTRIC Score for nutritional risk assessment of patients [7]. Compared with

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NUTRIC Score, NRS2002 score is simpler and more practical. The NRS2002 score is an evidence-based nutritional risk score, which can be used to screen nutritional risks for patients, evaluate the effect of nutritional support, and predict the clinical outcome of hospitalized patients. Our results also proved that NRS2002 was an independent risk factor for 28-day survival in enterally fed critical patients. The NRS2002 score could independently predict the 28-day clinical outcome, and when combined with prealbumin, PCT, transferrin, serum creatinine, urea, and AST, its predictive value would been further improved.

Procalcitonin is a precursor polypeptide of calcitonin. Under physiological conditions, the serum PCT level is extremely low (< 0.05 ng/mL). In viral and fungal infections, it remains at a low level [18-19], but in bacterial infections, PCT could surge to a very high level [20]. Studies have shown that in patients with sepsis, the use of PCT to guide early discontinuation of antibacterial drugs can reduce the 28-day mortality rate and hospitalization costs [21]. Meta-analysis also described that elevated serum PCT concentration was closely related to all-cause mortality in patients with sepsis [14]. Besides, PCT could be a good predictor for the prognosis of critically ill patients [22]. The results of this study proved that PCT could be predictive for 28-day outcome for enterally fed critical patients.

Results of this study showed that prealbumin, NRS2002 and PCT were all predictive for 28-day clinical outcome of critically ill patients with nasal feeding, and the combined index of prealbumin, NRS2002 and PCT had best predictive value.

Compared with the survival group, non-survivors had lower prealbumin levels and higher PCT levels, which indicated a high nutritional risk and inflammatory state relating with worse prognosis. Research had shown that the ratio of C-reactive protein (CRP) to albumin had predictive value for in-hospital mortality of patients with sepsis [23]. Li et al. showed that CRP/prealbumin was independently related to ICU mortality and length of stay [24]. In order to evaluate the comprehensive state of inflammation and nutrition, this study used the ratio of prealbumin to PCT as an indicator [25]. ROC curve analysis proved that prealbumin/PCT had a high predictive value for 28-day clinical outcome for nasal fed critical patients, and its AUROC was very close to APACHE II ($P < 0.01$). In addition, prealbumin/PCT was far more feasible and accessible than APACHE II [25].

According to NRS2002 scores and PCT levels, patients were divided for subgroup analysis. Results showed highest survival rate occurred in low inflammatory state and nutritional risk, and lowest survival rate in high inflammatory state and nutritional risk. These results all indicated that the composite indicators of inflammation and nutrition could be reliable to evaluate 28-day clinical outcome of critically ill patients. Therefore, for critically ill patients, nutritional screening should be carried out as early as possible, and appropriate nutritional support plans should be formulated, combining with infection control and inflammation regulation, so as to improve clinical outcomes.

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This study has several limitations. Firstly, this study was a retrospective design and the research data was relatively limited; Secondly, this was a single-center clinical study, and the average age of the patients was older, so subgroup analysis based on age could not be performed; Finally, the clinical outcome of this study was set to 28 days of survival or death. The outcome was not followed up to a longer period, and no secondary outcome was established.

In conclusion, critically ill patients were characterized with obvious nutritional deficiency, higher inflammatory state, and poor overall prognosis. As single indicators, PCT, APACHE II, NRS2002, prealbumin, serum creatinine and urea could be used in disease evaluation and prognosis prediction for enterally fed critical patients. As composite indicators, prealbumin/PCT and prealbumin + NRS2002 + PCT, both performed well in severity evaluation and prognosis prediction.

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Contributors Study concept and design: YH. Acquisition of data: JW, NZ, XC. Analysis and interpretation of data: JW, HQ, YT. Drafting of the manuscript: JW, YH. Critical revision of the manuscript for important intellectual content: JW, NZ. Statistical analysis: JW, NZ, XC. Administrative and technical support: YT.

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Competing interests None declared.

Patients and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethical approval The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of the First Affiliated Hospital of Nanjing Medical University (NO.: 2020-SR-055) and individual consent for this retrospective analysis was waived.

Data availability statement Data are available at: https://figshare.com/articles/dataset/EN3_original_data_xlsx/19960202.

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Figure Legends

Figure 1 Patient records enrollment flowchart

Figure 2 Receiver operator characteristic (ROC) curves for single and composite indicators in predicting 28-day outcome. (A) ROCs for single indicators; (B) ROCs for PCT-based composite indicators; (C) ROCs for NRS2002-based composite indicators; (D) ROCs for PA-based composite indicators. CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; Crea, serum creatinine; NRS: Nutrition Risk Screening; PA, prealbumin; PCT, procalcitonin; TRF, transferrin.

Figure 3 Survival curves for critically ill patients with enteral nutrition. (A) Survival curves for groups divided by conventional values of NRS2002 and PCT; (B) Survival curves for groups divided by cut-off values of NRS2002 and PCT. *P < 0.05, **P < 0.01. NRS, Nutrition Risk Screening; PCT, procalcitonin.

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Figure 5 Severity scores, nutrition status and inflammatory markers in different nutrition formulae groups. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Crea, serum creatinine; NRS, nutrition risk screening.

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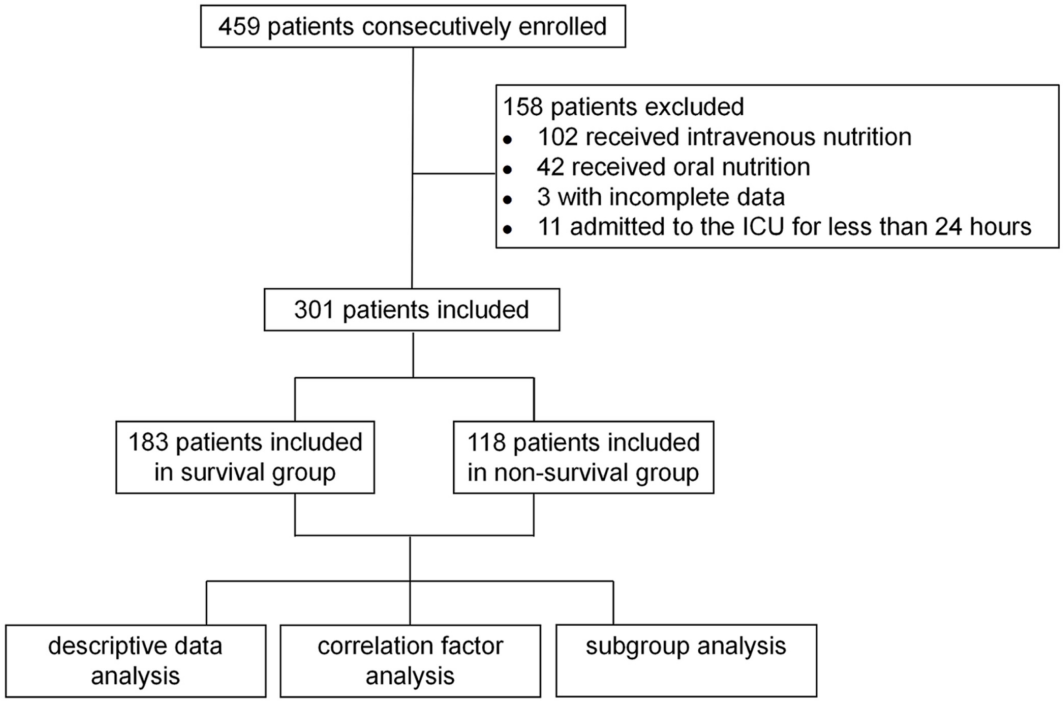

Fig. 1 Patient records enrollment flowchart

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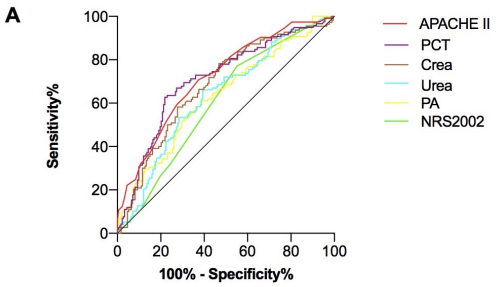
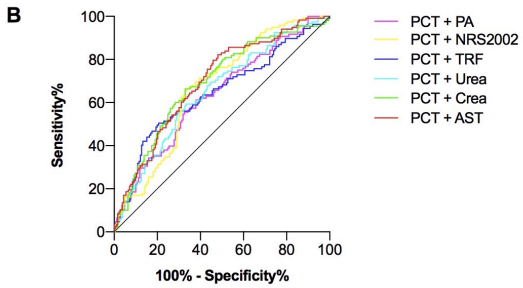
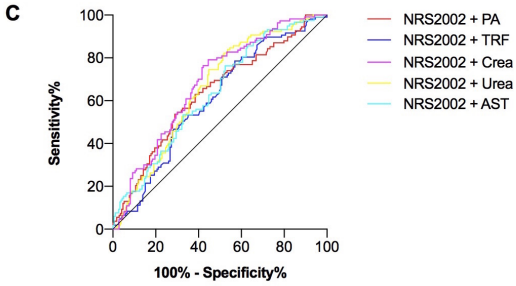


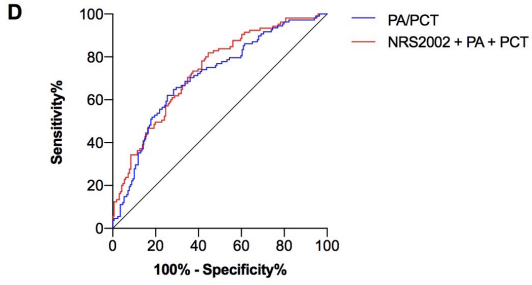
Variable	APACHE II	PCT	Crea	Urea	PA	NRS2002
Area	0.72	0.71	0.68	0.63	0.63	0.60
Std. Error	0.03	0.03	0.03	0.03	0.03	0.03
Lower 95% CI	0.66	0.65	0.62	0.57	0.57	0.54
Upper 95% CI	0.78	0.77	0.75	0.70	0.70	0.67
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Cut-off value	20.50	1.02	71.02	10.48	0.13	3.50
Sensitivity	70.80	62.71	78.18	66.10	61.11	77.12
Specificity	62.57	78.14	53.18	60.66	61.54	44.81



Variable	PCT + PA	PCT + NRS2002	PCT + TRF	PCT + Urea	PCT + Crea	PCT + AST
Area	0.63	0.67	0.65	0.65	0.69	0.70
Std. Error	0.03	0.03	0.04	0.03	0.03	0.03
Lower 95% CI	0.57	0.61	0.58	0.59	0.63	0.64
Upper 95% CI	0.70	0.73	0.71	0.72	0.75	0.76
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Sensitivity	61.11	66.10	50.47	59.32	66.36	82.20
Specificity	62.13	66.67	79.39	66.67	67.05	51.91



Variable	NRS2002 + PA	NRS2002 + TRF	NRS2002 + Crea	NRS2002 + Urea	NRS2002 + AST
Area	0.64	0.61	0.68	0.66	0.63
Std. Error	0.03	0.03	0.03	0.03	0.03
Lower 95% CI	0.57	0.54	0.62	0.60	0.57
Upper 95% CI	0.70	0.67	0.74	0.72	0.70
P value	<0.01	<0.01	<0.01	<0.01	<0.01
Sensitivity	53.70	78.50	79.09	83.90	76.27
Specificity	71.01	43.03	55.49	46.45	47.54



Variable	PA/PCT	PA + PCT + NRS2002
Area	0.71	0.73
Std. Error	0.03	0.03
Lower 95% CI	0.65	0.68
Upper 95% CI	0.77	0.79
P value	<0.01	<0.01
Cut-off value	0.13	—
Sensitivity	62.04	81.90
Specificity	74.56	55.42

Fig. 2 Receiver operator characteristic (ROC) curves for single and composite indicators in predicting 28-day outcome. **(A)** ROCs for single indicators; **(B)** ROCs for PCT-based composite indicators; **(C)** ROCs for NRS2002-based composite indicators; **(D)** ROCs for PA-based composite indicators. CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; Crea, serum creatinine; NRS: Nutrition Risk Screening; PA, prealbumin; PCT, procalcitonin; TRF, transferrin

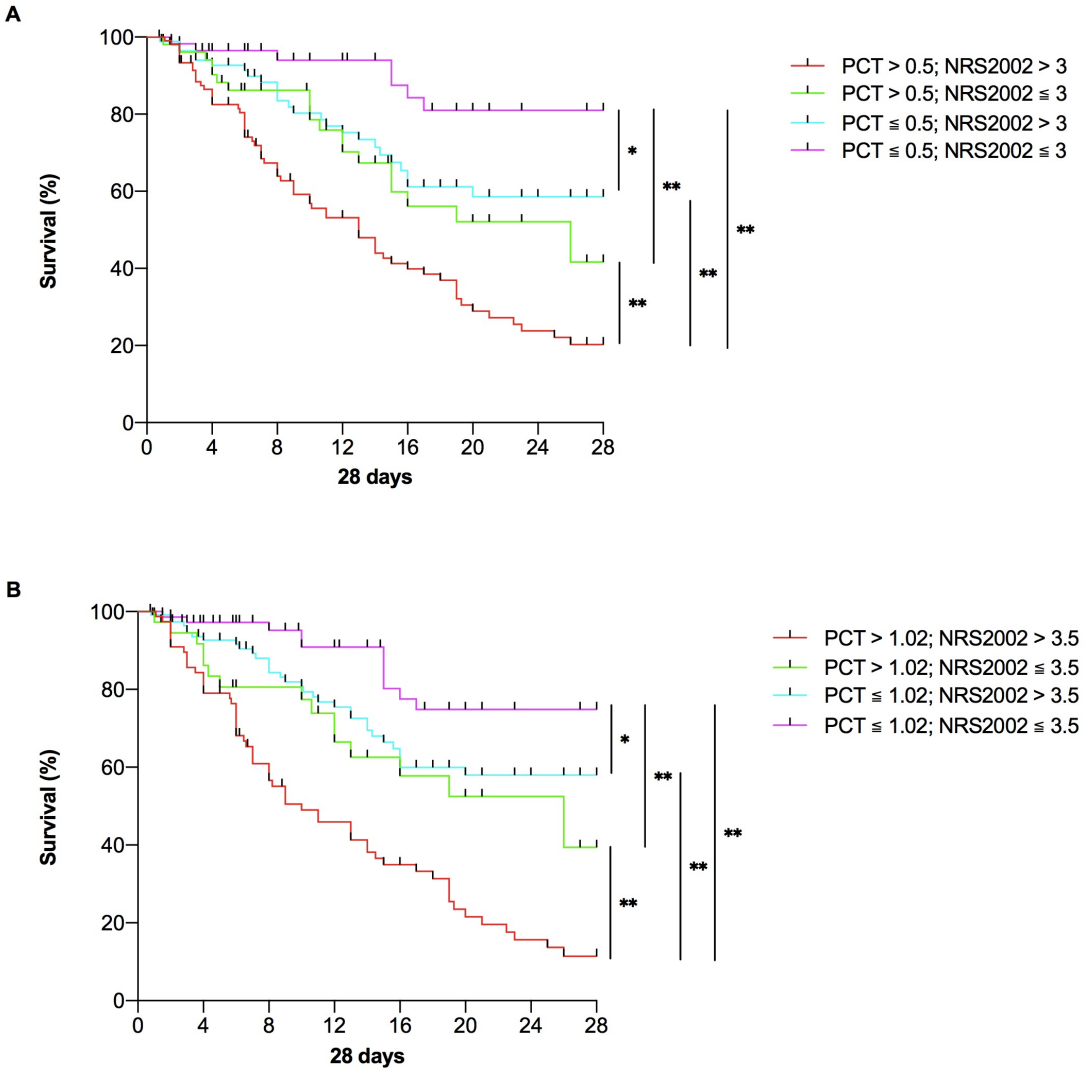


Fig. 3 Survival curves for critically ill patients with enteral nutrition. **(A)** Survival curves for groups divided by conventional values of NRS2002 and PCT; **(B)** Survival curves for groups divided by cut-off values of NRS2002 and PCT. *P < 0.05, **P < 0.01. NRS, Nutrition Risk Screening; PCT, procalcitonin

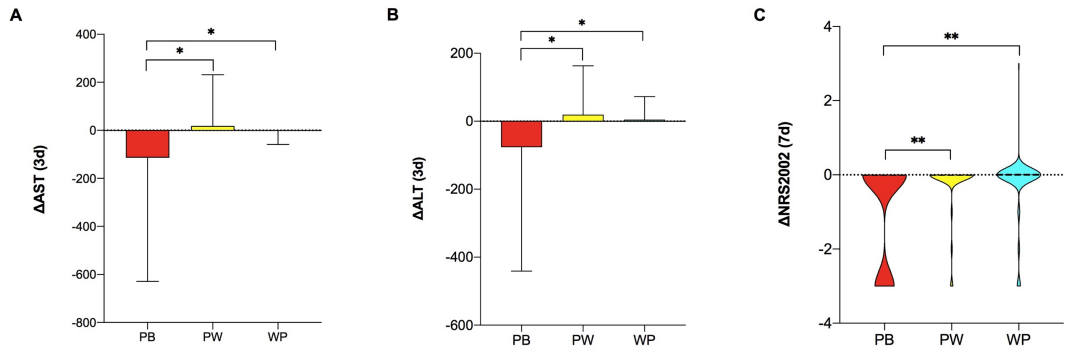


Fig. 4 Improvement of critically ill patients with different nutritional formulae. **(A)** Improvement of AST after 3 days of enteral nutrition; **(B)** Improvement of ALT after 3 days of enteral nutrition; **(C)** Improvement of NRS2002 after 7 days of enteral nutrition. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NRS, nutrition risk screening

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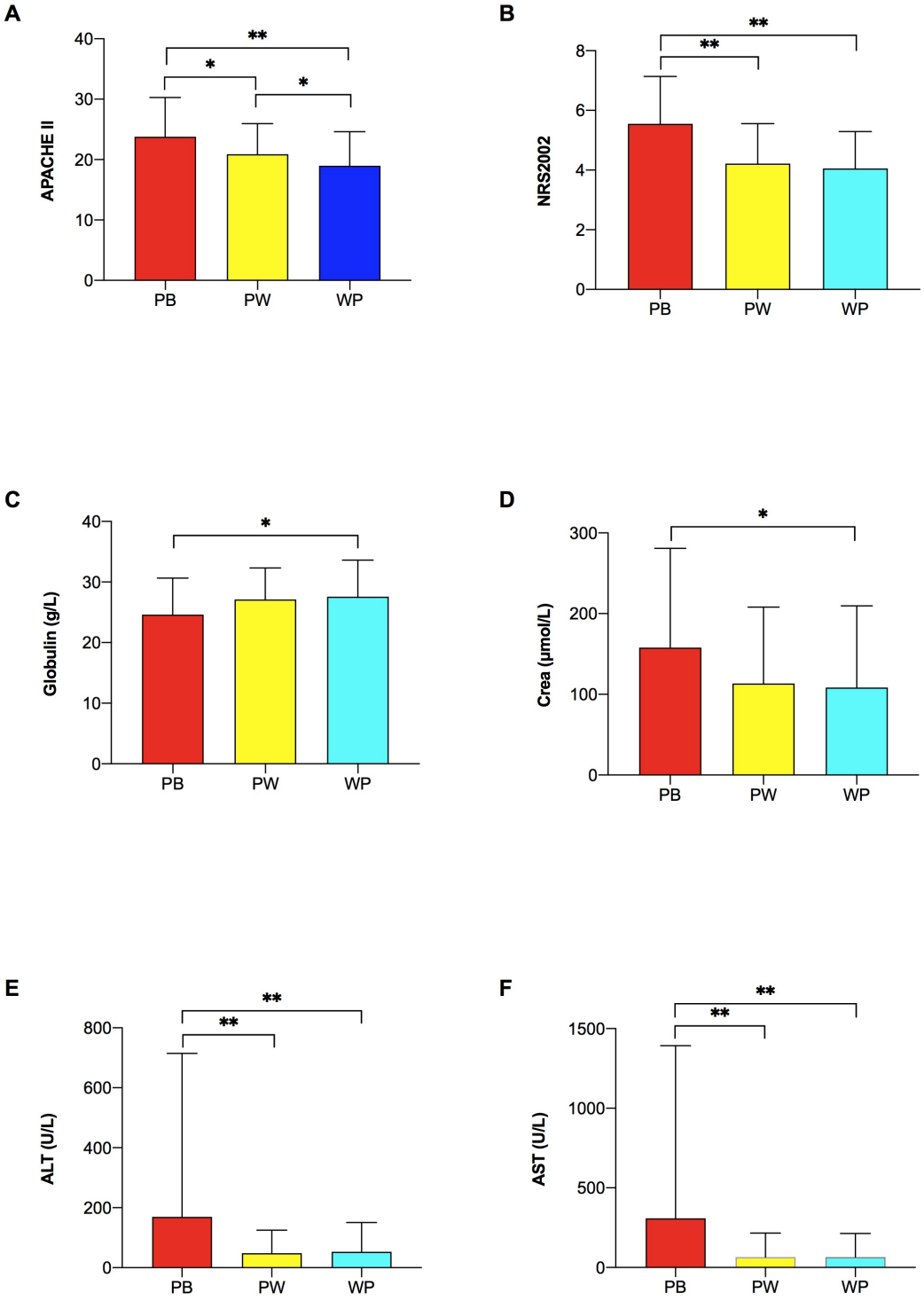

Fig. 5 Severity scores, nutrition status and inflammatory markers in different nutrition formulae groups. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Crea, serum creatinine; NRS, nutrition risk screening

Supplementary appendix

Table of contents

1. **Title**
2. **List of investigators**
3. **Text**
4. **Figures**

1. Title:

Nutritional risk factors for all -cause mortality of critically ill patients: a retrospective cohort study

2. List of investigators:

Jine Wang, Nan Zheng, Huitao Qian, Xinyi Chang , Yi Han*

3. Text:

Correlation analysis among various indicators

Spearman correlation analysis was used to draw a heat map and analyze the correlation between various nutritional indicators. The results showed that: albumin, prealbumin and transferrin were positively correlated with each other, and retinol-binding protein (RBP) was positively correlated with prealbumin, serum creatinine and urea [albumin and prealbumin (r = 0.40), albumin and transferrin (r = 0.34), prealbumin and transferrin (r = 0.43); RBP and prealbumin (r = 0.56), RBP and serum creatinine (r = 0.47), RBP and urea (r = 0.41), all P values < 0.01] (Figure S1).

Predictive values of prealbumin (PA) -based composite indicators for 28-day outcome

We also analyzed the predictive values of PA-based composite indicators for patients' 28-day outcome. Results showed that PA + transferrin, PA + urea, PA + serum creatinine, PA + AST, and PA + RBP had certain predictive values of critically ill patients with enteral nutrition. The

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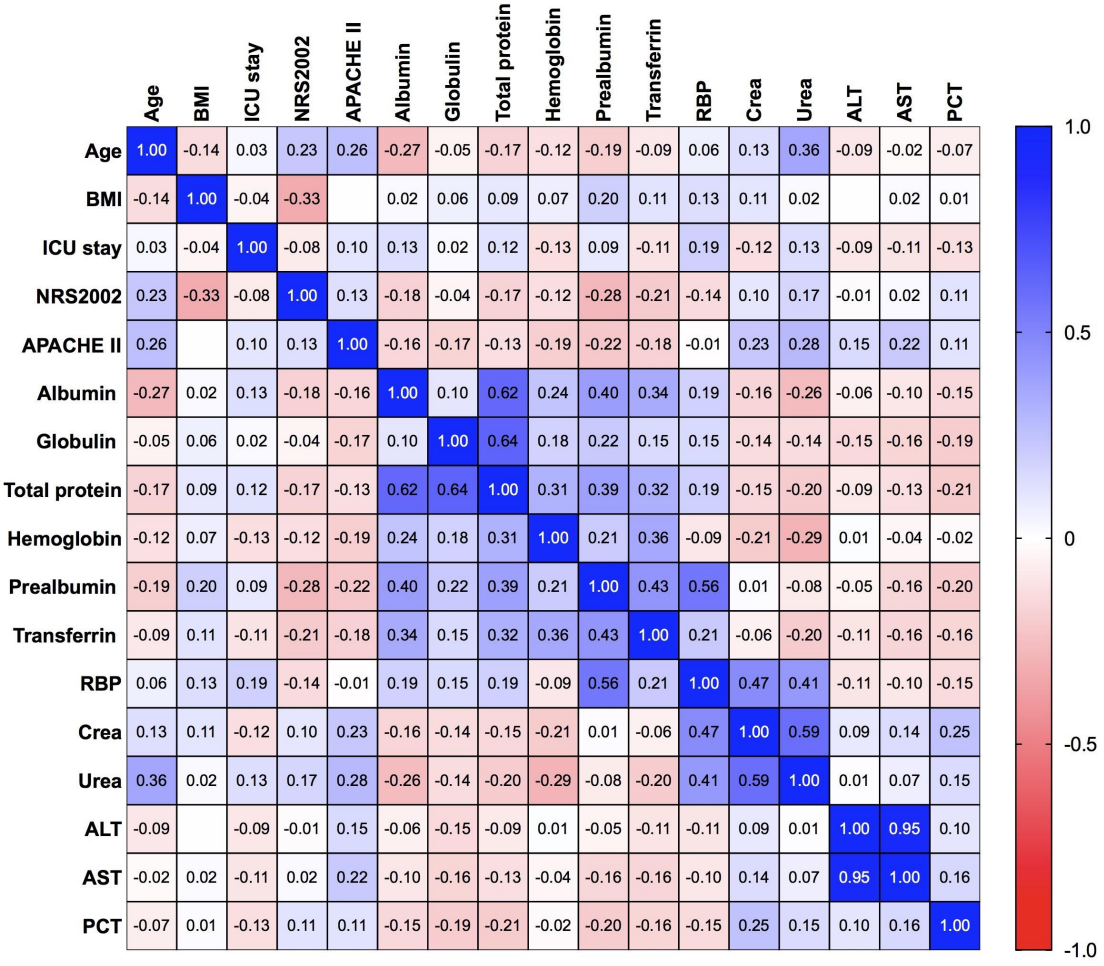
AUROC results were 0.64, 0.65, 0.67, 0.64 and 0.65 respectively, and all P values were < 0.01 (Figure S2).

4. **Figures**



Supplementary Figure 1 Heat map of the correlation of indicators in critically ill patients with enteral nutrition. APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Crea, serum creatinine; NRS, Nutrition Risk Screening; RBP, Retinol Binding Protein; PCT, procalcitonin.

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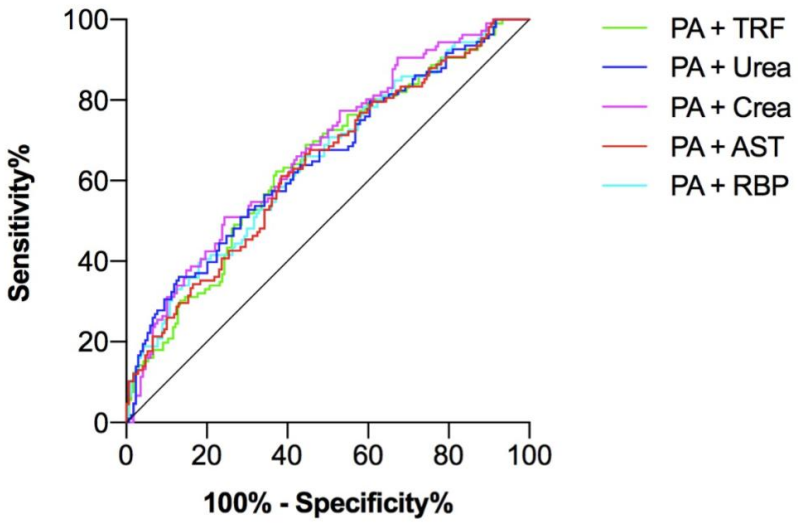

Variable	PA + TRF	PA + Urea	PA + Crea	PA + AST	PA + RBP
Area	0.64	0.65	0.67	0.64	0.65
Std. Error	0.03	0.03	0.03	0.03	0.03
Lower 95% CI	0.58	0.58	0.61	0.57	0.58
Upper 95% CI	0.71	0.72	0.74	0.70	0.71
P value	<0.01	<0.01	<0.01	<0.01	<0.01
Sensitivity	62.26	36.11	50.94	61.11	66.04
Specificity	62.80	86.98	75.60	61.54	56.29

Supplementary Figure 2 Receiver operator characteristic (ROC) curves for PA-based composite indicators in predicting 28-day outcome. CI, confidence interval; AST, aspartate aminotransferase; Crea, serum creatinine; PA, prealbumin; RBP, retinol binding protein; TRF, transferrin.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	4
		(*e*) Describe any sensitivity analyses	4
Results			4-6
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5 5 5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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BMJ Open

Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study

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Date Submitted by the Author:	07-Oct-2022
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Secondary Subject Heading:	Nutrition and metabolism
Keywords:	INTENSIVE & CRITICAL CARE, Nutritional support < GASTROENTEROLOGY, NUTRITION & DIETETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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Title:

Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study

Running title:

Nutritional risks in critical care

Authors:

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Word count: 3344
Number of figures: 7
Number of tables: 2

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Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study

ABSTRACT

Objectives This study aimed to explore the predictive value of single and multiple risk factors for the clinical outcomes of critically ill patients receiving enteral nutrition and to establish an effective evaluation model.

Design Retrospective cohort study.

Setting Retrospective cohort study. Data from the 2020-2021 period were collected from the electronic records of the First Affiliated Hospital, Nanjing Medical University.

Participants 459 critically ill patients with enteral nutrition in the geriatric intensive care unit were included in the study.

Primary and secondary outcome The primary outcome was 28-day mortality. The secondary outcomes were 28-day invasive mechanical ventilation time, ICU stay, nutritional risk screening 2002 (NRS2002) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Results Independent prognostic factors, including prealbumin/procalcitonin (PCT) ratio and APACHE II score, were identified using a logistic regression model and used in the nomogram. The area under the ROC curve and concordance index indicated that the predictive capacity of the model was 0.753. Moreover, both the prealbumin/PCT ratio and the combination model of (PCT, prealbumin and NRS2002) had a higher predictive value for clinical outcomes. Subgroup analysis also identified that a higher inflammatory state (PCT > 0.5 ng/mL) and major nutritional risk (NRS2002 > 3) led to worse clinical outcomes. In addition, patients on whole protein formulae beared less nutritional risk than those on short peptide formulae.

Conclusions This nomogram had a good predictive value for 28-day mortality in critically ill patients receiving enteral nutrition. Both the prealbumin/PCT ratio and the combination model (PCT, prealbumin and NRS2002), as composite models of inflammation and nutrition, could better predict the prognosis of critically ill patients.

Keywords: Critically ill patients, Enteral nutrition, Procalcitonin, NRS2002, Prognosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study investigated the nutritional risk factors in critical scenario
- This study produced a convenient prediction model for the outcomes of the critically ill
- The study was a retrospective and data were relatively abundant
- Since clinical data could not be obtained from other centers, no external validation was performed.

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INTRODUCTION

In critically ill patients, due to severe stress or trauma, the metabolic rate is significantly increased, metabolic disorders and malnutrition are very common, and the incidence of malnutrition can be as high as 30–50% [1]. Malnutrition prolongs the patients' hospital stay in the intensive care unit (ICU) and increases the incidence of infection and other complications, thus increasing mortality [2]. Studies have shown that early enteral nutritional support can reduce the severity of disease in critically ill patients, reduce the risk of complications, shorten the length of ICU stay, and improve the prognosis of patients [3]. Nutrition practice guidelines in Europe, Canada, and the United States suggest early implementation of enteral nutrition for critically ill patients with stable hemodynamics [4-7].

Nutritional therapy includes nutritional risk assessment, nutritional plan formulation, and implementation. Timely and accurate assessment of patients' nutritional risk is a prerequisite for providing reasonable nutrition therapy. At present, there are a wide variety of nutritional screening and evaluation tools. Single indicators include hemoglobin, albumin, prealbumin, creatinine, urea, body mass index (BMI), skinfold thickness, middle arm circumference, indirect calorimetry [8] and phase angle [9]. Composite indicators include Nutrition Risk Screening 2002 (NRS2002) score [10], Critical Care Nutrition Risk Score [11], and others. Each nutritional risk assessment tool has advantages and disadvantages. To date, there is no gold standard for nutritional risk assessment of critically ill patients.

Critically ill patients often present with infection. Moreover, procalcitonin (PCT), an inflammatory marker, usually reflects the infection [12-13]. Studies have shown that PCT has a predictive value for the prognosis of critically ill patients [14]. Therefore, in this study, we aimed to screen the risk factors for 28-day mortality of critically ill patients, and to establish a composite model of inflammatory and nutritional factors to predict 28-day mortality in critically ill patients.

We present the following article in accordance with the STROBE reporting checklist.

METHODS

Study design and participants

A retrospective study was conducted on critically ill patients in the geriatric intensive care unit of the First Affiliated Hospital of Nanjing Medical University from January 2020 to January 2021. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (approval number: 2020-SR-055). All the patients enrolled in this study received enteral nutrition. The data of all patients were reviewed and analyzed anonymously, and the requirement for informed consent was waived.

The inclusion criteria were as follows: (1) admission to the ICU, (2) enteral nutrition received within 24-48 hours after admission to the ICU, and (3) age > 18 years. The exclusion criteria were as follows: (1)

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ICU stay or death < 24 hours, (2) incomplete medical records, (3) patients receiving parenteral nutrition, and (4) patients receiving oral nutrition.

The goal of nutritional support was 25–30 kcal/kg/d calories and 1.2–2.0 g/kg/d protein [7] for each patient, via nasogastric or naso-intestinal tube. According to the patient's disease and nutritional status, a nutrition formula was applied.

Outcomes and risk factors

All the enrolled medical records were subjectively reviewed. The continuous laboratory test results were recorded within 2 weeks of ICU admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score, NRS2002, and BMI were withdrawn for 2 weeks after admission. Other clinical data, including age, gender, length of ICU stay, and 28-day mortality, were also collected. The value of the indicator was the average value within two weeks after admission. In this study, we analyzed the risk factors for 28-day mortality and evaluated the predictive values of single and composite predictors. Subgroup analysis was conducted according to nutritional scores and inflammatory status.

The primary outcome evaluated in this study was 28-day mortality. Secondary outcomes were 28-day invasive mechanical ventilation (IMV) time and ICU stay.

Statistical analysis

GraphPad Prism 8.0, SPSS 26.0 and R 4.2.1 software were used for statistical analysis. All continuous variables were tested for normal distribution. Normally distributed variables were expressed as mean ± standard deviation, and unpaired t-test was used for comparison between two groups. Non-normally distributed variables were expressed as the median and interquartile range, and the Mann-Whitney test was used for comparison between groups. Count data were expressed as percentages, and the chi-square test was used for comparison.

Univariable and multivariable logistic regressions were used to screen for risk factors for 28-day mortality. In the multivariable analysis, predictors were selected using forward stepwise regression. Multicollinearity among variables was evaluated before the regressions were conducted. A nomogram based on the results of the multivariable analyses was constructed. Calibration, discrimination, and clinical usefulness of the nomogram were calculated to evaluate its performance. The area under the receiver operating characteristic curve (AUROC) and concordance index were used to assess the predictive capacity of the prediction model. Concordance indices were obtained by creating 1000 bootstrap samples from the corresponding cohort and replicating the estimation process. A calibration curve was used to analyze the agreement between the nomogram and the actual observations. Decision curve analysis was performed to assess the clinical usefulness of the prognostic nomogram.

Receiver operating characteristic (ROC) curves were constructed to analyze the predictive power of single and composite predictors. According to the inflammatory and nutritional status, subgroup analysis

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was performed based on PCT and NRS2002 levels. Survival curves were drawn for subgroups using the critical value when the Youden's index was the largest as the best cut-off value. Statistical significance was set at $P < 0.05$.

Patients and public involvement

No patients or members of the public were involved in the design, conduct or reporting of this study. The study results were not disseminated to study participants.

RESULTS

Clinical and demographic characteristics of the studied patients

A total of 459 patients were enrolled in this study. Among the total enrolled population, 158 patients were excluded from the analysis because they met one or more of the exclusion criteria (Figure 1). Finally, data from 301 patients were analyzed, including 214 males and 87 females, 183 survivors, and 118 non-survivors. Among the 301 patients, cerebral hemorrhage was the main surgical cause and pneumonia was the main medical cause, with 78 (25.91%) cases of cerebral hemorrhage and 197 (65.45%) cases of pneumonia. Majority of the patients had comorbidities, including 154 (51.16%) cases of hypertension, 110 (36.54%) cases of heart failure, 82 (27.24%) cases of renal failure, 82 (27.24%) cases of cerebral infarction, and 73 (24.25%) cases of diabetes.

Compared with the survival group, the non-survivors had higher APACHE II and NRS2002 scores; higher serum creatinine, urea, aspartate aminotransferase (AST), and PCT levels; lower prealbumin (PA) and transferrin levels; and shorter ICU stay ($P < 0.05$). There was no difference in 28-day invasive mechanical ventilation time between the two groups (Table 1).

Table 1 Clinical characteristics of study population

Variables	**Survivors (n = 183)**	**Non-survivors (n = 118)**	**P-value**
	n (%) / mean ± SD / median (IQR)	**n (%) / mean ± SD / median (IQR)**	
Age (years)	70.0 (56.0,83.0)	74.0 (58.0,85.0)	0.13
Male	134 (73.2%)	81 (68.6%)	0.43
ICU stay (days)	13.0 (6.0,28.0)	8.9 (4.0,14.6)	**<0.01**
28d IMV time (hours)	63.0 (0,370.0)	140.0 (31.5,268.0)	**0.25**
NRS2002	4.0 (3.0,4.0)	4.0 (4.0,6.0)	**<0.01**
APACHE II	18.9 ± 5.3	23.3 ± 5.5	**<0.01**

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BMI (kg/m^2)	22.5 (20.5,25.3)	21.8 (19.1,25.2)	0.14
Lab testing results			
Albumin (g/L)	34.8 ± 4.7	34.0 ± 5.3	0.17
Globulin (g/L)	26.0 (22.7,28.3)	26.4 (23.2,29.1)	0.68
Total protein (g/L)	59.6 ± 8.7	58.9 ± 9.2	0.48
Retinol-binding protein (mg/L)	27.7 (19.2,39.0)	25.3 (16.5,36.6)	0.17
Prealbumin (g/L)	0.15 (0.10,0.20)	0.12 (0.08,0.17)	**<0.01**
Transferrin (g/L)	1.20 (0.97,1.65)	1.09 (0.83,1.46)	**0.01**
Hemoglobin (g/L)	100.8 (87.0,115.0)	96.3 (82.8,117.0)	0.31
Serum creatinine (μmol/L)	69.1 (51.9,105.6)	107.4 (72.5,176.3)	**<0.01**
Urea (mmol/L)	9.2 (6.9,13.9)	13.6 (8.5,18.6)	**<0.01**
ALT (U/L)	36.7 (24.5,63.5)	36.4 (23.6,71.8)	0.98
AST (U/L)	41.5 (29.2,64.5)	56.1 (31.6,85.4)	**<0.01**
Procalcitonin (ng/mL)	0.30 (0.13,0.94)	1.43 (0.37,3.64)	**<0.01**
Infective comorbidities			
Pneumonia	101 (55.19%)	96 (81.36%)	**<0.01**
Septic shock	14 (7.65%)	30 (25.42%)	**<0.01**
Blood stream infection	4 (2.19%)	8 (6.78%)	0.09
Urinary infection	11 (6.01%)	8 (6.78%)	0.79
Infections of the central nervous system	3 (1.64%)	4 (3.39%)	0.55
Intra-abdominal infection	3 (1.64%)	4 (3.39%)	0.55
Surgical disease			
Cerebral hemorrhage	45 (24.59%)	33 (27.97%)	0.51
Abdominal surgery	23 (12.57%)	7 (5.93%)	0.06
Multiple injuries	18 (9.84%)	5 (4.24%)	0.07
Complications			

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Heart failure	51 (27.87%)	59 (50.00%)	**<0.01**
Renal insufficiency	25 (13.66%)	57 (48.31%)	**<0.01**
Liver insufficiency	13 (7.10%)	18 (15.25%)	**0.02**
Hypertension	79 (43.17%)	75 (63.56%)	**<0.01**
Diabetes mellitus	30 (16.39%)	43 (36.44%)	**<0.01**
Hypoproteinemia	12 (6.56%)	9 (7.63%)	0.72
Cerebral ischemic stroke	49 (26.78%)	33 (27.97%)	0.82

APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; IMV, invasive mechanical ventilation; NRS, Nutrition Risk Screening; SD, standard error.

Screening of risk factors for 28-day mortality

In this study, univariable and multivariable logistic regressions were used to screen for risk factors for 28-day mortality in critically ill patients. Univariable regression showed that APACHE II, NRS2002, prealbumin, serum creatinine, urea, AST, PCT, and the ratio of prealbumin to procalcitonin (PA/PCT) affected the 28-day mortality of critically ill patients receiving enteral nutrition ($P < 0.05$). NRS2002 and PA are major predictors for nutrition status, and PCT for inflammatory status. Inflammatory and nutritional factors interact in critical illness. We tried to find out better predictors that could combine inflammatory and nutritional status to predict the outcomes. All candidate factors screened out from univariable regression were entered into a multivariable logistic regression model. The result showed that APACHE II and PA/PCT were included in the final prediction model ($P < 0.05$) (Table 2).

Table 2 Univariable and multivariable logistic regression analysis for critically ill patients with enteral nutrition

Variables	Univariable models		Multivariable model		
	OR (95% CI)	P-value	β[a]	OR (95% CI)	P-value
Age (years)	1.01 (1.00,1.02)	0.14			
Gender	1.25 (0.75,2.08)	0.39			
NRS2002	1.24 (1.05,1.47)	**0.01**			
APACHE II	1.17 (1.11,1.23)	**<0.01**	0.125	1.13 (1.08,1.20)	**<0.01**

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BMI (kg/m2)	0.95 (0.90,1.01)	0.08			
Albumin (g/L)	0.97 (0.92,1.01)	0.17			
Globulin (g/L)	1.01 (0.96,1.05)	0.83			
Total protein (g/L)	0.99 (0.96,1.02)	0.48			
Retinol-binding protein (mg/L)	0.99 (0.98,1.00)	0.16			
Prealbumin (g/L)	0.00 (0.00,0.02)	**<0.01**			
Transferrin (g/L)	0.80 (0.45,1.27)	0.39			
Hemoglobin (g/L)	0.99 (0.98,1.00)	0.38			
Serum creatinine (μmol/L)	1.00 (1.00,1.01)	**0.00**			
Urea (mmol/L)	1.04 (1.01,1.07)	**0.01**			
ALT (U/L)	1.00 (1.00,1.00)	0.18			
AST (U/L)	1.00 (1.00,1.00)	**0.04**			
Procalcitonin (ng/mL)	1.03 (1.01,1.07)	**0.03**			
PA/PCT	0.51 (0.36,0.69)	**<0.01**	-0.51	0.60 (0.43,0.84)	**<0.01**

APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; NRS, Nutrition Risk Screening; OR, odds ratios; PA, prealbumin; PCT, procalcitonin.

[a] Unstandardized β coefficients were calculated from the multivariable logistic regression model.

Prognostic nomogram for 28-day mortality

A prognostic nomogram for 28-day mortality was established using the two prognostic factors obtained from the multivariable logistic regression model (Figure 2). A nomogram was generated by assigning a weighted score to each independent prognostic parameter. The APACHE II and PA/PCT scales ranged from 5 to 40 and 8 to 0, respectively. The highest total score was 180 points and the 28-day mortality risk ranged from 0.01 to 0.8. A higher score on the nomogram corresponded to a higher probability of death in 28-day.

Performance evaluation of the prognostic nomogram

The AUROC and concordance index indicated that the predictive capacity of the model was 0.753 (95% CI, 0.694–0.811) (Figure 3A). The calibration plot demonstrated an adequate fit of the nomogram for predicting 28-day mortality, which was consistent with the Kaplan-Meier estimate (Figure 3B). Decision curve analysis showed the net benefit obtained from the application of our nomogram (Figure 3C).

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Predictive values of each model on 28-day outcome

ROC curves were drawn based on the 28-day mortality for each index. PCT and APACHE II had higher predictive value, with AUROC at 0.71 and 0.72 respectively. In addition, NRS2002, prealbumin, serum creatinine, and urea also had good predictive values for the 28-day mortality of critically ill patients receiving enteral nutrition. The AUROCs were 0.60, 0.63, 0.68, and 0.63, respectively, and all P values < 0.01 (Figure 4A).

Based on the inflammatory status, we analyzed the predictive value of the PCT-based composite model for patients' 28-day outcomes. Results showed that PCT + AST had a higher predictive value, with an AUROC of 0.70. In addition, PCT + prealbumin, PCT + NRS2002, PCT + transferrin, PCT + serum creatinine, and PCT + urea also performed well in predicting 28-day outcomes of studied patients, with AUROCs of 0.63, 0.67, 0.65, 0.65, and 0.69, respectively, and all P values < 0.01 (Figure 4B).

Based on nutritional risk, we analyzed the predictive values of the NRS2002 based composite model for patients' 28-day outcomes. The results showed that NRS2002 + prealbumin, NRS2002 + transferrin, NRS2002 + serum creatinine, NRS2002 + urea, and NRS2002 + AST had good predictive values for 28-day outcomes. The AUROCs were 0.64, 0.61, 0.68, 0.66, and 0.63, respectively, and all P values < 0.01 (Figure 4C).

Importantly, we combined the inflammatory and nutritional risks to establish a more effective model to predict patients' 28-day outcomes. The results showed that triple indicator (PCT + NRS2002 + prealbumin) and double indicator (prealbumin/PCT) performed better on predicting 28-day outcomes, with AUROCs at 0.73 and 0.71 respectively, and both P values < 0.01 (Figure 4D).

In addition, the predictive value of the prealbumin-based composite index for the 28-day outcome was less powerful in supplementary figure S1.

Survival analysis based on inflammatory and nutritional risks

In this study, patients were divided into groups based on whether the patients' NRS2002 score was at a high nutritional risk (> 3 or cut-off value 3.5) and whether the PCT level was in a severe inflammatory state (> 0.5, or cut-off value 1.02). Differences in the 28-day outcomes of each group were compared. Survival curves were drawn, and the results showed that the overall survival rate of the patients in each group was significantly different at 28 days (P < 0.01). For patients with higher inflammatory and nutritional risk, if PCT > 0.5 and NRS2002 > 3, the survival rate would be significantly lower than that of the other groups (Figure 5).

Influences of different enteral nutritional formulae

According to nutritional formula, patients were divided into three groups: peptide-based formula group (PB), peptide step to whole protein formula group (PW), and whole protein formula group (WP). The

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results showed that after 3 days of enteral nutrition, the improvement in AST and alanine aminotransferase (ALT) in the PB group was higher than that in the other groups ($P < 0.05$). After 7 days of enteral nutrition, the improvement in NRS2002 score in the PB group was higher than that in the other groups ($P < 0.01$) (Figure 6).

APACHE II, NRS2002, serum creatinine, ALT, and AST levels in the PB group were significantly higher than those in the other groups, while globulin levels were lower in the PB group than in the WP group at admission ($P < 0.05$) (Figure 7).

DISCUSSION

The mortality rate in critically ill patients is generally high. In this retrospective study, we observed enterally fed patients in ICU on their APACHE II score, NRS2002 score, serum creatinine, urea, AST, procalcitonin, prealbumin, and PA/PCT, to identify risk factors for their clinical outcomes. Univariable analysis showed that patients in the non-survival group had more severe inflammation and nutritional deficiency, with worse multiorgan dysfunction. Multivariable logistic regression analysis showed that APACHE II was a risk factor for 28-day survival in critically ill patients receiving enteral nutrition. Meanwhile, PA/PCT ratio was a protective factor against the 28-day outcome. These results are consistent with previous studies [15-16]. Based on the multivariable regression results, the APACHE II score and PA/PCT ratio were included to establish a prognostic nomogram. This nomogram showed satisfactory performance, as assessed by the AUC, calibration curve, and decision curve analysis. Therefore, this nomogram can be effectively applied in clinical practice.

This nomogram model included two factors, the APACHE II score and PA/PCT ratio, in which, both were available from clinical data. Studies have shown that the APACHE II score can be used to assess disease severity and predict disease prognosis [15]. Some studies have also shown that PA/PCT has a good predictive value for severe nonviral pneumonia in children treated with mechanical ventilation[16]. This study demonstrated that PA/PCT ratio has a high predictive value for critically ill patients receiving enteral nutrition. On the basis of fully considering the relationship between inflammation and nutrition in critically ill patients, the predictive model included PA/PCT, an indicator with high predictive value, which greatly improved the predictive value of the model.

Compared with the survival group, non-survivors had lower prealbumin levels and higher PCT levels, which indicated a high nutritional risk and inflammatory state related to a worse prognosis. Research has shown that the ratio of C-reactive protein (CRP) to albumin has predictive value for in-hospital mortality in patients with sepsis [17]. Li et al. showed that CRP/prealbumin ratio was independently associated with ICU mortality and length of stay [18]. To comprehensively evaluate the state of inflammation and nutrition, this study used the ratio of prealbumin to PCT as an indicator [16]. ROC curve analysis proved that prealbumin/PCT had a high predictive value for 28-day mortality for critically ill patients, and its

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AUROC was very close to that of APACHE II ($P < 0.01$). In addition, prealbumin/PCT is far more feasible and accessible than APACHE II [16].

Procalcitonin is a precursor polypeptide to calcitonin. Under physiological conditions, serum PCT levels are extremely low (< 0.05 ng/mL). In viral and fungal infections, PCT remains at a low level [19-20], but in bacterial infections, PCT can surge to a very high level [21]. Studies have shown that in patients with sepsis, the use of PCT to guide the early discontinuation of antibacterial drugs can reduce the 28-day mortality rate and hospitalization costs [22]. A meta-analysis also reported that elevated serum PCT levels were closely related to all-cause mortality in patients with sepsis [14]. In addition, PCT could be a good predictor of prognosis in critically ill patients [13]. The results of this study proved that PCT could be predictive of 28-day outcomes in enterally fed critically ill patients.

Guidelines issued by the American Society of Parenteral and Enteral Nutrition in 2016 recommended the use of NRS2002 and NUTRIC scores for the nutritional risk assessment of patients [7]. The NUTRIC score is more complex, involving plenty of parameters including age, APACHE II score, SOFA score, complications, duration of ICU stay and interleukin-6. Therefore, its clinical use is practically limited. Compared to the NUTRIC score, NRS2002 score is simpler and more practical. NRS2002 score is an evidence-based nutritional risk score that can be used to screen nutritional risks for patients, to evaluate the effect of nutritional support, and to predict the clinical outcomes of hospitalized patients. Our results also proved that NRS2002 could be a predictor for 28-day mortality in critically ill patients, and when combined with prealbumin, PCT, transferrin, serum creatinine, urea, and AST levels, its predictive value would be further improved.

The results of this study showed that prealbumin, NRS2002, and PCT were predictive of 28-day mortality of critically ill patients with nasal feeding, and the combined index of prealbumin, NRS2002, and PCT had a high predictive value. Patients were divided into subgroups according to the NRS2002 scores and PCT levels. The results showed that the highest survival rate occurred in the low inflammatory state and nutritional risk group, and the lowest survival rate in the high inflammatory state and nutritional risk group. These results indicate that composite indicators of inflammation and nutrition could be reliable for evaluating the 28-day mortality of critically ill patients. Therefore, for critically ill patients, nutritional screening should be performed as early as possible, and appropriate nutritional support plans should be formulated, combined with infection control and inflammation regulation, to improve clinical outcomes. Although the critically ill patients included in this study are a very heterogeneous group (different ages, comorbidities, surgical and medical causes), the coexistence of inflammation and malnutrition remains a common phenomenon, so the conclusions of this study can be generalized to most critically ill patients.

This study has several limitations. Firstly, this study was a retrospective design and the research data was relatively limited; Secondly, this was a single-center clinical study, and the average age of the patients was older, so subgroup analysis based on age could not be performed; Finally, the clinical

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outcome of this study was set to 28 days of survival or death. The outcome was not followed up to a longer period.

In conclusion, critically ill patients are characterized by obvious nutritional deficiency, a higher inflammatory state, and poor overall prognosis. As single indicators, PCT, APACHE II, NRS2002, prealbumin, serum creatinine, and urea can be used in disease evaluation and prognosis prediction for enterally fed critically ill patients. As composite indicators, prealbumin/PCT and prealbumin + NRS2002 + PCT performed well in the severity evaluation and prognosis prediction. This study developed a prognostic nomogram including APACHE II and PA/PCT for predicting 28-day survival in critically ill patients receiving enteral nutrition, and the nomogram had good predictive value.

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Competing interests None declared.

Patient consent for publication Not required.

Ethical approval The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of the First Affiliated Hospital of Nanjing Medical University (NO.: 2020-SR-055) and individual consent for this retrospective analysis was waived.

Data availability statement Data are available at: https://figshare.com/articles/dataset/EN3_original_data_xlsx/19960202.

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Figure legends

Figure 1 Patient records enrollment flowchart

Figure 2 Nomogram to calculate risk score and predict 28-day mortality. Scores were assigned for APACHE II and PA/PCT by drawing a line upward from the corresponding values to the 'Points' line. The sum of all these scores, plotted on the 'Total points' line, corresponds to predictions of 28-day mortality risk in critically ill patients. APACHE II, Acute Physiology and Chronic Health Evaluation II; PA, prealbumin; PCT, procalcitonin.

Figure 3 Performance evaluation of the nomogram in the primary cohort. (A) Receiver operating characteristic curve analysis; (B) Calibration curve analysis; (C) Decision curve analysis. N = 301. AUC, area under the curve; CI, confidence interval.

Figure 4 Receiver operator characteristic (ROC) curves for single and composite indicators in predicting 28-day outcome. (A) ROCs for single indicators; (B) ROCs for PCT-based composite indicators; (C) ROCs for NRS2002-based composite indicators; (D) ROCs for PA-based composite indicators. N = 301. CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; Crea, serum creatinine; NRS, Nutrition Risk Screening; PA, prealbumin; PCT, procalcitonin; TRF, transferrin.

Figure 5 Survival curves for critically ill patients with enteral nutrition. (A) Survival curves for groups divided by conventional values of NRS2002 and PCT; (B) Survival curves for groups divided by cut-off values of NRS2002 and PCT. N = 301. *P < 0.05, **P < 0.01. NRS, Nutrition Risk Screening; PCT, procalcitonin.

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Figure 6 Improvement of critically ill patients with different nutritional formulae. (A) Improvement of AST after 3 days of enteral nutrition; (B) Improvement of ALT after 3 days of enteral nutrition; (C) Improvement of NRS2002 after 7 days of enteral nutrition. N = 301. *P < 0.05, **P < 0.01. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NRS, nutrition risk screening.

Figure 7 Severity scores, nutrition status and inflammatory markers in different nutrition formulae groups. (A) APACHE II score in different groups; (B) NRS2002 score in different groups; (C) Globulin in different groups; (D) Crea in different groups; (E) ALT in different groups; (F) AST in different groups. N = 301. *P < 0.05, **P < 0.01. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Crea, serum creatinine; NRS, nutrition risk screening.

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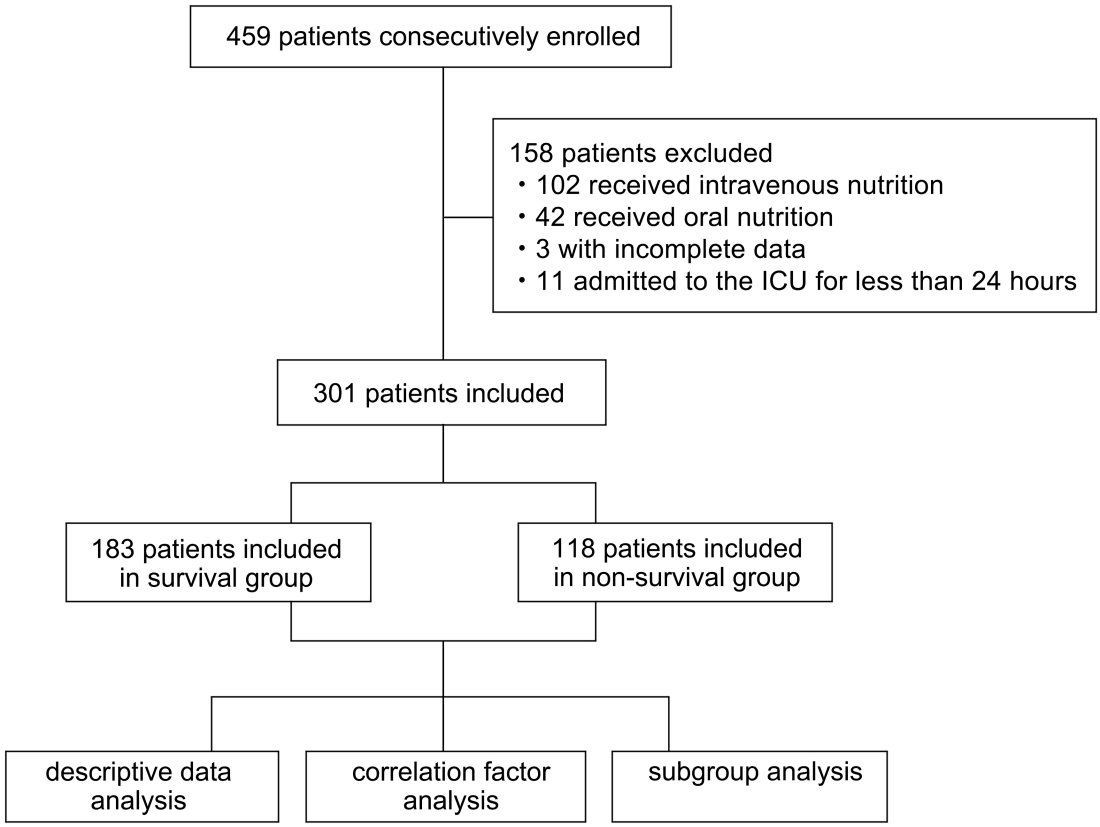


Figure 1 Patient records enrollment flowchart

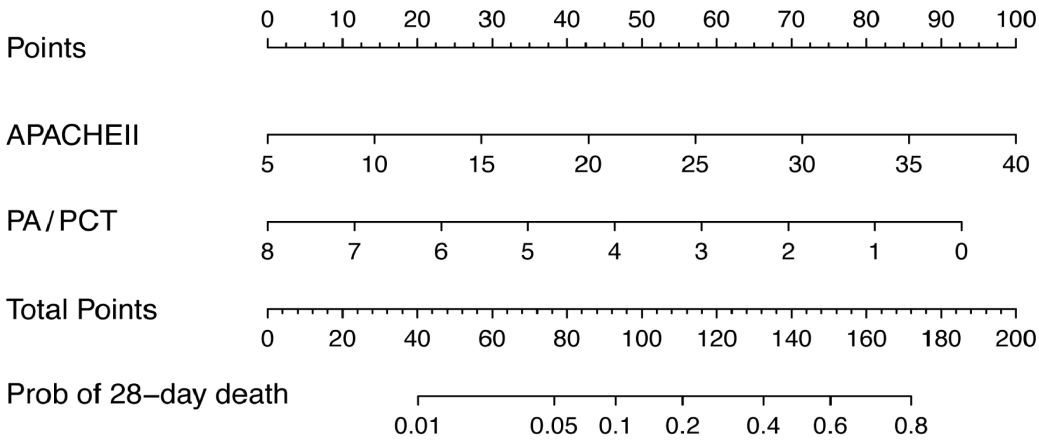


Figure 2 Nomogram to calculate risk score and predict 28-day mortality. Scores were assigned for APACHE II and PA/PCT by drawing a line upward from the corresponding values to the 'Points' line. The sum of all these scores, plotted on the 'Total points' line, corresponds to predictions of 28-day mortality risk in critically ill patients. N = 301. APACHE II, Acute Physiology and Chronic Health Evaluation II; PA, prealbumin; PCT, Procalcitonin.

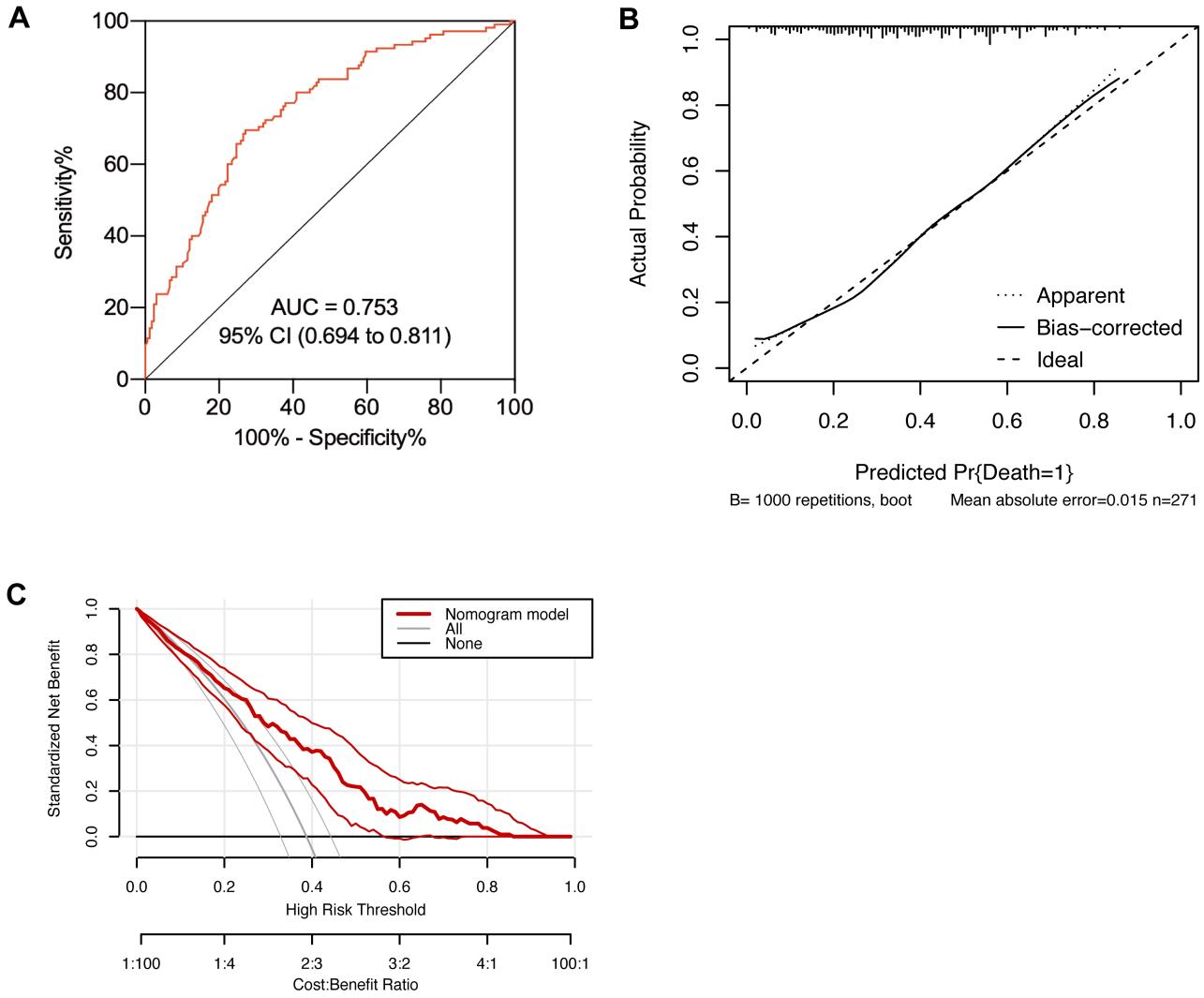
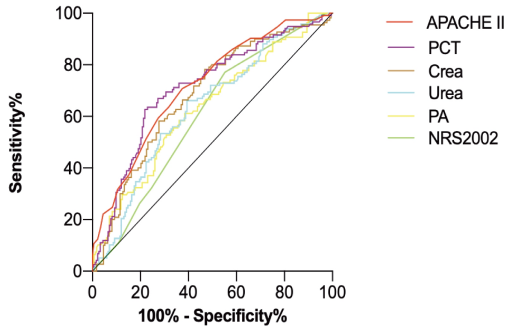


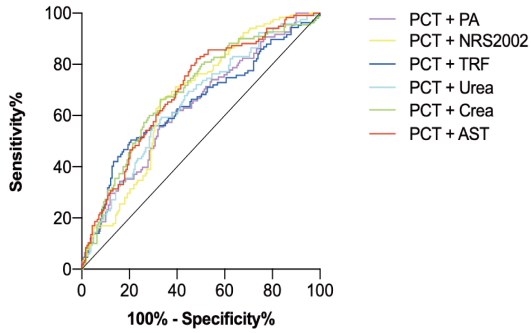
Figure 3 Performance evaluation of the nomogram in the primary cohort. (A) Receiver operating characteristic curve analysis; (B) Calibration curve analysis; (C) Decision curve analysis. N = 301. AUC, area under the curve; CI, confidence interval.

A



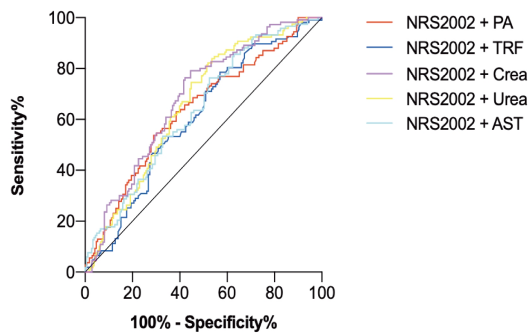
Variable	APACHE II	PCT	Crea	Urea	PA	NRS2002
Area	0.72	0.71	0.68	0.63	0.63	0.60
Std. Error	0.03	0.03	0.03	0.03	0.03	0.03
Lower 95% CI	0.66	0.65	0.62	0.57	0.57	0.54
Upper 95% CI	0.78	0.77	0.75	0.70	0.70	0.67
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Cut-off value	20.50	1.02	71.02	10.48	0.13	3.50
Sensitivity	70.80	62.71	78.18	66.10	61.11	77.12
Specificity	62.57	78.14	53.18	60.66	61.54	44.81

B



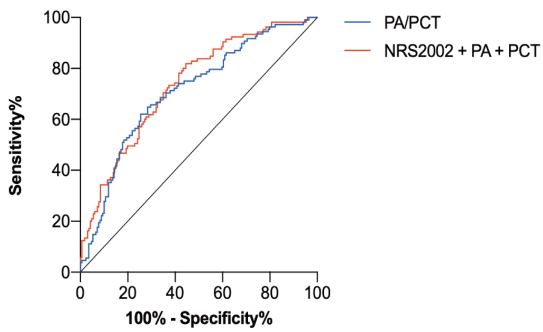
Variable	PCT + PA	PCT + NRS2002	PCT + TRF	PCT + Urea	PCT + Crea	PCT + AST
Area	0.63	0.67	0.65	0.65	0.69	0.70
Std. Error	0.03	0.03	0.04	0.03	0.03	0.03
Lower 95% CI	0.57	0.61	0.58	0.59	0.63	0.64
Upper 95% CI	0.70	0.73	0.71	0.72	0.75	0.76
P value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Sensitivity	61.11	66.10	50.47	59.32	66.36	82.20
Specificity	62.13	66.67	79.39	66.67	67.05	51.91

C



Variable	NRS2002 + PA	NRS2002 + TRF	NRS2002 + Crea	NRS2002 + Urea	NRS2002 + AST
Area	0.64	0.61	0.68	0.66	0.63
Std. Error	0.03	0.03	0.03	0.03	0.03
Lower 95% CI	0.57	0.54	0.62	0.60	0.57
Upper 95% CI	0.70	0.67	0.74	0.72	0.70
P value	<0.01	<0.01	<0.01	<0.01	<0.01
Sensitivity	53.70	78.50	79.09	83.90	76.27
Specificity	71.01	43.03	55.49	46.45	47.54

D



Variable	PA/PCT	PA + PCT + NRS2002
Area	0.71	0.73
Std. Error	0.03	0.03
Lower 95% CI	0.65	0.68
Upper 95% CI	0.77	0.79
P value	<0.01	<0.01
Cut-off value	0.13	—
Sensitivity	62.04	81.90
Specificity	74.56	55.42

Figure 4 Receiver operator characteristic (ROC) curves for single and composite indicators in predicting 28-day outcome. (A) ROCs for single indicators; (B) ROCs for PCT-based composite indicators; (C) ROCs for NRS2002-based composite indicators; (D) ROCs for PA-based composite indicators. N = 301. CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; AST, aspartate aminotransferase; Crea, serum creatinine; NRS: Nutrition Risk Screen-

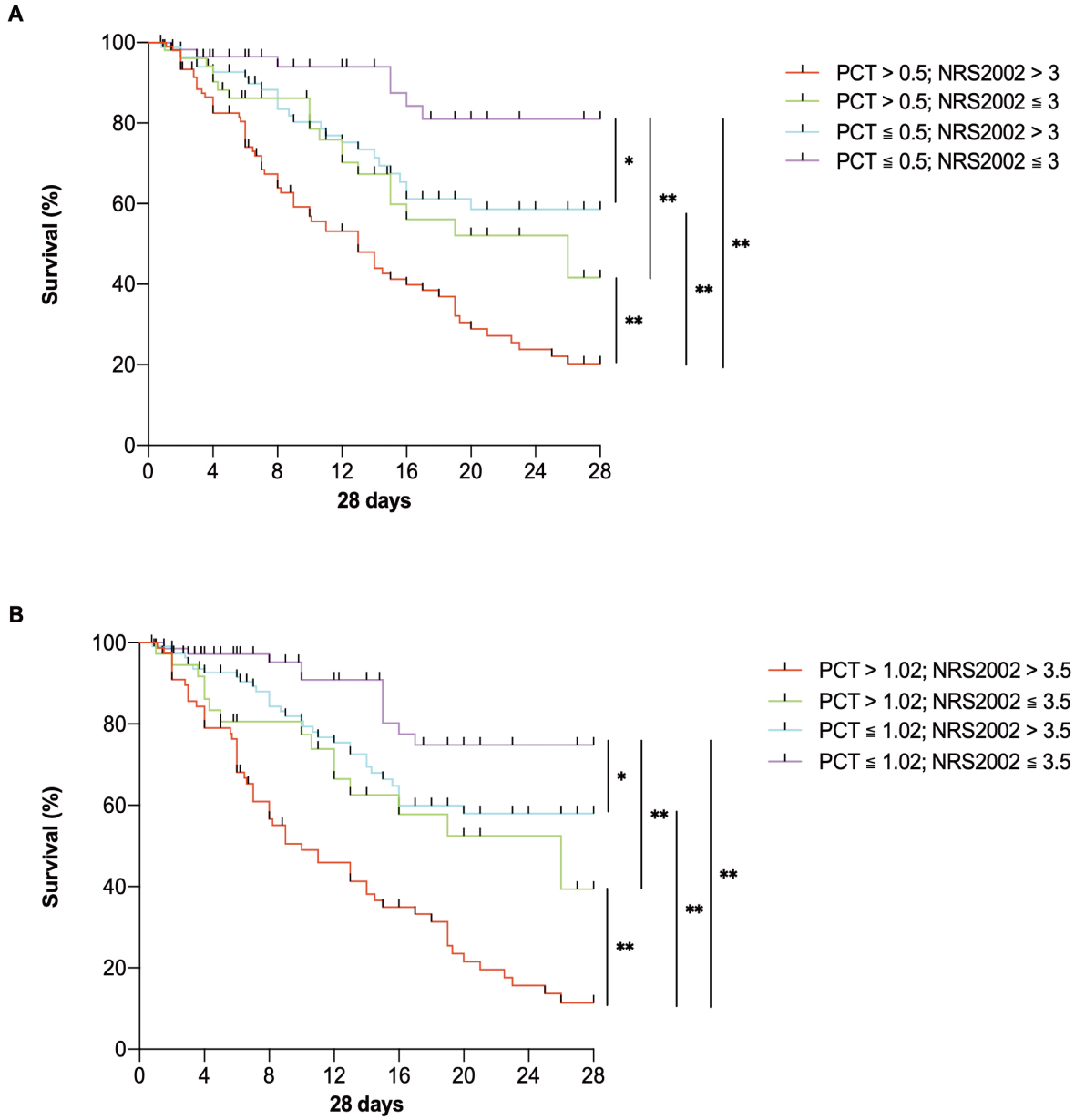


Figure 5 Survival curves for critically ill patients with enteral nutrition. (A) Survival curves for groups divided by conventional values of NRS2002 and PCT; (B) Survival curves for groups divided by cut-off values of NRS2002 and PCT. N = 301. *P < 0.05, **P < 0.01. NRS, Nutrition Risk Screening; PCT, procalcitonin.

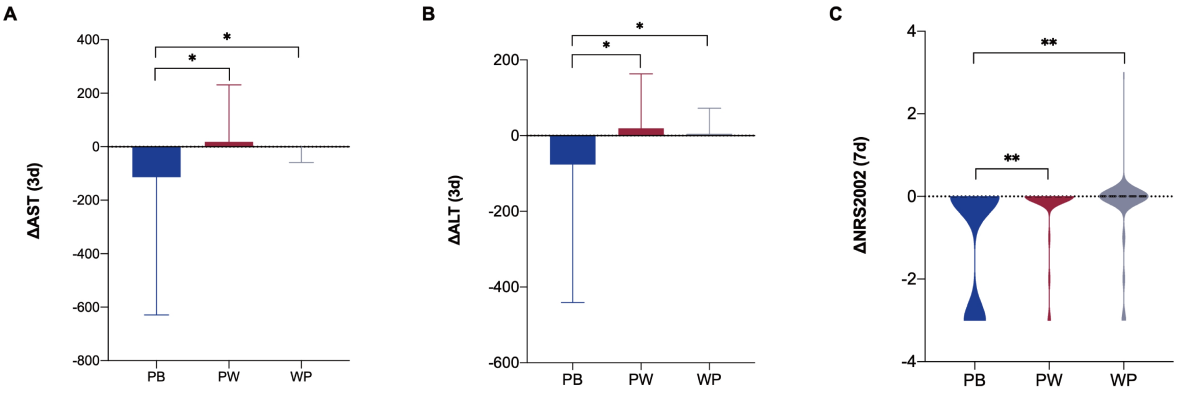


Figure 6 Improvement of critically ill patients with different nutritional formulae. (A) Improvement of AST after 3 days of enteral nutrition; (B) Improvement of ALT after 3 days of enteral nutrition; (C) Improvement of NRS2002 after 7 days of enteral nutrition. N = 301. *P < 0.05, **P < 0.01. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NRS, nutrition risk screening.

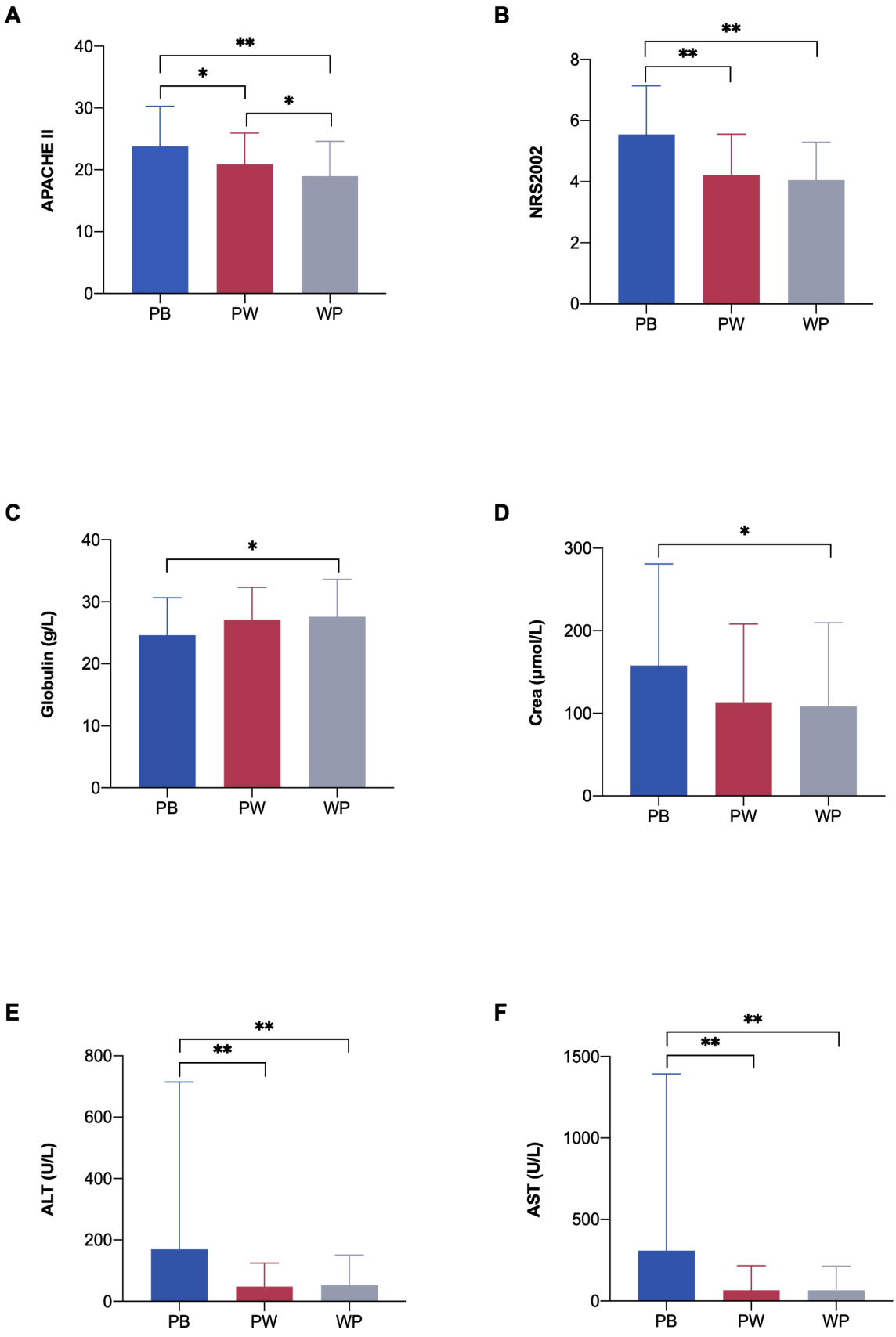


Figure 7 Severity scores, nutrition status and inflammatory markers in different nutrition formulae groups. (A) APACHE II score in three groups; (B) NRS2002 score in three groups; (C) Globulin in three groups; (D) Crea in three groups; (E) ALT in three groups; (F) AST in three groups. N = 301. *P < 0.05, **P < 0.01. PB, peptide-based formulae; PW, peptide step to whole protein formulae; WP, whole protein formulae; APACHE II, Acute Physiology and Chronic Health Evaluation II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Crea, serum creatinine; NRS, nutrition risk screening.

Supplementary appendix

Table of contents

1. Title
2. List of investigators
3. Text
4. Figures

1. Title:

Nutritional risk factors for all -cause mortality of critically ill patients: a retrospective cohort study

2. List of investigators:

Jine Wang[1], Nan Zheng[2], Xinyi Chang[2], Huitao Qian[2] and Yi Han[1*]

3. Text:

Predictive values of prealbumin (PA) -based composite indicators for 28-day outcome

We also analyzed the predictive values of PA-based composite indicators for patients' 28-day outcome. Results showed that PA + transferrin, PA + urea, PA + serum creatinine, PA + AST, and PA + RBP had certain predictive values of critically ill patients with enteral nutrition. The AUROC results were 0.64, 0.65, 0.67, 0.64 and 0.65 respectively, and all P values were < 0.01 (Figure S1).

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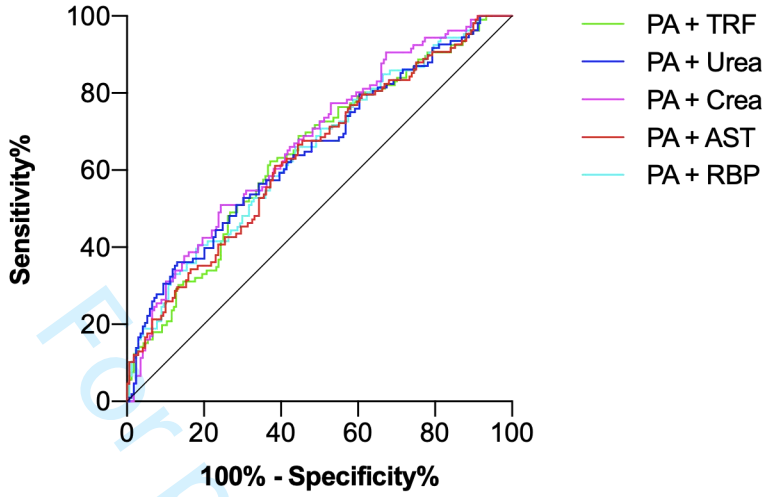
4. Figure



Variable	PA + TRF	PA + Urea	PA + Crea	PA + AST	PA + RBP
Area	0.64	0.65	0.67	0.64	0.65
Std. Error	0.03	0.03	0.03	0.03	0.03
Lower 95% CI	0.58	0.58	0.61	0.57	0.58
Upper 95% CI	0.71	0.72	0.74	0.70	0.71
P value	<0.01	<0.01	<0.01	<0.01	<0.01
Sensitivity	62.26	36.11	50.94	61.11	66.04
Specificity	62.80	86.98	75.60	61.54	56.29

Figure S1 Receiver operator characteristic (ROC) curves for PA-based composite indicators in predicting 28-day outcome. CI, confidence interval; AST, aspartate aminotransferase; Crea, serum creatinine; PA, prealbumin; RBP, retinol binding protein; TRF, transferrin.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	4
		(*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-7
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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