Optimize individualized energy delivery for septic patients using predictive deep learning models

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Running title: To optimize energy delivery for sepsis in ICU

Lu Wang MCs[1,2†], Li Chang BS[3†], Ruipeng Zhang BS[1,2], Kexun Li MCs[4], Yu Wang MCs[5], Wei Chen PhD[5], Xuanlin Feng BS[3], Mingwei Sun BS[1,2], Qi Wang PhD[6], Charles Damien Lu PhD[2], Jun Zeng, BS[1,2], Hua Jiang PhD[1,2,3]

[1]Department of Nutrition and Food Hygiene, School of Public Health, Peking University, Beijing, China
[2]Laboratory of Toxicological Research and Risk Assessment for Food Safety, Peking University, Beijing, China
[3]College of Sports and Human Sciences, Beijing Sport University, Beijing, China

Authors' email addresses and contributions:
LW:
Contribution: conceived and delineated the hypotheses, designed the study, acquired, data collection, data synthesis, model building and analyzed the data, and drafted the first version of this manuscript and edited the manuscript of the previous analysis.

LC:
Contribution: developed the original concepts for this study.

R-PZ:
Contribution: data collection, data synthesis and model building.

K-XL:
Contribution: data collection, data synthesis and model building.

YW:
Contribution: drafted the first version of this manuscript.

WC:
Contribution: developed the original concepts for this study.

X-LF:
Contribution: data collection, data synthesis and model building.

M-WS:
Contribution: developed the original concepts for this study.

QW:
Contribution: the English proofreading and editing of this manuscript.

Dr. Charles Damien Lu:
Contribution: the English proofreading and editing of this manuscript.

Corresponding Author: Dr. Hua Jiang, Institute for Emergency and Disaster Medicine, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, 32# W. Sec 2, 1st Ring Rd, Chengdu, 610072, China. Tel: Email: jianghua@uestc.edu.cn; Jun Zeng, Sichuan Provincial Research Center for Emergency Medicine and Critical Illness, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, 32# W. Sec 2, 1st Ring Rd, Chengdu, 610072, China Tel: Email: zengjun@med.uestc.edu.cn

ABSTRACT

Background and Objectives: We aim to establish deep learning models to optimize the individualized energy delivery for septic patients. **Methods and Study Design:** We conducted a study of adult septic patients in ICU, collecting 47 indicators for 14 days. We filtered out nutrition-related features and divided the data into datasets according to the three metabolic phases proposed by ESPEN: acute early, acute late, and rehabilitation. We then established optimal energy target models for each phase using deep learning, and conducted external validation. **Results:** A total of 179 patients in training dataset and 98 patients in external validation dataset were included in this study, which total data size was 3115. The age, weight and BMI of the t patients were 63.05 (95%CI 60.42-65.68), 61.31(95%CI 59.62-63.00) and 22.70 (95%CI 22.21-23.19), respectively. And 26.0% (72) of the patients were female. The models indicated that the optimal energy targets in the three phases were 900kcal/d, 2300kcal/d, and 2000kcal/d, respectively. Excessive energy intake increased mortality rapidly in the early period of the acute phase. Insufficient energy in the late period of the acute phase significantly raised the mortality of septic patients. For the rehabilitation phase, too much or too little energy delivery were both associated with high mortality. **Conclusions:** Our study established time-series prediction models for septic patients to optimize energy delivery in the ICU. We recommended permissive underfeeding only in the early acute phase. Later, increased energy intake may improve survival and settle energy debts caused by underfeeding.

Key Words: sepsis, machine learning, deep learning, nutrition support, energy delivery

INTRODUCTION

Septic patients in intensive care unit (ICU) often suffer from malnutrition. As a result, nutrition support has become one of the most essential therapies.[1-3] However, optimal energy targets for critically ill patients in the ICU remain controversial.[4-5] Energy expenditure (EE) was recommended to guide nutrition in critically ill patients, and the measurements included direct calorimetry, indirect calorimetry, and predictive formulas. Indirect calorimetry was the gold standard for measuring EE, but it was difficult to put into clinical practice due to its expensive equipment required and complicated operation.[6] Nowadays, clinical practitioners prefer to apply prediction formulas because of their simplicity and convenience. Moreover, ICU patients might have the greatest heterogeneity, thus nutrition and micronutrient therapy in critical illness should be individualized.[7] However, recent studies indicated that prediction

formulas are not able to meet individualized needs.[7-9] An applicable and easy-to-use tool that can help clinicians to predict the optimal energy target for septic patients is urgently needed.

Nowadays, machine learning (ML) technology is growing rapidly and widely used in the medical field. However, most MLmodels do not work well when implemented in clinical settings. From a data science perspective, the major obstacle is the “curse of dimensionality”, which is a phenomenon in vector problems where the amount of computation increases exponentially as the number of dimensions increases.[10] In the ICU setting, deciding the nutritional therapy protocol for a specific patient requires the consideration of many influencing factors represented by a range of clinical indicators (e.g., dozens of biochemical and blood test parameters, patients’ nutritional data, etc.). With the rapid development of data science, deep learning (DL) has shown as a powerful tool to take on such challenges since researchers have realized that applying DL may help to reduce the dimensions and thus overcome the curse of dimensionality.[11-12]

In 2011, the tight calorie control study (TICACOS) indicated that both overfeeding and underfeeding were associated with a higher risk of death in critically ill patients.[13] Recently, several researchers introduced the concept of identifying the "sweet spot" (the spot where nutrition may have a positive impact on outcomes) or “personalized target” for nutrition doses based on the severity of illness/nutrition risks.[14] In this study, we propose the hypothesis that for septic patients in different metabolic phases, there is an individual optimal energy target or sweet spot that can minimize the risk of death. Subsequently, we aim to establish DL models to determine such energy targets.

MATERIALS AND METHODS

Aim

We aim to establish DL models to optimize the individualized energy delivery for septic patients.

Inclusion and exclusion criteria

Our study enrolled hospital patients suffering from sepsis in an ICU of a single center between September 2018 and January 2023. The Inclusion criteria are as follows:

(1) Age ≥ 18 years (adult patients);

(2) Patients who meet the criteria of Sepsis 3.0 on admission;

(3) APACHE II score ≥ 10;

(4) Patients hospitalized for more than 3 days in ICU and received nutritional support during the stay

Exclusion criteria are as follows:

(1) Patients received extracorporeal membrane oxygenation (ECMO) or renal replacement therapy;

(2) Women who are pregnant or breastfeeding;

(3) Patients participating in other clinical trials.

Our study has been reviewed by the Medical Ethics Committee of Sichuan Provincial People's Hospital (No. 190 in 2019) and has been registered in the China Clinical Trial Registration Center (Clinical Registration No.: ChiCTR1900024746. Registered 26 July 2019. https://www.chictr.org.cn/index.html). This study is an observational study and will not interfere with the treatment plan of patients, the ethics committee waived informed consent.

Data collection and cleaning

The collected indicators included both static and dynamic indicators. The static indicators were cross-sectional data at the time of patient admission and were collected only once. Dynamic indicators were collected at 8:00 a.m. during the first 14 days of ICU hospitalization. The included variables were listed in Supplementary Table 1. Mean ± standard deviation was applied uniformly to express continuous data, and the median (inter-quartile) applied for categorical data. Moreover, we conducted a standard procedure of data cleaning, including data alignment, data complementation, and invalid data screening, to make sure that our datasets were of high quality. The details are shown in Supplementary Table 2.

Statistical analysis

The continuous data was analyzed with t-test if it fit the normal distribution, otherwise, the Wilcoxon test (rank sum test) was used. For categorical data, the chi-square test or Wilcoxon test (rank sum test) was used. The correlation analysis was applied to choose the features which exhibit strong correlations with the daily energy target of septic patients. According to the data distribution, we conducted the correlation analysis via the Spearman analysis, and defined strong correlations as when the p value was lower than 0.01. If there is a disagreement, we invited senior physicians (HJ, Wei Chen and LC) to discuss and make decisions. We conducted the statistical analysis using SPSS 26 (IBM, Chicago, USA).

Modeling

The metabolic pathophysiological status after sepsis can be divided into three phases, the data-set is divided to three sub-datasets consequently (Supplementary Figure 1).[5]

The line graph showed that trends in mortality with increasing daily energy target which was inputted in the models over early period of acute phase (red), late period of acute phase (orange), and rehabilitation phase (green). The dots showed the lowest point of this curve, which were mapped to the vertical and horizontal axes indicates the lowest mortality and the optimal energy target in the phases, respectively.

These three sub-datasets were called early period of acute phase, late period of acute phase and rehabilitation phase, and represented data from 1-2, 3-7, and 8-14-days during the entire data collection period. We adopted the Convolutional Neural Networks (CNN) method to build the prognostic models of these three phases, and predicted the optimal energy targets which caused the lowest mortality. The modeling datasets were separated into a training set and a testing set in a 7:3 ratio. A training set was applied to build the model, and the testing set was used for validation by running the models and predicting the optimal energy target of each phase (Supplementary Figure 2). In this study, Python 3.8 software was applied for prediction model building.

RESULTS

Data collection

A total of 208 retrospective samples from September 2018 to January 2020 were included in this study as the datasets used to establish the models. To ensure the accuracy of the interpolated data, samples with more than 30% missing data for the same variable were excluded, and a total of 179 patients in the emergency intensive care unit (EICU) with sepsis data were finally included in the study. Of these, 78 patients died, and 101 patients survived at least 14-day after admission to the ICU. After establishing the models successfully, we further enrolled 98 patients who were admitted to the surgery intensive care unit (SICU) from September 2020 to January 2023 as the external validation datasets to predict the optimal energy target (Figure 3). The age, weight and BMI of involving patients were 63.05 (95%CI 60.42-65.68), 61.31 (95%CI 59.62-63.00) and 22.70 (95%CI 22.21-23.19) respectively. And 26.0% (72) of the patients were female.

Ethics approval and consent to participate

Our study has been reviewed by the Medical Ethics Committee of Sichuan Provincial People's Hospital (No. 190 in 2019) and has been registered in the China Clinical Trial Registration Center (Clinical Registration No.: ChiCTR1900024746. Registered 26 July 2019.). This study is an observational study and will not interfere with the treatment plan of patients, the ethics committee waived informed consent

Data preprocessing

The missing rates of data among all features during the 14 days after patients were admitted to the ICU were shown in Supplementary Table 3. Procalcitonin (PCT) was well over 30% and as high as 82.45% and was excluded which resulted in 34 features being enrolled in our study.

Energy intake

We compared the daily energy targets between the deceased and surviving patients. The results (Supplementary Figure 3 and Supplementary Table 4) showed that the patients of the survival group had higher daily energy targets than those in the deceased group. In addition, the result of cumulative energy debt showed that both groups were at high risks of malnutrition due to increased energy debt during the whole ICU stay (Figure 4).

However, the cumulative energy debt of the deceased group increased between the 7th and 14th days of ICU stay, while it decreased in the surviving group, although the difference was not significant (Supplementary Table 4).

Dimension reduction

As it is shown in Table 1, there were 12 features that are strongly related to the daily energy target. However, the leukocyte count (WBC) and neutrophil count (NEUT) have extremely stable and strongly correlate during the whole hospitalization of septic patients. We therefore chose the NEUT as the feature to be used for prediction (Supplementary Figure 4). In addition, body mass index (BMI) was still the main consideration in the development of nutritional programs, and the primary diagnosis of patients and the application of mechanical ventilation were both key influencing factors during the implementation of nutritional support therapy. Thus, we included them in the features. Finally, we enrolled a total of 15 features, including age, BMI, NRS2002, diagnosis number, mechanical ventilation therapy, temperature, diastolic blood pressure (DBP), mean arterial pressure (MAP), urine volume, fluid input, creatinine (Cr), aspartate aminotransferase (AST), NEUT, lactate (Lac) and

oxygen saturation (SaO2), to build the prognostic prediction models for the optimal energy target.

Models

Prognostic prediction models

By the application of CNN methods, we successfully established the prognostic prediction models for the early period of acute phase (data size: 358), late period of acute phase (data size: 889) and rehabilitation phase (data size: 837) of septic patient. In addition, we employed the under-sampling strategy to make sure that the training set was balanced while building the models.

The results validated our hypothesis and we identified the optimal energy target during each phase. The optimal energy target in early period of acute phase (data size: 196), late period of acute phase (data size: 461) and rehabilitation phase (data size: 374) of septic patients was 900kcal/d, 2300kcal/d and 2000kcal/d, which led to a minimum mortality rate of 16%, 28%, and 21%, respectively (Supplementary Figure 5).

The histogram graph compared the optimal daily energy target (left) and the lowest mortality (right) which was derived from models of early period of acute phase (red), late period of acute phase (orange), and rehabilitation phase (green).

As shown in Figure 3, mortality raised rapidly while the energy intake fell below the optimal energy target (2300kcal/d) in the late period of the acute phase. In contrast, excessive energy intake increased the mortality rapidly in the early period of acute phase. For the rehabilitation phase, energy targets that are too high or too low both caused high mortality.

DISCUSSION

Individualized nutritional support is one of the unresolved clinical issues. According to the updated guideline of critically ill patients by ESPEN, full nutrition supplement is not appropriate in early stage of the illness but should be gradually achieved within 3-7 days of ICU admission.[15] This study provided strong evidence for the above recommendation and found that excessive energy delivery in the early period and under-energy delivery in the late

period of the acute phase could lead to worsening prognosis for septic patients. For the rehabilitation phase, both caused high mortality.

Permissive underfeeding strategy of nutrition support was proposed and discussed for decades.[16] With the growing attention of nutrition support, researchers found that early full-feeding was associated with better clinical outcome of critically ill septic patients.[5] However, subsequent evidence showed that high-energy intake in the acute period is detrimental to the recovery of critically ill patients.[17-18] Previous studies indicated the benefit of using permissive underfeeding in the acute phase of sepsis.[19] In 2004, Jeejeebhoy KN et al. published a review and indicated that permissive underfeeding may optimize the energy delivery for septic patients.[20] In 2014, Anwar Elias Owais et al. conducted a randomized clinical trial and demonstrated that permissive underfeeding was associated with fewer septic complications (p = 0.003).[21] Then in 2021, Sun JK et al. conducted a randomized clinical study (RCT) including 54 septic patients and found that early moderate enteral underfeeding (60% of goal requirements) could improve the intestinal barrier function and reduced inflammatory responses.[22] Notably, Mette M. Berger et al. published a comment according to the 'French-Speaking ICU Nutritional Survey' (FRANS) study conducted in 26 ICUs over 3 months in 2015.[23] In the FFRANS study, full-feeding during the first two days in the ICU led to negative outcomes, and the overfeeding (exceeded the 40kcal/kg) may lead to apparent worse outcomes.[24] This comment emphasized the damage of "too much too early" energy intake in the acute phase of critically illnesses and suggested the feeding dose of 10-20kcal/kg during the first days in ICU. Our study provided objective evidence that permissive underfeeding may lead to a positive prognosis for septic patients in the first two days of ICU. However, the growing energy debt caused by permissive underfeeding raise the death risk of patients, which may outweigh the benefits. Tomoaki Yatabe published a review in 2019 and declared that negative energy balancing is beneficial to patients during unstable periods but may turn to be harmful while it accumulates.[25] Thus, the review suggested to increase the patient's energy supply at appropriate times to cover the energy debt. Our study provided direct evidence for the above problem. In the late period of the acute phase, appropriate overfeeding may increase the opportunity to survive and safely settle the energy debt caused by permissive underfeeding for septic patients.

In addition, we provided evidence that it is possible to create practical tools which can minimize nutrition-related mortality. As early as 40 years ago, it was discovered that energy expenditure in critically ill patients might be associated with the regular changes of metabolic phases.[26] In 2019, ESPEN published a guideline on clinical nutrition in the intensive care unit

and proposed the three phases of metabolism.[5] In fact, the trend of metabolic indicators varied among individuals, and the importance of them changed in different phases.[27] A study in 2021 showed that the importance of features was dynamic in septic patients.[28] WBC was one of the most important features for the prediction of patient deaths in the early course of sepsis. Then it gradually worked in predicting survival rate in the late course. Our study conducted further multivariate analysis for the time-series data using the partial least squares discriminant analysis (PLS-DA) methods and came to similar conclusions (Supplementary Figure 6). With the rapid growth of artificial intelligence (AI) technology, precision nutrition gained widespread attention.[29] Current reviews emphasized the necessity of personalized nutrition support for critically ill patients and provided several recommendations according to expert experiences.[30-33] However, it was difficult to develop a practical tool due to the lack of direct evidence about its feasibility. In our study, we validated the existence of sweet spots during different metabolic phases, and successfully predicted the optimal energy targets for septic patients, which demonstrated the possibility of developing personalized nutritional tools for critically ill patients.

Although we successfully established the individual prediction models to optimize the energy delivery for septic patients, this study still had limitations. The limitation of sample size made it difficult to apply in clinical practice immediately. In addition, the extrapolation of our results needs to be further verified because we conducted this study in a single center. PCT is a density of PCT in our ICU was too low to be included in the analysis, but it is widely accepted that it is an important indicator for infection. Moreover, several important variables, such as APACHE II or SOFA might differ dramatically between admission and discharge. These were collected only one time at admission in our study, this may make us miss some important information. We will take care that such indicators are dynamically assessed and collected in future studies. Finally, different pathways may influence the course of clinical outcomes, and its clinical implications are complex and variable, we will discuss this topic specifically in a follow-up study.

Conclusion

This study establishes time-series prediction models for septic patients admitted to ICU to optimize their energy delivery. It demonstrates the positive influence of permissive underfeeding strategy in the early period of the acute phase of sepsis while emphasizing the importance of settling the energy debt in the late period of the acute phase. When implemented in the ICU, this could serve as an invaluable aide for clinicians.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that they have no competing interests.

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Table 1. The correlation analysis results between daily energy target and other features

Feature	Coefficient	*p* value	Feature	Coefficient	*p* value
Age	-0.060**	<0.001	Urea	0.034*	0.023
Height	0.023	0.138	Cr	-0.134**	<0.001
Weight	-0.005	0.744	Glu	0.017	0.258
BMI	-0.021	0.165	Alb	0.031*	0.035
SOFA	0.016	0.297	AST	-0.057**	<0.001
NRS2002	-0.054**	0.002	ALT	0.01	0.508
Nutricscore	-0.013	0.431	TB	-0.007	0.634
APACHE II	0.012	0.418	WBC	-0.052**	0.001
Temperature	0.048**	0.002	NEUT	-0.060**	<0.001
HR	-0.026	0.081	PLT	0.022	0.135
RR	0.009	0.569	hs-CRP	-0.019	0.213
SBP	-0.011	0.443	Lactate	-0.051**	0.001
DBP	-0.044**	0.004	S_aO_2	0.061**	<0.001
MAP	-0.033*	0.026			
SI	-0.004	0.811			
Urine volume	0.102**	<0.001			
Fluid intake	0.217**	<0.001			
Fluid input	0.019	0.191			

Cr: creatinine; Glu: blood glucose; BMI: body mass index; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TB: total bilirubin; WBC: leukocyte count; NEUT: neutrophil count; HR: heart rate; PLT: platelet count; RR: respiratory rate; hs-CRP: hypersensitive C-reactive protein; SBP: systolic blood pressure; Lac: lactate; DBP: diastolic blood pressure; SaO2: oxygen saturation; MAP: mean arterial pressure; SI: shock index
*p ≤0.05; **p ≤0.001

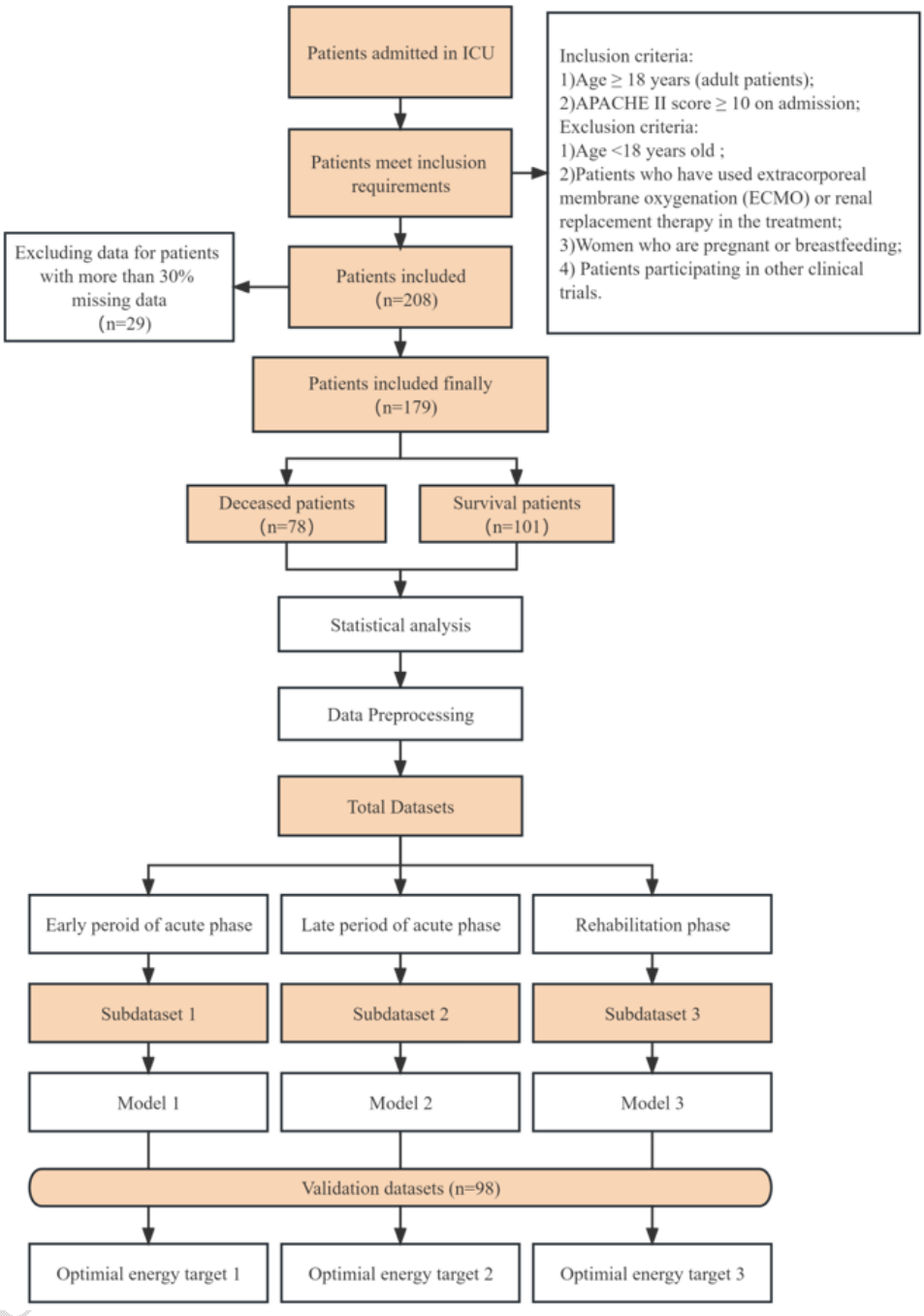


Figure 1. The flowchart of patient enrolment and data collation.

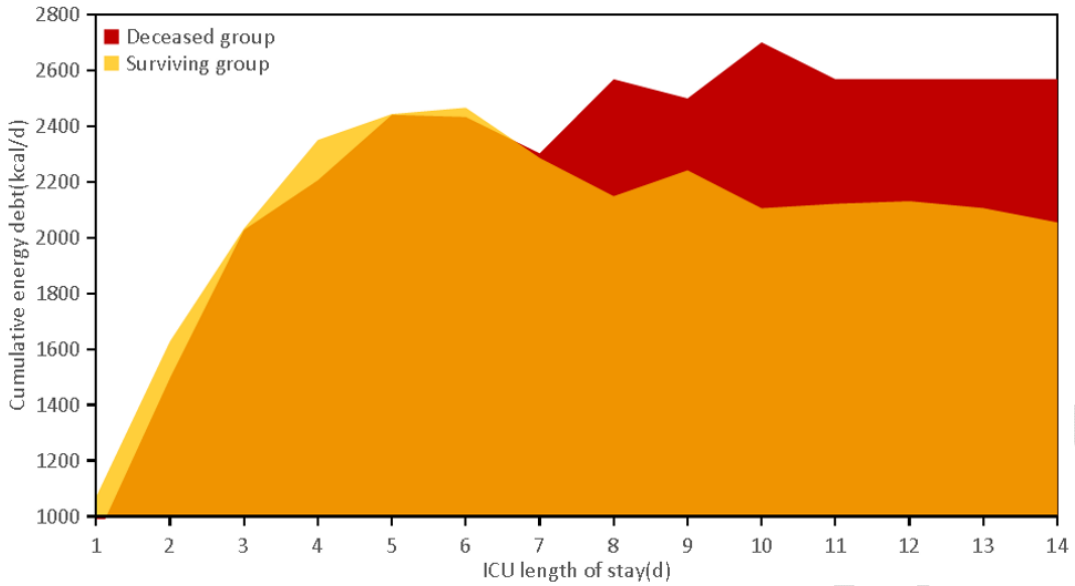


Figure 2. Trend of energy debt over time in deceased and surviving groups

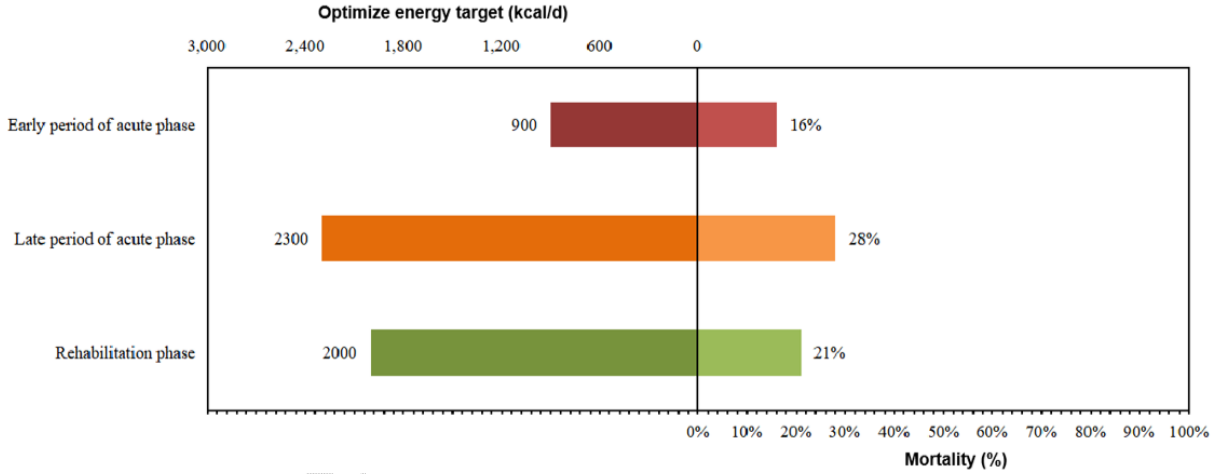


Figure 3. The trends in mortality with increasing daily energy target for septic patients during each phase

Supplementary Tables and Figures

Supplementary Table 1. The variables included in this study

1) Static variables	Including gender, age, primary diagnosis, mental state, mechanical Ventilation, height, weight, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APAHCEII), Sepsis-related Organ Failure Score (SOFA). All the static variables were collected only one time at admission or discharge by electronic medical record system.
2) Dynamic variables	Including physiological indicator variables, biochemical indicator variables and daily nutritional support plan. (a) Physiological indicator variables: temperature, heart rate(HR), respiratory rate (RR),systolic blood pressure (SBP), diastolic blood pressure(DBP), daily urine volume, daily fluid intake, daily fluid input. The variables created before 2019 were captured through the Electronic Medical Record (EMR), and those created after 2019 are captured through the DoCare critical care system. (b) Biochemical variables: white blood cell count (WBC), neutrophil count (NEUT), hypersensitive C-reactive protein (hs-CRP), platelet count (PLT) , aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine (Cr), glucose (Glu), albumin (ALB), total bilirubin (TB), direct bilirubin (DB), indirect bilirubin (IB), lactate (Lac), oxygen saturation (S_aO_2). In addition, blood gas analysis indicators, and inflammatory indicators such as procalcitonin (PCT) were all collected. The blood gas analysis results were collected manually, and the rest of the indicators were collected through the Electronic Medical Record (EMR). (c) Nutritional support indicator variables: include nutritional approach and total amount of glucose given by both parenteral and enteral approach. In addition, some composite indicators are calculated from the above variables with the following equations: BMI = [Weight (kg)/ Height $(m)^2$] (2) Mean arterial pressure (MAP) = [(SBP + DBP x 2)/3] (3) Shock index (SI) = [SBP/HR] (4) Energy (from parenteral or enteral approach)(kcal) = [Glucose (g) x 4 + Lipids (g) x 9] (5) Total Energy (kcal) = Energy from parenteral approach (kcal) + Energy from enteral approach (kcal) (6)
3) Outcomes	The all-cause mortality at 14th day since admission.

TWI: total water intake; TDF: total drinking fluids; WFF: water from food; EFI: exercise-related fluid intake; NEFI: non-exercise-related fluid intake.
Values were shown as medians (QR).
$^{*}p<0.05$ there were statistically significant differences between different PAEE or MET groups; $^{**}p<0.05$ there was statistically significant trend with the PAEE or MET level increase.
$^{\dagger}p<0.05$ compared with Gp1; $^{\ddagger}p<0.05$ compared with Gp2; $^{\S}p<0.05$ compared with Gm1; $^{\P}p<0.05$ compared with Gm2; $^{\dagger\dagger}p<0.05$ compared with Gm3.

Supplementary Table 2. The variables included in this study

1) Alignment	As mentioned, most of our variables were dynamic. Thus, datasets which following time series can greatly help us for discovering the important information of data. We aligned the dynamic data following the ICU-admitted days , and reorganize the data according to the time-series of each patient.
2) Data preprocessing	As a real world clinical study (RWS), it is difficult to avoid the data missing. However, a high percentage of missing data in any variable can significantly reduce the accuracy of the ML models. We defined the variable (or sample) as invalid data if it met anyone of the following conditions: 1)variables with more than 30% missing data on any given day; 2) samples with more than 30% missing data on any variable within the 14 days after admission in ICU; 3) duplicate data; 4) the data from patients who were not admitted to the ICU for the first time during this hospitalization. 5)Invalid data were defined as the data which exceeded the high or bottom clinical limit by three SDs. All invalid value should be deleted and not participate in any analysis that follows. For the remaining part of missing data, we adopted the mean imputation method for static variables and cubic spline interpolation method for dynamic variables to conduct the data complementation.
3) Data standardization	Different characteristics often have different units of magnitude. For healthcare data, they can vary greatly from one organization to the next and are collected for different purposes. Moreover, these data stored in different formats using different database systems, and the same concept may be represented in different ways from one setting to the next. Data standardization is the critical process of bringing data into a common format that allows for ML methods. In this study, the mean-variance normalization method will be used to standardize the continuous variables, meanwhile, One-Hot Encoding (OHC) is for attribute data which are not well handled by the classifier.

TWI: total water intake; TDF: total drinking fluids; WFF: water from food; EFI: exercise-related fluid intake; NEFI: non-exercise-related fluid intake.

Supplementary Table 3. Missing rates of data among all features

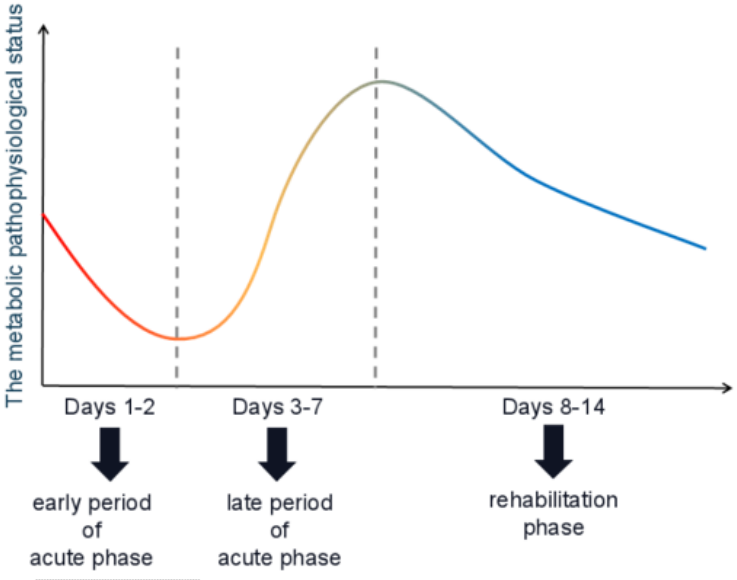
Feature	Missing rate (%)	Feature	Missing rate (%)
Temperature	0.06	Urea	0.87
HR	0.06	Cr	3.62
RR	0.06	Glu	3.19
SBP	0.06	Alb	3.75
DBP	0.87	AST	3.19
Daily urine volume	0.81	ALT	3.19
Daily fluid intake	0.81	TB	3.19
Daily fluid input	2.87	PCT	82.45
Height	8.94	WBC	3.59
Weight	24.58	NEUT	3.62
BMI	24.58	PLT	3.62
APACHE II score	4.47	Hs-CRP	3.62
S_aO_2	5.60	Lac	5.05

HR: XXX; Cr: xxxx; RR: xxxx; Glu: xxxx

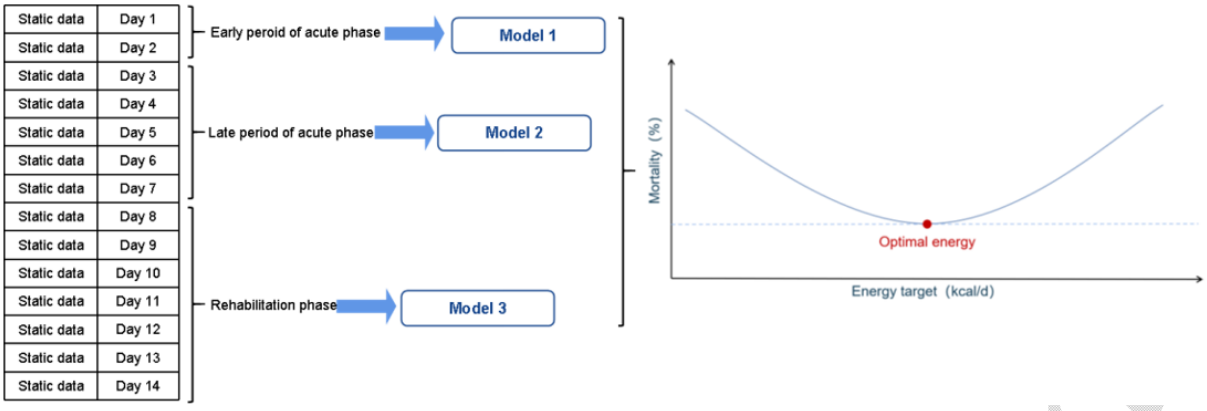
Supplementary Table 4. Comparison of daily energy target and between deceased and surviving patients

The length of ICU stay	Total	Deceased group		Surviving group		p value
		No.	Mean ± standard deviation	No.	Mean ± standard deviation	
D1	179	78	407.71±61.86	101	340.90±48.05	0.395
D2	179	78	725.10±52.73	101	844.95±76.08	0.224
D3	179	78	1005.83±48.1	101	1074.02±70.64	0.454
D4	179	78	1071.72±50.11	101	1243.63±70.02	0.047*
D5	179	78	1195.19±52.03	101	1356.84±69.97	0.065
D6	178	78	1249.88±68.06	100	1346.22±60.88	0.293
D7	173	75	1307.09±73.00	98	1425.32±64.46	0.227
D8	161	71	1254.24±61.53	90	1433.37±64.52	0.046*
D9	149	67	1282.45±71.89	82	1436.30±71.07	0.13
D10	131	60	1321.61±73.15	71	1557.67±71.31	0.022*
D11	122	56	1341.12±67.94	66	1446.64±82.99	0.327
D12	112	53	1397.19±76.81	59	1510.18±90.85	0.344
D13	90	40	1452.81±83.33	50	1595.79±80.09	0.219
D14	81	35	1383.59±96.54	46	1566.08±89.67	0.17

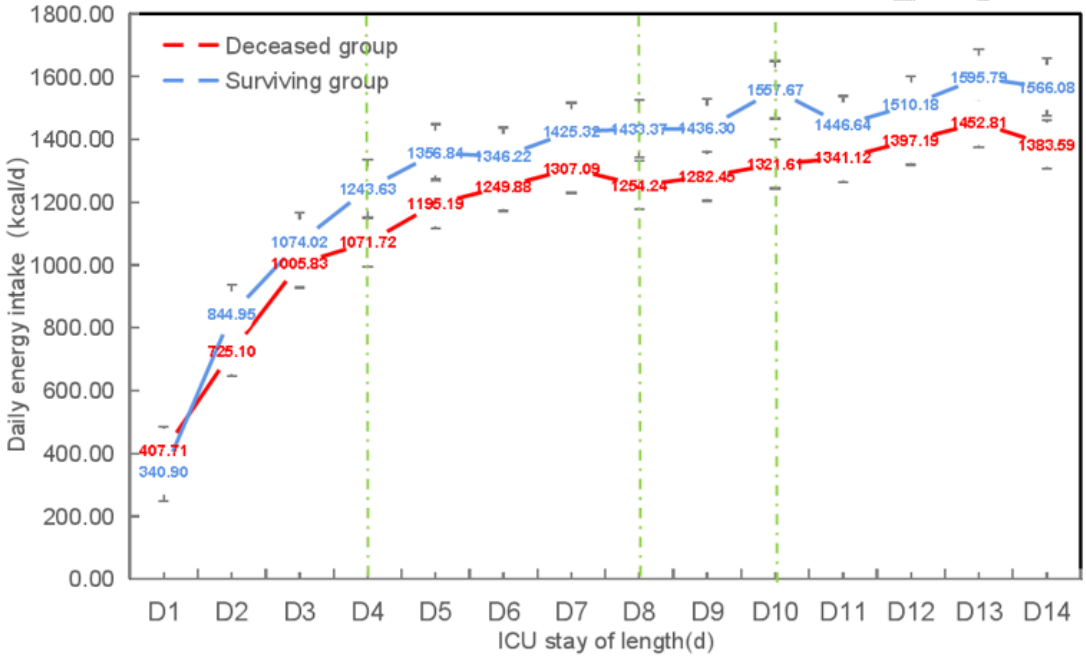
*p value ≤0.05



Supplementary Figure 1. The description of the early period of acute phase, late period of acute phase and rehabilitation phase



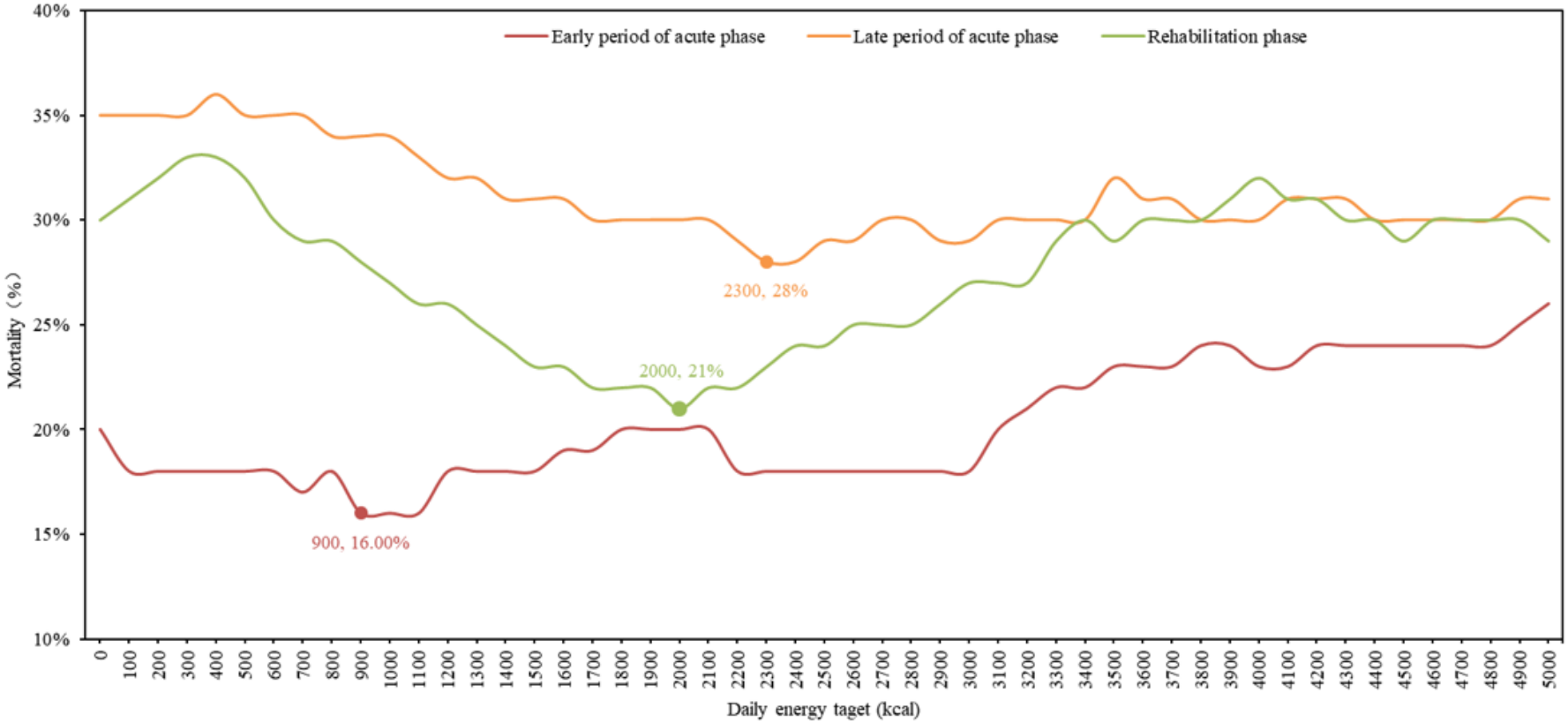
Supplementary Figure 2. The procedure to build the prediction model of the optimal energy target



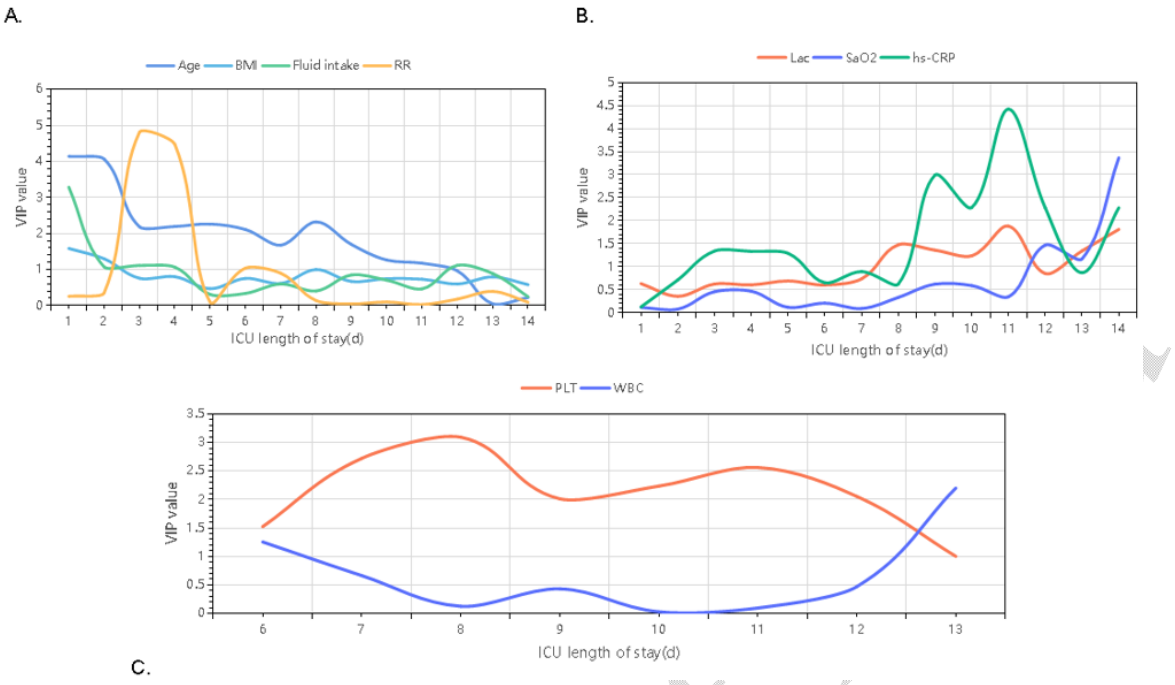
Supplementary Figure 3. Trends in daily energy intakes over time for deceased and surviving patients. The deceased and surviving patients were represented by blue and red curves, respectively. Green dashed line highlights significant difference ($P<0.05$) in energy intake between groups at corresponding days.

	Age	Height	Weight	BMI	APACHE II	SOFA	NRS2002	Nutricsoore	T°C	HR	RR	SBP	DBP	MAP	SI	Urine volume	Fluid intake	Fluid input	Urea	Cr	Glu	Alb	AST	ALT	TB	WBC	NEUT	PLT	hs-CRP	lactate	SaO2	Daily energy target
Age	1	-.352**	-.181**	-0.033	.176**	-.092**	.504**	.515**	-.070**	-.130**	-.052*	.073**	-.212**	-.108**	-.145**	-.236**	-.056*	-.176**	.397**	.369**	.253**	-.131**	-.112**	-.275**	-.207**	-.043*	-0.006	-.185**	-0.013	0.042	-0.026	-.087**
Height		1	.570**	0.031	-.156**	-0.038	-.227**	-.296**	0.013	.066**	.101**	.072**	.140**	.132**	0.011	.169**	.048*	.061**	-.093**	-.073**	-.107**	-0.019	0.031	.108**	.087**	-.062**	-.071**	.100**	.068**	-.101**	-.050*	0.033
Weight			1	.793**	-.060**	-0.035	-.190**	-.094**	.055*	0.019	.082**	.178**	.131**	.178**	-.093**	.129**	-.049*	.104**	0	.110**	0.042	-0.031	.073**	.117**	.122**	-.066**	-.085**	.099**	.055*	-.048*	-.132**	-0.007
BMI				1	.060**	-0.005	-.099**	.088**	.074**	-0.019	0.013	.162**	.070**	.129**	-.117**	.062**	-.079**	.077**	.069**	.202**	.112**	-0.017	.067**	.073**	.098**	-0.036	-.058**	.068**	0.033	-0.008	-.124**	-0.028
APACHE II					1	.351**	.413**	.514**	.139**	.078**	-.063**	0.004	-0.006	-0.004	.063**	.048*	0.003	0.017	.249**	.241**	.069**	-.057**	.047*	-0.007	-.072**	0.01	0.012	-.186**	.048*	.069**	.084**	0.017
SOFA						1	.233**	.415**	.064**	0.006	-.098**	0.007	-0.037	-0.025	0.002	0.041	-.065**	.108**	.199**	.131**	-0.029	-.059**	.069**	-0.018	.246**	0.022	0.01	-.259**	.077**	.119**	.095**	0.025
NRS2002							1	.414**	0.026	-.060**	-.053*	.058**	-.044*	-0.005	-.081**	-.121**	.092**	-.183**	.203**	.189**	0.041	-0.037	-0.02	-.117**	-.275**	-0.007	-0.009	-.083**	-.050*	-0.036	.134**	-.069**
Nutricsoore								1	-0.013	-.113**	-.120**	.129**	-.202**	-.068**	-.157**	-.089**	-.150**	.056**	.319**	.313**	.182**	-.107**	-.071**	-.217**	-.050*	-.093**	-.071**	-.255**	-0.008	.181**	0.023	-0.018
T°C									1	.283**	.097**	0.003	0.005	0.003	.216**	.125**	.060**	.104**	.094**	.105**	0.024	-.065**	.124**	.128**	.075**	.055*	.052*	-0.037	.188**	.081**	-.095**	.070**
HR										1	.286**	-.081**	.154**	.059**	.813**	-0.023	-0.017	.105**	.084**	.084**	-0.019	-.051*	.054*	.067**	.050*	.209**	.209**	0.008	.176**	.129**	-.106**	-0.039
RR											1	0.017	0.012	0.022	.210**	-.045*	.086**	-0.021	-0.025	-0.039	-.067**	-0.032	-0.006	.101**	-0.01	.049*	.048*	.114**	0.029	0.003	-.139**	0.011
SBP												1	.410**	.773**	-.608**	.088**	-0.04	0.023	.049*	.088**	.072**	0.035	-.059**	-.074**	-0.003	-.043*	-0.037	-0.006	-0.001	-0.008	-0.039	-0.017
DBP													1	.878**	-.109**	.055*	.140**	-.148**	-.153**	-.111**	-0.031	.109**	0.035	.097**	0.04	0.041	0.022	.160**	-.065**	-.111**	0.015	-.064**
MAP														1	-.377**	.083**	.071**	-.081**	-.080**	-0.032	0.021	.092**	-0.005	0.029	0.021	0.001	-0.01	.106**	-.049*	-.075**	-0.012	-.048*
SI															1	-.053*	0.015	.079**	0.042	0.007	-.062**	-.055*	.066**	.089**	.045*	.183**	.180**	0.007	.138**	.105**	-.055*	-0.005
Urine volume																1	.076**	.324**	-.053*	-.065**	0.022	-.061**	0.039	.076**	.092**	-.046*	-0.04	-.087**	.118**	0.038	0.007	.148**
Fluid intake																	1	-.487**	.069**	-.117**	-0.007	.127**	-0.025	.054*	-.202**	-.050*	-.073**	.158**	-.197**	-.207**	.109**	.311**
Fluid input																		1	-.063**	-0.003	0.002	-.194**	0.028	0.002	.292**	.087**	.094**	-.182**	.254**	.275**	-.092**	0.029
Urea																			1	.679**	.175**	-.061**	0.01	-.080**	-0.012	0.039	.053*	-.266**	.068**	.062**	-0.017	.051*
Cr																				1	.153**	-.069**	.046*	-.099**	-.104**	.074**	.075**	-.243**	.199**	.072**	-.077**	-.196**
Glu																					1	-0.036	-0.016	-.080**	-.064**	-0.033	-0.002	-.118**	.047*	.255**	-0.021	0.026
Alb																						1	0.005	0.021	0.002	0.012	-0.005	.224**	-.250**	-.143**	.107**	.046*
AST																							1	.661**	.261**	.098**	.098**	-.109**	0.023	.205**	-0.007	-.085**
ALT																								1	.177**	.095**	.088**	0.009	-.044*	.043*	-0.018	0.015
TB																									1	.084**	.079**	-.128**	.176**	.191**	-0.042	-0.011
WBC																										1	.976**	.275**	.098**	.063**	-0.034	-.077**
NEUT																											1	.241**	.120**	.083**	-0.041	-.090**
PLT																												1	-.089**	-.216**	0.032	0.034
hs-CRP																													1	.058**	-.147**	-0.026
lactate																														1	-.058**	-.075**
SaO2																															1	.088**
Daily energy target																																1

Supplementary Figure 3. The results of correlation analysis of dynamic data within 14 days of sepsis patients' hospitalization. *p value <0.05; **p value <0.01



Supplementary Figure 4. The comparison of the optimal daily energy target and mortality of each phase



Supplementary Figure 5. The VIP values over time of the basic characteristics whose value > 1. A. The characteristics of a decreasing trend of VIP value over time; B. The characteristics of an increasing trend of VIP value over time; C. Trend of change in VIP values of WBC and platelet count from 5 to 14 days after ICU admission