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The early prognostic value of the 1–4-day BCM/PA trend after admission in neurocritical patients

Jingjing Peng[1,5], Yanling Xiang[2,5], Guangwei Liu[3], Shuya Ling[4] & Feng Li[3]✉

The purpose of this study was to investigate early stage dynamic changes in relevant indicators in neurocritical patients to identify biomarkers that can predict a poor prognosis at an early stage (1–4 days after admission). This study retrospectively collected clinical data, inflammatory indicators, and nutritional indicators from 77 patients at the neurology intensive care unit. The 3-month modified Rankin scale score was used as the outcome indicator. A linear mixed model was used to analyze changes in inflammatory indicators and nutritional indicators in neurocritical patients over time from 1–4 days after admission. Logistic regression was used to determine the independent risk factors for a poor prognosis in neurocritical patients and to construct a predictive model. The predictive efficacy of the model was verified using leave-one-out cross-validation and decision curve analysis methods. The analysis results showed that 1–4 days after admission, the inflammatory indicators of white blood cell and absolute monocyte counts and the nutritional indicators of body cell mass(BCM), fat-free mass, body cell mass/phase angle (BCM/PA), intracellular water, extracellular water, and skeletal muscle index increased overall, while the nutritional indicators of albumin and visceral fat area decreased overall. The logistic multivariate regression model showed that the Charlson comorbidity index (CCI) (odds ratio (OR) = 2.526, 95% CI [1.202, 5.308]), hemoglobin (Hb)(on admission)-Hb(min) (OR = 1.049, 95% CI [1.015, 1.083), BCM(on admission) (OR = 0.794, 95% CI [0.662, 0.952]), and the change in BCM/PA 1–4 days after admission (OR = 1.157, 95% CI [1.070, 1.252]) were independent risk factors for a poor prognosis in neurocritical patients. The predictive analysis showed that the predictive power of Model 1 with BCM/PA (area under the curve (AUC) = 0.95, 95% CI (0.90, 0.99)) was 93%, 65%, 141%, and 133% higher than that of Model 2 without BCM/PA, the CCI, the APACHE II score, and the NRS2002 score (all $P < 0.05$), respectively. The CCI, Hb(on admission)-Hb(min), BCM(on admission), and an increase in BCM/PA 1–4 days after admission were independently associated with a poor prognosis in neurocritical patients. Of these variables, BCM/PA may be a valid indicator for early stage prediction of a poor prognosis in neurocritical patients.

Keywords Biomarkers, Bioelectrical impedance, Systemic inflammatory response syndrome, Modified Rankin Scale, Neurocritical patient

Abbreviations

Alb	Albumin;
ALC	Absolute lymphocyte count;
AMC	Absolute monocyte count
ANC	Absolute neutrophil count
APACHE II	Acute Physiology and Chronic Health Evaluation II;

[1]Department of Neurosurgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China. [2]Department of Operation Anaesthesia, University-Town Hospital of Chongqing Medical University, Chongqing, People's Republic of China. [3]Department of Neurology, The First Affiliated Hospital, Chongqing Medical University, Chongqing, People's Republic of China. [4]Department of Internal Medicine-Cardiovascular Department, The First Branch of the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China. [5]These authors contributed equally: Jingjing Peng and Yanling Xiang. ✉email: 204267@hospital.cqmu.edu.cn

AUC	Area under the receiver operator characteristic curve
BCM	Body cell mass;
BIA	Bioimpedance analysis;
BMI	Body mass index;
CCI	Charlson Comorbidity Index;
CI	Confidence interval;
CNS	Central nervous system;
DCA	Decision curve analysis
ECW	Extracellular water;
FFM	Fat-free mass;
Glu	Blood glucose
Hb	Hemoglobin
hsCRP	High-sensitivity C-reactive protein
ICW	Intracellular water
IDI	Integrated discrimination improvement index
NICU	Neurology intensive care unit;
NLR	Neutrophil-to-lymphocyte ratio
NRI	Net reclassification improvement
NRS2002	Nutrition Risk Screening 2002
mRS	Modified Rankin scale
OR	Odds ratios;
PA	Phase angle;
PEM	Protein-energy malnutrition
PLR	Platelet-to-lymphocyte ratio
PLT	Platelet count
ROC	Receiver operator characteristic
SIRS	Systemic inflammatory response syndrome
SMI	Skeletal muscle index
TBW	Total body water.
WBC	White blood cell
VFA	Visceral fat area

In recent years, the mortality and disability rates of neurocritical patients have increased yearly, which has resulted in substantial medical and social burdens[1]. A large number of studies have found that a persistent severe inflammatory response can lead to aggravation of the primary disease. It is an important cause of poor prognosis and even death in neurocritical patients[2–6]. Brain-body crosstalk is an important component of the pathophysiological process of systemic inflammatory response syndrome (SIRS) in neurocritical patients[7,8]. In related studies of patients with acute cerebral hemorrhage and status epilepticus, mortality and disability rates were higher in the patients with SIRS than in the non-SIRS group[8,9]. In a study of stroke patients, Vahidy[10] found that after stroke, the spleen was activated and contracted, releasing a large number of immune cells into the bloodstream that migrate to the brain and infiltrate the brain parenchyma through the damaged blood–brain barrier. The number of immune cells in the brain reaches its peak within 1–4 days after stroke and further promotes the release of inflammatory factors in brain glial cells, causing an inflammatory cascade reaction that induces a large amount of neuronal cell necrosis, which affects the patient's prognosis. Therefore, the severity of SIRS in neurocritical patients in the early stage (1–4 days after admission) may be the key to determining their prognosis, possibly related to neuronal cell necrosis due to inflammation. The pathogenesis is abnormal accumulation of misfolded/unfolded proteins within the endoplasmic reticulum of nerve cells[11]. Normally, DNA information transmission translates into polypeptide chains[12–14], which are folded into functional proteins within the cellular endoplasmic reticulum, and protein folding is important for maintaining the balance of cellular homeostasis[15–17]. At the onset of neurocritical illness, abnormal accumulation of misfolded/unfolded proteins provokes endoplasmic reticulum stress in neuronal cells, which induces a cascade of cell death and inflammatory processes when endoplasmic reticulum stress is persistent and intense. The inflammatory cascade in turn aggravates endoplasmic reticulum stress, creating a vicious cycle that triggers neuronal cell death and further leading to the occurrence of a poor prognosis[11].

Previous studies have suggested that the severity of SIRS is affected by nutritional status[18].The main manifestation of malnutrition in neurocritical patients is protein-energy malnutrition (PEM)[19]. By damaging the immune system's defense ability, PEM leads to a significant reduction in the body's resistance to infection[20]. Its pathophysiological mechanism manifests primarily as atrophy of thymus and lymph node immune tissues, impaired humoral and cellular immune functions, weakened leukocyte phagocytosis and reduced protein synthesis, which create favorable conditions for infection[21]. After infection, inflammatory cytokines act on the neuroendocrine system to stimulate the release of stress hormones (including cortisol and catecholamines) and increase catabolism, leading to further deterioration of immune system function in neurocritical patients, aggravating the degree of inflammatory response, accelerating death and leading to a poor prognosis[22].

Currently, the relevant indicators that can be used to predict adverse outcomes in neurocritical patients include neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, albumin, and hemoglobin. However, the specificity of these indicators is not high[23–26], and most studies are based on a one-time cutoff point and lack observations of dynamic change trends; thus, the predictive performance of these indicators is controversial, and they are not suitable as early stage and

effective prognostic indicators for neurocritical patients. In recent years, studies have confirmed that relevant indicators measured by bioelectrical impedance analysis (BIA), such as phase angle (PA), body cell mass(BCM), and hydration status, are associated with inflammatory responses and a poor prognosis in patients who are elderly, have cancer, are undergoing hemodialysis, or are critically ill[27–31]. They are expected to become novel indicators for predicting patient prognosis, but their predictive efficacy needs to be further verified.

Therefore, this study continuously and dynamically collected the clinical data (demographic characteristics + disease-related indicators), inflammatory indicators, and nutritional indicators (biochemical and BIA indicators) of 77 neurocritical patients who were admitted to the neurology intensive care unit (NICU) from January to July 2021 in the early stage (1–4 days after admission). A retrospective analysis of the changes in the data was conducted to identify objective occurrence and development patterns and to identify novel and sensitive early stage indicators for the objective prediction of poor prognosis in neurocritical patients.

Methods

Study design and participants

This was a case–control study. The subjects were patients who were admitted to the NICU of the First Affiliated Hospital of Chongqing Medical University from January 2021 to July 2021. Medical case data during hospitalization were collected. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. This study was registered with the China Clinical Trials Registry with registration number ChiCTR1800014324.

Inclusion criteria

(1) since the hospital is an adult hospital, the age of the included subjects was ≥ 18 years; (2) NICU admission ≥ 4 days; (3) patients or their guardians provided written informed consent; and (4) patients who can remain in a static supine position after sedation.

Exclusion criteria

(1) patients with moderate or severe disability and no self-care in life before admission; (2) patients with agitation, those who were unable to undergo BIA treatment due to the implantation of metal devices (such as pacemakers or artificial femoral heads), and those with incorrect BIA values; (3) patients whose conditions relapsed during hospitalization and those who required two or more transfers to the NICU; (4) patients with unstable hemodynamics; (5) patients who required surgical treatment; and (6) patients with incomplete data; (7) patients who received a red blood cell transfusion (Fig. 1).

Outcome indicator

The outcome indicator was the 3-month modified Rankin scale (mRS) score. According to the mRS score, the patients were divided into two groups: the poor prognosis group (mRS 3–6) and the good prognosis group (mRS 0–2).

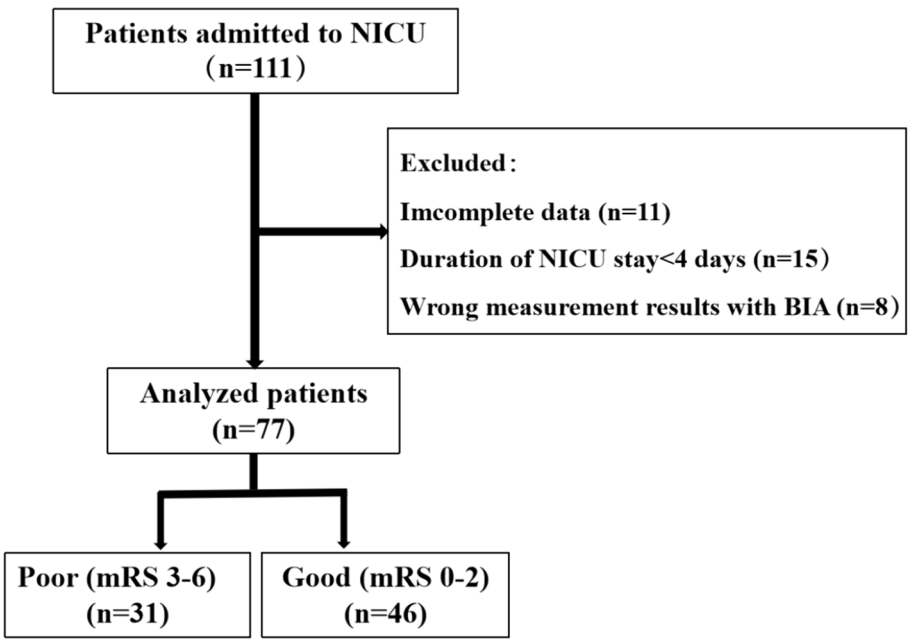

Fig. 1. Flowchart of patient recruitment.

Data collection

In this study, a retrospective data collection method was used to continuously and dynamically collect the clinical data, inflammatory indicators, and nutritional indicators (including biochemical and BIA indicators) of 77 NICU patients over 1–4 days of admission. All data were collected and compiled by two dedicated research assistants using the electronic medical record system and the BIA instrument recording system, and data entry was performed separately. After data entry was completed, the patient's name and medical record number were deleted, and the patient was given a unique study number. All data were reviewed by a dedicated study coordinator to confirm their accuracy and to manually verify inconsistent or outlier values. Prior to the statistical analysis, the dataset was validated and cleaned to prevent any further changes and ensure the consistency and completeness of the data in the statistical report and analysis. All researchers who collected and compiled the data were unaware of the contents of the study.

Clinical data:

Demographic characteristics. Sex, age, and body mass index (BMI).

Disease-related indicators. Acute Physiology and Chronic Health Evaluation (APACHE) II score, CCI, Nutrition Risk Screening 2002 (NRS 2002) results, disease diagnosis, and history of previous neurological diseases.

Inflammation-related indicators

White blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), platelet count (PLT), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and high-sensitivity C-reactive protein (hsCRP).

Nutrition-related indicators

Nutritional biochemical indicators. Albumin (Alb), Hb, and random blood glucose (Glu).

BIA indicators. BCM, PA, BCM/PA, intracellular water (ICW), extracellular water (ECW), total body water (TBW), fat-free mass (FFM), skeletal muscle index (SMI), whole-body protein (WBP), and visceral fat area (VFA).

Definition of relevant indicators

CCI[32]: The patient's medical history was obtained through the electronic medical record system, and CCI scores were calculated according to the patient's comorbidities. APACHE II score[33]: The assessment value within 24 h after admission was used. If there were multiple assessment values, the highest assessment value was selected. NRS2002 score[34]: The assessment value within the first day of admission was used.

All laboratory indicators were evaluated at the Department of Laboratory Medicine, the First Affiliated Hospital of Chongqing Medical University, and uploaded to the electronic medical record system. The patients' test values 1–4 days after admission were collected based on the time blood specimens being taken. In this context, Hb(on admission) is the value detected within 24 h after admission and Hb(min) is the minimum value of Hb detected within 1–4 days after admission. In this study, the normal reference ranges for the relevant laboratory indicators were WBC (3.50–9.50*10^9/L), ANC (1.80–6.30*10^9/L), ALC (1.10–3.20*10^9/L), AMC (0.10–0.60*10^9/L), PLT (85–303*10^9/L), hsCRP (0–10 mg/ml), Alb (35–50 g/L), Hb (130–175 g/L), and Glu (< 11.1 mmol/L). The BIA indicators were measured by physicians of the Department of Nutrition of the First Affiliated Hospital of Chongqing Medical University using BIA according to a uniform and standardized method on days 1–4 of admission, and the measurement values were collected. The BIA model was InBody S10 from Biospace Co., Ltd., South Korea[35]. In this study, the normal reference ranges for BIA indicators were PA (> 3 degrees), TBW (0.36–0.39%), TBW/FFM (72.7–74.3%), SMI (men > 7 kg/m^2; women > 5.5 kg/m^2), and VFA (< 100 cm^2).

The guidelines of the European Working Group on sarcopenia suggest that the BIA indicator skeletal muscle mass is closely related to height, and the composite index SMI, which is the combination of skeletal muscle and height, can accurately reflect the nutritional status of the human body[36]. Therefore, this study included the composite indicator SMI, which was calculated using the following formula: SMI = skeletal muscle mass/height^2. Furthermore, the BIA measurement BCM is the sum of the number of metabolically active and functionally intact somatic cells in human lean body mass. PA is the cotangent value of reactance (Xc) and impedance (Z) generated by a current flowing through the human body. Its formula is sin(PA) = Reactance(Xc)/Impedance(Z), which reflects the integrity of the cell membrane. Relevant studies have pointed out that a decrease in PA reflects poor structure and low function of the cell membrane as a result of a decrease in BCM, and there is a strong interaction between BCM and PA[37]. Therefore, this study innovatively combined BCM and PA detection into one BIA measurement as the second-level indicator BCM/PA and calculated the ratio to determine the prognostic value of this second-level indicator.

In recent years, a large amount of evidence has shown that there is a strong interaction among inflammatory cytokines and between inflammatory cytokines and platelets in the pathophysiological development of systemic inflammatory responses[38]. Therefore, this study included the analysis of relevant composite inflammatory indicators, including NLR and PLR. The NLR and PLR values were calculated using the same blood specimen. The calculation formulas are NLR = ANC/ALC and PLR = PLT/ALC.

Statistical description

Normally distributed measurement data are described as the mean ± standard deviation, and two independent sample t tests were used for comparisons between groups. Measurement data with a skewed distribution are described as the median and interquartile range, and the Mann–Whitney U test was used for comparisons between groups. Count data are described as the number of cases and rate, and comparisons between groups were performed using the chi-square test or Fisher's exact probability test. This study was reported based on the TRIPOD guidelines for prediction model development/validation[38]. A mixed linear model was used to calculate the slopes of the changes in inflammatory and nutritional indicators over time on days 1–4 of admission, and the slope for each patient was calculated using the random effects model. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate analysis, and the variables were screened using the stepwise method. Multivariate logistic regression was used to investigate the risk factors associated with the prognosis at discharge. The area under the receiver operator characteristic (ROC) curve (AUC), accuracy, sensitivity, specificity, integrated discrimination improvement index (IDI), net reclassification improvement (NRI), and decision curve analysis (DCA) were used to compare the value of different indicators or models for predicting the prognosis at discharge. AUCs were compared using the Delong test. The leave-one-out cross-validation method was used for internal validation. The Delong test, IDI, NRI, and DCA were performed in the nsROC, PredictABEL, nricens, and rmda packages in R (version 4.0.0), respectively, and the other analyses were performed in SAS 9.4 (Copyright ©2016 SAS Institute, Inc., Cary, NC, USA).

Results

Baseline data analysis

A total of 77 neurocritical patients were included in this study. The analysis of their baseline data is shown in Table 1. There were 31 patients with a poor prognosis according to the mRS (3–6), of whom 16 died; 46 patients had a good prognosis according to the mRS (0–2). The analysis results showed that indicators within the first day of admission (age, APACHE II score, CCI, NRS2002, hsCPR, BCM/PA ratio, TBW) and $Hb_{(on\ admission)}$-$Hb_{(min)}$ were higher in the poor prognosis group than in the good prognosis group, and the differences between the two groups were statistically significant (all P values < 0.05) (Table 1).

Within the first day of admission, the Hb, BCM, PA, ICW, FFM, SMI, and WBP of the poor prognosis group were all lower than those of the good prognosis group, and the differences between the two groups were statistically significant (all $P < 0.05$). Additionally, among the outcome indicators, the differences in mortality, mechanical ventilation time, length of NICU stay, and hospitalization expenses between the two groups were statistically significant (all P values < 0.05) (Table 1).

Analysis of the change trends in inflammatory and nutritional indicators 1–4 days after admission

The inflammatory and nutritional indicators of the 77 neurocritical patients were repeatedly measured (1–4 days after admission) and were treated as time-dependent variables. The analysis of the change trends in the indicators over time is shown in Table 2. Inflammation indicators (WBC, AMC) showed an overall upward trend over time from day 1 to day 4 after admission. The nutritional index albumin (Alb) decreased gradually with time; BIA indicators (BCM, BCM/PA, ICW, ECW, FFM, SMI) showed an overall upward trend over time from day 1 to day 4 after admission. However, the trend of BIA indicator (VFA) changes with time is gradually declining (Table 2).

The results of the differential analysis based on time-dependent variables showed that the BCM/PA of the poor prognosis group had a higher change trend 1–4 days after admission than the good prognosis group ($P < 0.05$) (Table 3).

Correlation analysis for poor prognosis in neurocritical patients

The above variables with $P < 0.05$, which included age, APACHE II, CCI, NRS2002, indicators within the first day of admission (hsCPR, Hb, BCM, PA, BCM/PA, ICW, TBW, FFM, SMI, WBP), $Hb_{(on\ admission)}$-$Hb_{(min)}$ and change in BCM/PA 1–4 days after admission (Table 1), were included in multivariate analysisin.

The results showed that CCI (odds ratio (OR) = 2.526, 95% confidence interval (CI) [1.202, 5.308]), $Hb_{(on\ admission)}$-$Hb_{(min)}$ (OR = 1.049, 95% CI [1.015, 1.083]) and change in BCM/PA 1–4 days after admission (OR = 1.157, 95% CI [1.070, 1.252]) were independent risk factors for poor prognosis in neurocritical patients. In contrast, higher $BCM_{(on\ admission)}$ (30.54 ± 5.1) was a protective factor (OR = 0.794, 95% CI [0.662, 0.952]) (Table 4).

Predictive analysis results

The variables that were significant in the multivariate analysis, including CCI, $Hb_{(on\ admission)}$-$Hb_{(min)}$, and $BCM_{(on\ admission)}$, and the change in BCM/PA 1–4 days after admission were used to establish Model 1 and Model 2, respectively. The change in BCM/PA 1–4 days after admission was included in Model 1 but not in Model 2. The remaining predictors were the same in both Model 1 and Model 2. The results of the predictive analysis showed that the AUC of Model 1 (AUC = 0.95, 95% CI (0.90, 0.99)) was higher than that of Model 2 (AUC = 0.85, 95% CI (0.76, 0.95)) ($P < 0.05$). The accuracy, sensitivity, and specificity of Model 1 were all higher than those of Model 2, the CCI, the APACHE II score, and the NRS2002 score. The NRI indicator of IDI in Model 1 was higher than that in Model 2, CCI, APACHE II and NRS2002. That is, compared with Model 2, the CCI, the APACHE II score, and the NRS2002 score, the proportion of correct patient classifications by Model 1 increased by 20%, 43%, 40%, and 37%, respectively, and its predictive ability increased by 93%, 65%, 141% and 133%, respectively (all $P < 0.05$) (Table 5).

According to the results of the decision curve analysis, the standard net benefit values of Model 1 were all higher than those of Model 2, the CCI, the APACHE II score, and the NRS2002 (Fig. 2).

Indicator	Group		χ2/t/Z	P value
	Good (mRS 0–2) (n = 46)	Poor (mRS 3–6) (n = 31)		
Clinical data				
Sex				
Male	33(71.74)	16(51.61)	3.242	0.072
Female	13(28.26)	15(48.39)		
Age, years	59.13 ± 16.23	71.45 ± 13.77	− 3.467	0.001
BMI, kg/m2	24.43 ± 4.14	23.38 ± 3.85	1.087	0.281
APACHE II	9.61 ± 4.96	15 ± 5.2	− 4.584	< 0.001
CCI	0.43 ± 0.75	1.48 ± 1.36	− 3.905	< 0.001
NRS2002	2.87 ± 2.01	5.13 ± 2	− 4.856	< 0.001
Diagnosis (classification)				
Cerebrovascular diseases	31(67.39)	21(67.74)	/	> 0.999
CNS infectious diseases	5(10.87)	3(9.68)		
Neuromyelitis optica	1(2.17)	1(3.23)		
Epilepsy	7(15.22)	4(12.90)		
Metabolic encephalopathy	1(2.17)	1(3.23)		
Degenerative diseases of the nervous system	1(2.17)	1(3.23)		
Previous history of neurological diseases				
No	41(89.13)	28(90.32)	/	> 0.999
Yes	5(10.87)	3(9.68)		
Inflammatory indicators within the first day of admission				
WBC, $*10^9$/L	9.63 ± 3.12	10.77 ± 4.72	− 1.181	0.244
ANC, $*10^9$/L	7.78 ± 3.12	8.56 ± 3.87	− 0.98	0.33
ALC, $*10^9$/L	1.22 ± 0.55	0.99 ± 0.51	1.806	0.075
AMC, $*10^9$/L	0.55 ± 0.23	0.61 ± 0.44	− 0.766	0.448
PLT, $*10^9$/L	208.96 ± 71.23	184.45 ± 60.1	1.574	0.12
NLR	8.62 ± 7.44	10.57 ± 6.77	− 1.171	0.245
PLR	196.58 ± 103.67	217.98 ± 106.03	− 0.876	0.384
hsCPR, mg/L	5.22(2.46,10.87)	14.91(6.21,20)	− 3.317	0.001
Nutritional biochemical indicators				
$Alb_{(on\ admission)}$, g/L	39.67 ± 5.02	37.32 ± 5.88	1.865	0.066
$Hb_{(on\ admission)}$, g/L	140.57 ± 16.48	127.29 ± 24.69	2.625	0.012
$Hb_{(on\ admission)}$-$Hb_{(min)}$, g/L	9.5(5,20)	35(6,59)	3.166	0.002
$Glu_{(on\ admission)}$, mmol/L	6.5(5.4,8.9)	7.9(6.5,8.7)	1.369	0.171
BIA indicators within the first day of admission				
BCM, kg	30.54 ± 5.1	27.1 ± 5.8	2.659	0.01
PA, degree	5.57 ± 0.86	4.06 ± 0.93	7.077	< 0.001
BCM/PA, kg/degree	5.53 ± 0.83	6.89 ± 1.64	− 4.04	< 0.001
ICW, L	21.33 ± 3.56	18.92 ± 4.06	2.663	0.01
ECW, L	13.27 ± 2.07	12.53 ± 2.41	1.396	0.167
TBW, %	0.38 ± 0.01	0.4 ± 0.01	− 6.733	< 0.001
FFM, kg	46.97 ± 7.57	42.57 ± 8.65	2.287	0.025
TBW/FFM, %	73.64 ± 0.38	73.79 ± 0.37	− 1.722	0.089
SMI, kg/m^2	9.55 ± 1.32	8.53 ± 1.62	2.929	0.005
WBP, kg	9.21 ± 1.54	8.18 ± 1.75	2.649	0.01
VFA, cm^2	93.9 ± 49.57	118.33 ± 63.64	− 1.834	0.071
Outcome indicators				
Mortality rate within 3 months				
Survival	46(100.00)	15(48.39)	29.969	< 0.001
Death	0(0.00)	16(51.61)		
Mechanical ventilation time, days	0(0,0)	6(0,13)	4.597	< 0.001
NICU hospital stay, days	4(2,10)	13(7,23)	4.551	< 0.001
Continued				

Indicator	Group		χ2/t/Z	P value
	Good (mRS 0–2) (n = 46)	Poor (mRS 3–6) (n = 31)		
Total hospital stay, days	15.5(13,25)	25(13,37)	1.763	0.078
Hospitalization expenses, thousand yuan	29.15(20.11,69.84)	112.97(56.2,192.59)	4.072	< 0.001

Table 1. Comparison of baseline data between the poor prognosis group and the good prognosis group. Cerebrovascular diseases which include ischemic stroke, intracerebral hemorrhage; CNS infectious diseases = Central nervous system infection diseases, CNS infectious diseases which include N-methyl-D-aspartate receptors, tuberculous meningitis, viral encephalitis, toxoplasma encephalitis, purulent meningitis; Degenerative diseases of the nervous system which include parkinson's disease, Alzheimer's disease.

Variable	Day 1	Day 2	Day 3	Day 4	Coefficient	Standard error	t value	*P* value
Inflammatory indicators								
WBC, $*10^9$/L	10.09 ± 3.85	10.98 ± 4.95	12.17 ± 5.47	11.50 ± 4.76	0.549	0.213	2.58	0.012
ANC, $*10^9$/L	8.09 ± 3.44	8.47 ± 3.67	9.68 ± 4.93	9.37 ± 4.48	0.397	0.203	1.96	0.055
ALC, $*10^9$/L	1.13 ± 0.54	1.20 ± 0.50	1.19 ± 0.54	1.18 ± 0.59	0.04	0.021	1.93	0.058
AMC, $*10^9$/L	0.57 ± 0.33	0.72 ± 0.27	0.87 ± 0.39	0.84 ± 0.42	0.099	0.018	5.41	< .0001
PLT, $*10^9$/L	199.09 ± 67.65	183.24 ± 60.97	193.54 ± 74.38	189.85 ± 70.01	− 1.516	2.322	− 0.65	0.516
NLR	9.40 ± 7.20	8.27 ± 4.67	10.30 ± 8.14	9.81 ± 5.99	0.061	0.363	0.17	0.868
PLR	205.31 ± 104.47	177.82 ± 89.17	193.06 ± 111.96	187.92 ± 89.47	− 7.504	4.572	− 1.64	0.105
Nutritional biochemical indicators								
Alb, g/L	38.71 ± 5.47	36.56 ± 5.51	36.25 ± 5.21	35.75 ± 5.64	− 0.984	0.227	− 4.34	< .0001
BIA indicators BCM, kg	29.22 ± 5.60	29.14 ± 5.76	29.53 ± 5.76	29.88 ± 5.49	0.119	0.059	2.02	0.047
PA, degree	4.99 ± 1.15	4.92 ± 1.28	8.18 ± 18.43	4.96 ± 1.30	0.159	0.511	0.31	0.757
BCM/PA, kg/degree	6.05 ± 1.37	6.19 ± 1.51	6.42 ± 2.17	6.31 ± 1.54	0.112	0.041	2.71	0.008
ICW, L	20.41 ± 3.91	20.35 ± 4.01	20.62 ± 4.03	20.88 ± 3.83	0.086	0.04	2.14	0.035
ECW, L	12.99 ± 2.22	13.02 ± 2.28	13.28 ± 2.22	13.35 ± 2.11	0.109	0.03	3.59	0.001
TBW, %	0.39 ± 0.01	0.39 ± 0.01	0.39 ± 0.01	0.46 ± 0.47	0.015	0.021	0.7	0.486
FFM, kg	45.28 ± 8.23	45.23 ± 8.41	45.90 ± 8.39	46.38 ± 7.95	0.244	0.095	2.58	0.012
SMI, kg/m^2	9.16 ± 1.52	9.15 ± 1.56	9.24 ± 1.52	9.41 ± 1.53	0.043	0.02	2.18	0.033
WBP, kg	8.82 ± 1.69	8.79 ± 1.75	8.91 ± 1.73	9.00 ± 1.67	0.032	0.019	1.71	0.091
VFA, cm^2	103.27 ± 56.25	102.13 ± 52.49	102.40 ± 51.29	95.80 ± 54.02	− 1.879	0.711	− 2.64	0.01

Table 2. Trend analysis of the change in indicators in neurocritical patients 1–4 days after admission.

Indicator	Group		t	*P* value
	Good (mRS 0–2) (n = 46)	Poor (mRS 3–6) (n = 31)		
Inflammatory indicators				
WBC slopes, $*10^9$/L/day	0.46 ± 0.79	0.68 ± 0.91	− 1.114	0.269
AMC slopes, $*10^9$/L/day	0.09 ± 0.07	0.11 ± 0.09	− 0.936	0.352
Nutritional biochemical indicators				
Alb slopes, g/L/day	− 0.88 ± 0.8	− 1.14 ± 1.07	1.24	0.219
BIA indicators				
BCM slopes, kg/day	0.1 ± 0.17	0.14 ± 0.32	− 0.616	0.541
BCM/PA slopes, kg/degree/day	0.04 ± 0.11	0.22 ± 0.21	− 4.448	< 0.001
ICW slopes, L/day	0.07 ± 0.11	0.11 ± 0.22	− 0.767	0.448
ECW slopes, L/day	0.09 ± 0.1	0.14 ± 0.2	− 1.195	0.239
FFM slopes, kg/day	0.2 ± 0.31	0.31 ± 0.57	− 0.939	0.353
SMI slopes, kg/m^2/day	0.04 ± 0.05	0.05 ± 0.1	− 0.829	0.412
VFA slopes, cm^2/day	− 1.62 ± 3.17	− 2.26 ± 3.81	0.793	0.43

Table 3. Differential analysis of the change trends in indicators between the two groups 1–4 days after admission.

Variable	β	Standard error	$\chi 2$	*P*	OR(95%CI)
CCI	0.926	0.379	5.978	0.014	2.526(1.202,5.308)
$Hb_{(on\ admission)}$-$Hb_{(min)}$, g/L	0.047	0.017	8.041	0.005	1.049(1.015,1.083)
$BCM_{(on\ admission),\ kg}$	− 0.231	0.093	6.179	0.013	0.794(0.662,0.952)
BCM/PA slopes, $*10^{-2}$, kg/degree/day	0.146	0.04	13.315	< 0.001	1.157(1.070,1.252)

Table 4. Results of the multivariate logistic regression model analysis for poor prognosis in neurocritical patients.

Predictors	AUC(95%CI)	P	Accuracy%	Sensitivity%	Specificity%	IDI(95%CI)	P	NRI(95%CI)	P
Model 1	0.95(0.90,0.99)		85.71	93.55	80.43				
Model 2	0.85(0.76,0.95)	0.024a	81.82	80.65	82.61	0.93(0.57,0.93)a	< 0.001a	0.20(0.09, 0.31)a	0.003a
CCI	0.74(0.63,0.95)	< 0.001a	70.13	70.97	69.57	0.65(0.39,0.65)a	< 0.001a	0.43(0.31,0.55)a	< 0.001a
APACHEII	0.77(0.66,0.88)	0.002a	71.43	80.65	65.22	1.41(1.14,1.41)a	< 0.001a	0.40(0.27,0.53)a	< 0.001a
NRS2002	0.79(0.68,0.89)	0.003a	72.73	80.65	67.39	1.33(1.01,1.33)a	< 0.001a	0.37(0.23,0.51)a	< 0.001a

Table 5. Comparison of the efficacy of different indicators for predicting the prognosis of neurocritical patients. Model 1 cannot be calculated at admission since the indicator (BCM/PA) is to be obtained upon continuous measurement within the first 4 days after admission. Model 1: Includes BCM/PA slopes, CCI, $Hb_{(on\ admission)}$-$Hb_{(min)}$, and $BCM_{(on\ admission)}$. Model 2: Includes CCI, $Hb_{(on\ admission)}$-$Hb_{(min)}$, and $BCM_{(on\ admission)}$. a: Compared with Model 1.

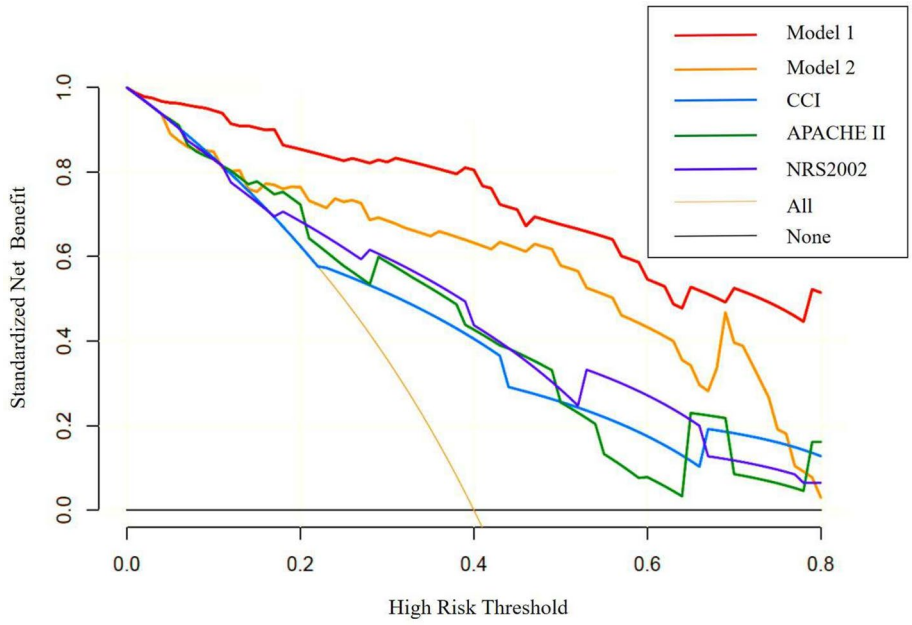

Fig. 2. Decision curves of different indicators for predicting the prognosis of discharged patients.

Discussion

This was a case–control study that included 77 neurocritical patients. The study retrospectively analyzed the patients' clinical data (demographic characteristics, disease-related indicators), inflammatory indicators, and nutritional indicators (nutritional biochemical indicators, BIA indicators). The results of the linear mixed model analysis showed that the inflammatory indicators (WBC and AMC) and BIA indicators (BCM, BCM/PA, ICW, ECW, FFM, and SMI) increased overall 1–4 days after admission, while the nutritional biochemical indicators (Alb) and BIA indicator (VFA) decreased overall. After adjusting for confounding factors using the logistic multivariate regression model, CCI, $Hb_{(on\ admission)}$-$Hb_{(min)}$, $BCM_{(on\ admission)}$, and the change in BCM/PA 1–4 days after admission were independently correlated with a poor prognosis in neurocritical patients.

The CCI is an assessment scale that reflects patient comorbidity and can be used to predict patients' mortality, disability rate, and risk of readmission[39]. Previous studies have shown that the CCI is independently associated

with functional deterioration within 1 year and increased 30-day mortality in stroke patients[32]. This study also found that the CCI was independently associated with a 3-month poor prognosis in neurocritical patients. Furthermore, Arata[26] et al. pointed out that decreased Hb during hospitalization is associated with a poor prognosis in neurocritical patients. Kellert[40] et al. also found that the occurrence of anemia within 5 days after stroke was associated with an increase in the mortality rate of patients in the short term. Additionally, a decrease in Hb greater than 15 g/L during hospitalization in patients with acute stroke is an independent risk factor for poor prognosis at discharge[26]. This study found that the greater the decrease in Hb during hospitalization was, the worse the prognosis of neurocritical patients was; the decreasing values of Hb during hospitalization among the neurocritical patients was 35(6, 59) g/L, which was independently associated with the 3-month poor prognosis. Infection or inflammation may stimulate neutrophils to release the iron-binding protein lactoferrin. Lactoferrin is internalized by bacteria, sequestering iron and leading to iron deficiency anemia manifested by decreased hemoglobin. An increase in the hemoglobin D-value reflects worsening anemia in neurocritical patients and will accelerate the course of the disease and affect patient outcomes[41].

BCM is an important indicator in the analysis of human body composition; it is defined as the total mass of metabolically active, viable, functional cells[42]. Increasing evidence shows that BCM is closely related to the inflammatory response in cancer patients, elderly patients, patients with chronic diseases, and hemodialysis patients, and it has an impact on patients' clinical outcomes[31,43–45]. Toshimi[46] et al. confirmed that low preoperative BCM (BCM ≤ 23 kg) was a risk factor for sepsis and death from infection after liver transplantation. This study also found that a low BCM (27.1 ± 5.8) kg at admission can affect the 3-month prognosis of neurocritical patients and can be used as an effective indicator for predicting poor prognosis and death.

At the same time, this study for the first time observed the relationship between the dynamic trend of BCM and other related indicators and the prognosis of neurocritical patients 1–4 days after admission. One to four days after admission is the peak period for the occurrence of SIRS in neurocritical patients, and the severity of the inflammatory response at this stage directly affects the patient's prognosis. A study of the prognosis of neurocritical patients found that 43% of patients with status epilepticus developed SIRS at admission, which was independently related to their drug resistance and 30-day mortality[9]. SIRS occurred in 64% of patients with spontaneous intracerebral hemorrhage and in 78% of patients with spontaneous subarachnoid hemorrhage within 3 days of admission and was closely associated with increased cerebral hemorrhage, exacerbation of vasospasm, and delayed cerebral ischemia[47–49]. Fifty-six percent of patients with ischemic stroke will develop SIRS within 4 days of admission[47]. Moreover, the greater the severity of SIRS is, the higher the 3-month disability rate and mortality rate[50]. Severe brain injury can induce SIRS, and the occurrence of SIRS further aggravates the severity of brain injury and adversely affects patient prognosis. We further analyzed the trend and found that a gradual increase in BCM was an important factor in the poor prognosis of neurocritical patients. This relationship may be related to the pathological process of tissue cell degeneration and necrosis caused by acute inflammation in the SIRS state. Tissue and cell necrosis caused by acute inflammation specifically manifests as necroptosis, that is, cell swelling, cell membrane rupture, and the release of cell contents[51–53]. Therefore, cell swelling is an early stage manifestation of tissue cell programmed necrosis caused by acute inflammation, and the main reason for cell swelling is the increase in ICW content[54]. However, BIA estimates BCM by measuring ICW using the formula BCW = WBP + ICW[55] . In this study, the WBP of neurocritical patients did not change significantly 1–4 days after admission, but both ICW and BCM gradually increased; that is, the more intracellular water there was, the more obvious the swelling was, which may reflect early stage changes in the acute inflammatory phase with reduced somatic cell function and programmed cell necrosis. However, in the multivariate analysis, we did not find that an increase in the BCM was independently associated with poor prognosis. The reason for this result may be related to inadequate consideration of the functional state of the cell membrane, i.e., its permeability[56].

To improve the efficacy for predicting a poor prognosis, this study innovatively combined BCM and PA into the secondary index BCM/PA. PA is the cotangent value of the reactance (Xc) generated by the current flowing through the human cell membrane and the impedance (Z) generated by the water flowing inside and outside the cells. It can reflect the functional status of the cell membrane. The lower the PA value is, the more severe the damage to the cell membrane structure and the worse the cell's functional status[57]. A number of previous studies have shown that a low PA value at a specific time point is an effective predictor of inflammatory status, adverse functional outcomes, and death in elderly, obese, cancer, and hemodialysis patients[27–29,58,59]. In this study, the PA of the patients in the poor prognosis group (4.06 ± 0.93) within the first day of admission was lower than that of the patients in the good prognosis group (5.57 ± 0.86), and the difference between the two groups was statistically significant ($P < 0.05$). Therefore, the gradual increase in BCM at low PA values may truly reflect the early stage changes in cell membrane damage, gradual swelling of cells, gradual deterioration of cell function, and programmed cell necrosis in the SIRS state. That is, the larger the BCM/PA value is, the more severe the degree of SIRS, and the worse the patient's prognosis. Further analysis of the prediction model showed that the model that included the secondary index BCM/PA had significantly higher predictive value than the prediction model that did not include BCM/PA. Moreover, compared with the traditional prognostic scoring scales (CCI, APACHE II, and NRS2002), the sensitivity (93.55%) and specificity (80.43%) of the prediction model that included the secondary index BCM/PA were both higher, suggesting that the model has high predictive ability for the prognosis of neurocritical patients. Therefore, BCM/PA plays an important role in improving the predictive value of the model and can be used as an effective early stage predictive indicator of poor prognosis in neurocritical patients.

Limitations

1. This study is a single-center retrospective case–control study with a relatively small sample size. A larger sample size and prospective studies are needed in the future to verify the findings of this study. 2. Since the severity of SIRS in neurocritical patients in the early stage (1–4 days after admission) is the key to determining

their prognosis, we focused on the correlation between the dynamic changes in relevant indicators during this time period and the 3-month prognosis of patients to identify effective indicators for the early stage prediction of patient prognosis. However, this study did not observe the impact of relevant indicators on the prognosis of neurocritical patients after 4 days of admission. Therefore, subsequent studies can explore the change in relevant indicators after 4 days of admission to more realistically depict the correlation between the pathological changes in SIRS and poor prognosis. 3. The prediction model that included BCM/PA was verified only internally, and the conclusion requires external verification. 4. BIA devices from different manufacturers are affected by age and geographical population, which may lead to differences in measurement results. Therefore, in clinical application, the use of BIA equipment that is appropriate for the research subjects should be carefully selected. The subjects in this study were all Asian individuals older than 18 years of age, which essentially ensured the homogeneity of the study samples and reduced the impact of measurement differences on the accuracy of human body composition indicators. 5. Indicators for the predictive model in this study can be directly measured by BIA tool. However, BCM/PA slope has to be calculated by using the statistical method in a specific program. In the future, collaborative efforts with BIA technology research team are needed to optimize software technology, so as to improve the accuracy and convenience of the predictive model in clinical application.

Conclusions

In summary, BCM/PA is a sensitive indicator of SIRS severity in the early stage and can effectively predict the 3-month prognosis of neurocritical patients. Its measurement is noninvasive and simple. Medical and nursing staff can complete the procedure and interpret the results within a few minutes after simple training. This method is promising and universally easy to use in the ICU, thus warranting further validation and promotion.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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References

1. Global, regional, and national burden of epilepsy, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18**(4), 357–375 (2019).
2. Sharma, R. *et al.* Infections after a traumatic brain injury: The complex interplay between the immune and neurological systems. *Brain Behav. Immun.* **79**, 63–74 (2019).
3. Learoyd, A. E. *et al.* Infections Up to 76 Days After Stroke Increase Disability and Death[J]. *Transl Stroke Res* **8**(6), 541–548 (2017).
4. Badjatia, N. *et al.* Inflammation, negative nitrogen balance, and outcome after aneurysmal subarachnoid hemorrhage. *Neurology* **84**(7), 680–687 (2015).
5. Heikinheimo, T. *et al.* Preceding and poststroke infections in young adults with first-ever ischemic stroke: Effect on short-term and long-term outcomes. *Stroke* **44**(12), 3331–3337 (2013).
6. Wastfelt, M., Cao, Y. & Strom, J. O. Predictors of post-stroke fever and infections: A systematic review and meta-analysis. *BMC Neurol.* **18**(1), 49 (2018).
7. Huang, Y. *et al.* Crosstalk between Inflammation and the BBB in Stroke. *Curr. Neuropharmacol.* **18**(12), 1227–1236 (2020).
8. Saand, A. R. *et al.* Systemic inflammation in hemorrhagic strokes-A novel neurological sign and therapeutic target?. *J. Cereb. Blood Flow Metab.* **39**(6), 959–988 (2019).
9. Szklener, S. *et al.* Systemic inflammatory response syndrome in the course of status epilepticus: 7-year, two-center observational study. *Epilepsy Res.* **137**, 53–55 (2017).
10. Vahidy, F. S. *et al.* Acute splenic responses in patients with ischemic stroke and intracerebral hemorrhage. *J. Cereb. Blood Flow Metab.* **36**(6), 1012–1021 (2016).
11. Shi, M. *et al.* Endoplasmic reticulum stress-associated neuronal death and innate immune response in neurological diseases. *Front. Immunol.* **12**, 794580 (2021).
12. Marjani, N. *et al.* Evaluation of the binding effect and cytotoxicity assay of 2-Ethyl-5-(4-methylphenyl) pyramido pyrazole ophthalazine trione on calf thymus DNA: Spectroscopic, calorimetric, and molecular dynamics approaches. *Luminescence* **37**(2), 310–322 (2022).
13. Zare-Feizabadi, N. *et al.* Determining the interaction behavior of calf thymus DNA with anastrozole in the presence of histone H1: Spectroscopies and cell viability of MCF-7 cell line investigations. *DNA Cell Biol.* **40**(8), 1039–1051 (2021).
14. Dareini, M. *et al.* A novel view of the separate and simultaneous binding effects of docetaxel and anastrozole with calf thymus DNA: Experimental and in silico approaches. *Spectrochim Acta A Mol. Biomol. Spectrosc.* **228**, 117528 (2020).
15. Chamani, J. *et al.* Cooperative alpha-helix formation of beta-lactoglobulin induced by sodium n-alkyl sulfates. *J. Colloid Interface Sci.* **293**(1), 52–60 (2006).
16. Sadeghzadeh, F. *et al.* Characterizing the binding of angiotensin converting enzyme I inhibitory peptide to human hemoglobin: Influence of electromagnetic fields. *Protein Pept. Lett.* **27**(10), 1007–1021 (2020).
17. Chamani, J. & Moosavi-Movahedi, A. A. Effect of n-alkyl trimethylammonium bromides on folding and stability of alkaline and acid-denatured cytochrome c: A spectroscopic approach. *J. Colloid Interface Sci.* **297**(2), 561–569 (2006).
18. Anrather, J. & Iadecola, C. Inflammation and stroke: An overview. *Neurotherapeutics* **13**(4), 661–670 (2016).
19. Smith, S. E. *et al.* Protein-energy malnutrition developing after global brain ischemia induces an atypical acute-phase response and hinders expression of GAP-43. *PLoS One* **9**(9), e107570 (2014).
20. Bresnahan, K. A. & Tanumihardjo, S. A. Undernutrition, the acute phase response to infection, and its effects on micronutrient status indicators. *Adv. Nutr.* **5**(6), 702–711 (2014).
21. Chandra, R. K. Protein-energy malnutrition and immunological responses. *J. Nutr.* **122**(3 Suppl), 597–600 (1992).
22. Zhang, J. *et al.* Organ- and cell-specific immune responses are associated with the outcomes of intracerebral hemorrhage. *FASEB J.* **32**(1), 220–229 (2018).
23. Zhu, W., Guo, Z. & Yu, S. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. *Neurology* **86**(11), 1077 (2016).
24. Guldolf, K. *et al.* Neutrophil-to-lymphocyte ratio predicts delirium after stroke. *Age Ageing* **50**(5), 1626–1632 (2021).

25. Soeters, P. B., Wolfe, R. R. & Shenkin, A. Hypoalbuminemia: Pathogenesis and clinical significance. *JPEN J. Parenter. Enteral Nutr.* **43**(2), 181–193 (2019).
26. Abe, A. *et al.* Decline in hemoglobin during hospitalization may be associated with poor outcome in acute stroke patients. *J. Stroke Cerebrovasc. Dis.* **27**(6), 1646–1652 (2018).
27. Matthews, L. *et al.* The use of bioelectrical impedance analysis to predict post-operative complications in adult patients having surgery for cancer: A systematic review. *Clin. Nutr.* **40**(5), 2914–2922 (2021).
28. Garlini, L. M. *et al.* Phase angle and mortality: A systematic review. *Eur. J. Clin. Nutr.* **73**(4), 495–508 (2019).
29. Tomeleri, C. M. *et al.* Phase angle is related with inflammatory and oxidative stress biomarkers in older women. *Exp. Gerontol.* **102**, 12–18 (2018).
30. Samoni, S. *et al.* Impact of hyperhydration on the mortality risk in critically ill patients admitted in intensive care units: Comparison between bioelectrical impedance vector analysis and cumulative fluid balance recording. *Crit. Care* **20**, 95 (2016).
31. Oliveira, T. *et al.* Low body cell mass index in hemodialysis patients: Association with clinical parameters and survival. *Hemodial Int.* **24**(2), 228–236 (2020).
32. Schmidt, M. *et al.* Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. *Neurology* **82**(4), 340–350 (2014).
33. Su, Y. Y. *et al.* Predicting hospital mortality using APACHE II scores in neurocritically ill patients: A prospective study. *J. Neurol.* **256**(9), 1427–1433 (2009).
34. Majari, K. *et al.* Comparison of modified NUTRIC, NRS-2002, and MUST scores in Iranian critically Ill patients admitted to intensive care units: A prospective cohort study. *JPEN J. Parenter. Enteral Nutr.* **45**(7), 1504–1513 (2021).
35. Kyle, U. G. *et al.* Bioelectrical impedance analysis–part I: Review of principles and methods. *Clin. Nutr.* **23**(5), 1226–1243 (2004).
36. Cruz-Jentoft, A. J. *et al.* Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **48**(1), 16–31 (2019).
37. Lukaski, H. C., Kyle, U. G. & Kondrup, J. Assessment of adult malnutrition and prognosis with bioelectrical impedance analysis: Phase angle and impedance ratio. *Curr. Opin. Clin. Nutr. Metab. Care* **20**(5), 330–339 (2017).
38. Collins, G. S. *et al.* Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. *BMJ* **350**, g7594 (2015).
39. Roffman, C. E., Buchanan, J. & Allison, G. T. Charlson comorbidities index. *J. Physiother.* **62**(3), 171 (2016).
40. Kellert, L. *et al.* The impact of low hemoglobin levels and transfusion on critical care patients with severe ischemic stroke: STroke: RelevAnt Impact of HemoGlobin, Hematocrit and Transfusion (STRAIGHT)–an observational study. *J. Crit. Care* **29**(2), 236–240 (2014).
41. Fraenkel, P. G. Anemia of inflammation: A review. *Med. Clin. North Am.* **101**(2), 285–296 (2017).
42. Moore, F. D. & Boyden, C. M. Body cell mass and limits of hydration of the fat-free body: Their relation to estimated skeletal weight. *Ann. N. Y. Acad. Sci.* **110**, 62–71 (1963).
43. McMillan, D. C. *et al.* Relationship between weight loss, reduction of body cell mass and inflammatory response in patients with cancer. *Br. J. Surg.* **81**(7), 1011–1014 (1994).
44. McMillan, D. C. *et al.* Albumin concentrations are primarily determined by the body cell mass and the systemic inflammatory response in cancer patients with weight loss. *Nutr. Cancer* **39**(2), 210–213 (2001).
45. Rondanelli, M. *et al.* Beyond Body Mass Index. Is the Body Cell Mass Index (BCMI) a useful prognostic factor to describe nutritional, inflammation and muscle mass status in hospitalized elderly?: Body Cell Mass Index links in elderly. *Clin. Nutr.* **37**(3), 934–939 (2018).
46. Kaido, T. *et al.* Pre- and perioperative factors affecting infection after living donor liver transplantation. *Nutrition* **28**(11–12), 1104–1108 (2012).
47. Kalita, J. *et al.* Systemic inflammatory response syndrome predicts severity of stroke and outcome. *J. Stroke Cerebrovasc. Dis.* **24**(7), 1640–1648 (2015).
48. Hagen, M. *et al.* Systemic inflammatory response syndrome and long-term outcome after intracerebral hemorrhage. *Neurol. Neuroimmunol. Neuroinflamm.* **6**(5), e588 (2019).
49. Rass, V. *et al.* Systemic inflammatory response syndrome as predictor of poor outcome in nontraumatic subarachnoid hemorrhage patients. *Crit. Care Med.* **46**(12), e1152–e1159 (2018).
50. Xu, X. *et al.* Systemic inflammatory response syndrome and outcomes in ischemic patients treated with endovascular treatment. *Clin. Interv. Aging* **15**, 2331–2340 (2020).
51. Heckmann, B. L., Tummers, B. & Green, D. R. Crashing the computer: Apoptosis vs. necroptosis in neuroinflammation. *Cell Death Differ.* **26**(1), 41–52 (2019).
52. Yuan, J., Amin, P. & Ofengeim, D. Necroptosis and RIPK1-mediated neuroinflammation in CNS diseases. *Nat. Rev. Neurosci.* **20**(1), 19–33 (2019).
53. Duprez, L. *et al.* RIP kinase-dependent necrosis drives lethal systemic inflammatory response syndrome. *Immunity* **35**(6), 908–918 (2011).
54. Lorenzo, I., Serra-Prat, M. & Yebenes, J. C. The role of water homeostasis in muscle function and frailty: A review. *Nutrients* **11**(8), 63 (2019).
55. Earthman, C. *et al.* Bioimpedance spectroscopy for clinical assessment of fluid distribution and body cell mass. *Nutr. Clin. Pract.* **22**(4), 389–405 (2007).
56. Lang, F. Mechanisms and significance of cell volume regulation. *J. Am. Coll. Nutr.* **26**(5 Suppl), 613S-623S (2007).
57. Norman, K. *et al.* Bioelectrical phase angle and impedance vector analysis–clinical relevance and applicability of impedance parameters. *Clin. Nutr.* **31**(6), 854–861 (2012).
58. Barrea, L. *et al.* Phase angle as an easy diagnostic tool of meta-inflammation for the nutritionist. *Nutrients* **13**(5), 31 (2021).
59. Wirth, R. *et al.* Bioelectric impedance phase angle is associated with hospital mortality of geriatric patients. *Arch. Gerontol. Geriatr.* **51**(3), 290–294 (2010).

Author contributions

F.L. J.P. and Y.X. contributed to the conception and study design. J.P. Y.X. G.L. and S.L. performed data acquisition; F.L. J.P. Y.X. G.L. and S.L. participated in the interpretation of data; J.P. and Y.X. performed statistical analysis and drafted the manuscript. F.L. and J.P. contributed to revisions of the manuscript. All authors read and approved the final manuscript, and all authors agreed to be accountable for all aspects of the work.

Competing interests

The authors declare no competing interests.

Consent for publication

All the coauthors have approved this version of the manuscript and consent to publication.All the coauthors confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

Ethical approval/Informed consent

This retrospective study was approved by the institutions ethics committee.

Additional information

Correspondence and requests for materials should be addressed to F.L.

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