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Original Article

Risk factors and a prediction model for sepsis: A multicenter retrospective study in China☆

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ABSTRACT

Background: Sepsis is typically associated with poor outcomes. There are various risk factors and predictive models for sepsis based on clinical indicators. However, these models are usually predictive of all critical patients. This study explored the risk factors for 28-day outcomes of patients with sepsis and developed a prognosis prediction model.

Methods: This was a multicenter retrospective analysis of sepsis patients hospitalized in three intensive care units (ICUs) from September 1st 2015, to June 30th 2020. Demographic, clinical history, and laboratory test data were extracted from patient records. Investigators explored the risk factors affecting 28-day sepsis prognosis by univariate analysis. The effects of confounding factors were excluded by multivariate logistic regression analysis, and new joint predictive factors were calculated. A model predicting 28-day sepsis prognosis was constructed through data processing analysis.

Results: A total of 545 patients with sepsis were included. The 28-day mortality rate was 32.3%. Risk factors including age, D-dimer, albumin, creatinine, and prothrombin time (PT) were predictive of death from sepsis. The goodness-of-fit value for this prediction model was 0.534, and the area under the receiver operating characteristic curve was 0.7207. Further analysis of the immune subgroups (n=140) revealed a significant decrease in CD3+, CD4+CD8-, and CD4+CD29+ memory effector T lymphocytes and an increase in CD56+ natural killer (NK) cells in the hypoalbuminemia group compared with the normal albumin group (65.5 *vs.* 58.3, P=0.005; 41.2 *vs.* 32.4, P=0.005; 21.8 *vs.* 17.1, P=0.029; 12.6 *vs.* 17.6, P=0.004).

Conclusions: Risk factors for 28-day sepsis mortality include age, D-dimer, creatinine, PT, and albumin. A decrease in albumin level may exacerbate immunosuppression in patients with sepsis. This study establishes a prediction model based on these indicators, which shows a good degree of calibration and differentiation. This model may provide good predictive value for clinical sepsis prognosis.

Introduction

Sepsis is a common disease in intensive care unit (ICU) and is associated with high morbidity and mortality rates. Approximately 30 million people worldwide are diagnosed with sepsis every year, with >5 million people dying from sepsis.[1] Sepsis survivors face long-term complications, such as underlying chronic disease progression and disability.[2] Therefore, early identification of sepsis patients at high risk for poor outcome is particularly important.

Various predictive models for sepsis prognosis have been reported; however, these models are usually predictive of all crit-

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ical patients. The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a validated predictor of hospital mortality for ICU patients; however, its calculation requires extensive clinical data, and it is not specifically designed for sepsis.[3] In addition, specific laboratory tests are used in predicting sepsis mortality. There is a model based on early plasma interleukin (IL)−8 and soluble tumor necrosis factor receptor (sTNFR)−1 measurements to predict the mortality rate of severe patients, but the model only includes patients who meet the systemic inflammatory response syndrome criteria, which are not routinely tested clinically.[4] Various biomarkers, such as IL-6, IL-10, CD28, mCD14, monocytic human leukocyte antigen receptor (mHLA-DR.), antithrombin, thermoregulatory protein, and lactic acid, are applicable to identifying sepsis severity or prognosis.[5,6]

Despite recent progress in the management of sepsis, the mortality rate has not decreased. Several prognostic models have been proposed, but some indexes are not available clinically. To address this problem, the authors constructed a predictive model with a series of common clinical indicators. In addition, by measuring patients' lymphocyte subset counts, this study found that the immune status of patients appears to correlate with their albumin levels.

Methods

Design and setting

This retrospective, multicenter, observational study was conducted from September 1st 2015, to June 30th 2020. A total of 568 adults with sepsis from three ICUs were included. All patients were followed for 28 days, and then were divided into death and survival groups. In subgroup analysis, investigators divided the patients into hypoproteinemia and normal albumin groups to explore the effect of albumin levels on immune status. This study was approved by the Ethics review board of the Shanghai General Hospital (approval no. 2020KY216).Due to its retrospective nature, informed consent was not required.

Inclusion and exclusion criteria

Sepsis 3.0 diagnostic criteria were used as inclusion criteria. Exclusion criteria were pregnancy and lactation, severe hepatic or renal insufficiency, history of disease with abnormal bone marrow hematopoiesis, currently undergoing chemoradiotherapy, and loss to follow-up.

Outcomes

The primary outcome was the 28-day mortality rate. The secondary outcome was the level of immunosuppression.

Definition

Hypoalbuminemia was defined as a serum albumin level <35 g/L.[7] Severe hepatic insufficiency was defined as Child–Pugh score >9. Severe renal insufficiency was defined as a creatinine level >550 μmol/L.

Data collection

Baseline data, including gender, age, and medical history, were collected. Laboratory data, including blood routine, liver and kidney function, albumin, coagulation function, heart function, C-reactive protein, procalcitonin (PCT), IL-6, and immune function indexes (such as cluster of differentiation[CD] series), were collected within 24 h after sepsis diagnosis. Sequential organ failure assessment (SOFA) and APACHE II scores were calculated on the first day in the ICU.

Statistical analysis

SPSS, version 19.0 software (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Mean ± standard deviation applied to the variables conformed to a normal distribution. An independent sample *t*-test was used for homogeneous variance. Non-conforming normal distribution was represented by median (25th and 75th percentiles [interquartile range]), and a non-parametric Mann–Whitney *U* test was adopted. The authors conducted univariate analysis and multivariate logistic regression analysis to determine the factors affecting the prognosis of sepsis. A *P*-value of <0.05 was considered statistically significant. Stata, version 12.0 software (Stata Corp., College Station, TX, USA) was used to establish the prediction model.

Results

Comparison of baseline data

A total of 568 sepsis patients were included in the study. However, 23 patients were excluded owing to severe hepatic or renal insufficiency, and loss to follow-up. Finally, 545 sepsis patients remained in this study [Figure 1]. Within 28 days, 176 deaths were recorded (mortality rate was 32.3%). In this study, 341 male and 204 female patients were assessed, and the median age was 68 years. The median SOFA and APACHE II scores were 6 and 17, respectively. A total of 347 patients had a chronic disease. No significant difference in gender (or complications) was observed between the death and survival groups [Table 1]. The SOFA and APACHE II scores were higher in the death group than in the survival group ($P < 0.001$).

Univariate analysis of 28-day mortality risk

The results of the univariate analysis showed that age, SOFA score, APACHE II score, prothrombin time (PT), troponin, b-type natriuretic peptide, creatinine, D-dimer, IL-6, platelets, albumin, and antithrombin III were associated with mortality rate [Table 2].

Multivariate logistic regression analysis of factors affecting sepsis prognosis

The investigators selected 12 variables to establish a multivariate logistic regression model. The enter method was used while conducting multivariate logistic regression analysis. After removing the effects of confounding variables, five variables (age, albumin, D-dimer, creatinine, and PT) were retained in the final logistic regression model [Table 3].

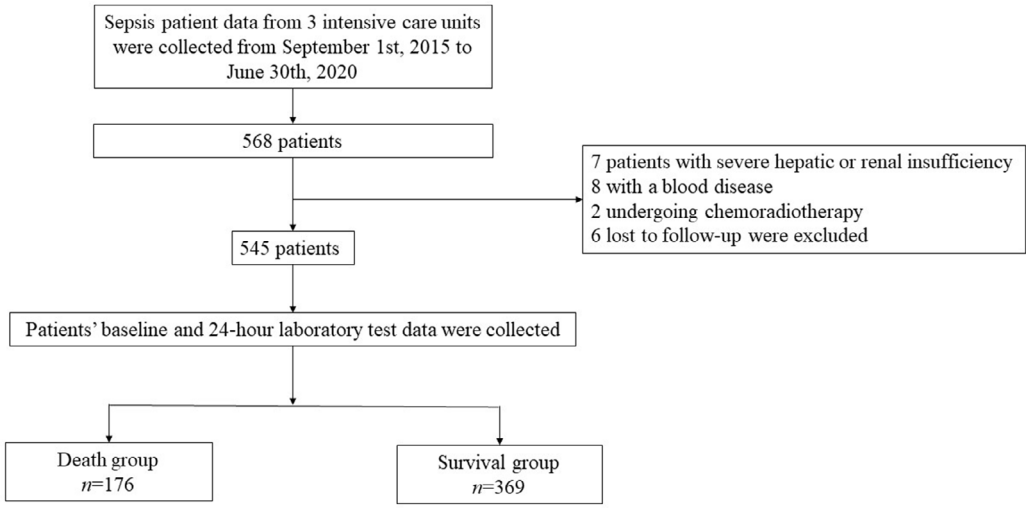

Figure 1. Research flowchart.

Table 1
Patients' demographics and clinical characteristics (n = 545).

Characteristics	Survival group (n = 369)	Death group (n = 176)	χ^2/Z	P-value
Female sex	139(37.7)	65(36.9)	0.005	0.943
Age(years)	66.0(55.5,74.0)	70.0(61.0,78.0)	−3.526	<0.001
Complications				
Hypertension	145(39.3)	76(43.2)	0.594	0.441
Diabetes	78(21.1)	26(14.8)	2.728	0.099
COPD	44(11.9)	33(18.8)	4.031	0.045
Cardiovascular diseases	48(13.0)	37(21.0)	5.222	0.022
SOFA	5(3,8)	9(6,13)	−10.049	<0.001
APACHE II	15.0(10.0,21.0)	23.5(17.3,30.0)	−10.509	<0.001
Infection Sites				
Respiratory Tract	149(40.4)	92(52.3)	6.360	0.012
Abdomen	125(33.9)	49(27.8)	1.729	0.189
Blood	56(15.2)	26(14.8)	0.000	0.997
Skin and Soft Tissue	11(3.0)	5(2.8)	0.033	0.857
Urinary Tract	25(6.8)	3(1.7)	5.289	0.022
Others	3(0.8)	1(0.6)	0.050	0.823

Data is presented as n(%) or mean(interquartile range).
APACHE: Acute Physiology And Chronic Health Evaluation; COPD: Chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment.

Table 2
Univariate analysis of 28-day mortality risk (n = 545).

Variables	Survival group (n = 369)	Death group (n = 176)	t/Z	P-value
WBC($\times 10^9$/L)	11.2(6.8,17.4)	12.4(7.0,18.8)	−0.831	0.406
Platelet($\times 10^9$/L)	137.0 (78.0,214.0)	104.0 (52.8,186.8)	−2.962	0.003
MPV(fL)	10.1(9.2,11.2)	10.3(9.3,11.4)	−0.799	0.424
PDW(%)	16.4(16.0,16.8)	16.4(15.8,16.9)	−0.915	0.360
Neutrophils($\times 10^9$/L)	10.0(5.8,15.4)	11.2(6.0,16.5)	−1.150	0.250
Lymphocytes ($\times 10^9$/L)	0.6(0.4,1.0)	0.6(0.3,1.0)	−0.590	0.555
Monocytes($\times 10^9$/L)	0.4(0.2,0.7)	0.4(0.2,0.7)	−0.689	0.491
Creatinine(μmol/L)	98.7(62.5,175.8)	147.2(81.7,260.9)	−3.766	<0.001
Albumin(g/L)	28.4 ± 5.8	26.5 ± 6.0	−3.679	<0.001
D-dimer (mg/L)	4.6(2.3,9.5)	7.3(3.9,13.1)	−4.347	<0.001
PCT (ng/mL)	4.1(0.8,38.6)	5.3(1.1,29.8)	−0.690	0.490
CRP (mg/L)	156.6(74.7,231.0)	158.5(76.1,242.2)	−0.481	0.631
IL-6 (pg/mL)	66.2(24.4,259.3)	244.1(68.0,1245.0)	−6.178	<0.001
PT(s)	13.9(12.7,15.9)	15.8(14.0,19.0)	−6.438	<0.001
AT-III (%)	67.5 ± 21.0	61.1 ± 27.2	−2.860	0.004
TNI(ng/mL)	0.1 (0.0,0.2)	0.2(0.1,0.8)	−6.239	<0.001
BNP (pg/mL)	287.0(93.5,1147.6)	528.0(232.8,1530.0)	−3.613	<0.001

Data is presented as mean(interquartile range) and mean±standard deviation.
AT-III: Antithrombin III; BNP: b-type natriuretic peptide; CRP: C reactive protein; IL-6: Interleukin-6; MPV: Mean platelet volume; PCT: Procalcitonin; PDW: Platelet distribution width; PT: Prothrombin time; TNI: Troponin. WBC: White blood cell.

Table 3
Multivariate logistic regression analysis of 28-day mortality risk in sepsis.

Variables	OR	95% *CI*	*P*-value
Age	1.002	1.008–1.036	0.002
Albumin	0.966	0.934–0.999	0.046
Creatinine	1.002	1.000–1.003	0.026
D-dimer	1.018	1.004–1.034	0.015
PT	1.054	1.007–1.104	0.024

CI: Confidence interval; OR: Odd ratio; PT: Prothrombin time.

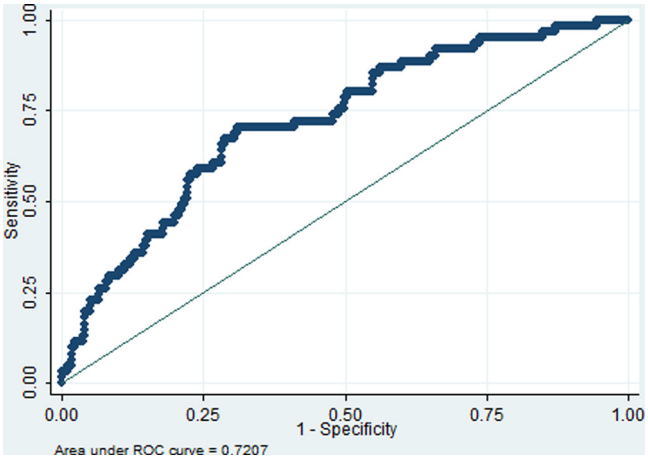

Figure 2. ROC analysis of the sepsis prognosis prediction model. ROC: Receiver operating characteristic.

Establishment of a prediction model

Based on the multivariate logistic regression analysis, the authors used Stata, version 12.0 software to establish the following prediction model: $\ln[P/(1-P)] = 0.016age - 0.024Alb + 0.01dimer + 0.002Scr + 0.055PT$. The goodness of fit for the model was 0.534, and the area under the receiver operating characteristic curve was 0.7207 [Figure 2]. Therefore, the model showed a good degree of calibration and differentiation. In order for the model to be more intuitive and understandable, a nomogram was configured [Figure 3].

A low albumin level is associated with decreased immune function in sepsis patients

Albumin is an important clinical index and is associated with major surgery prognosis. In this study, the investigators intended to explore the association between albumin and immune function in sepsis patients. Surprisingly, the study found that a low albumin level was associated with decreased immune function. When the albumin level was <35 g/L, immune function was markedly suppressed. In this study, 140 sepsis patients were randomly selected and included in an analysis of immune indexes. These 140 patients were divided into the hypoalbuminemia group (albumin level <35 g/L) and normal albumin group. Surprisingly, $CD3^+$ mature, $CD4^+CD8^-$, and $CD4^+CD29^+$ memory effector T lymphocytes were significantly decreased in the hypoalbuminemia group compared with the normal albumin group (65.5 *vs.* 58.3, P=0.005; 41.2 *vs.* 32.4, P=0.005; 21.8 *vs.* 17.1, P=0.029). Additionally, the quantity of $CD56^+$ natural killer (NK) cells was significantly increased in the hypoalbuminemia group compared with the normal albumin group (12.6 *vs.* 17.6, P=0.004) [Figure 4].

Discussion

Sepsis is a life-threatening organ dysfunction syndrome caused by a dysregulated host immune response to infection[8] and characterized by high morbidity and mortality rates. Sepsis is now a major challenge for the World Health Organization. Combing global epidemiological sepsis data showed that the in-hospital mortality rate of patients with severe sepsis was 26%.[1] In this study, the 28-day mortality rate of septic patients was 32.3%, which is higher than that reported in the relevant literature.[9] The reason underlying this finding may be that the patients in this study were older, with comorbidities and severe cases. Among the included patients, 70.1% were aged >60 years, and 65.3% of patients with ≥1 comorbidity. Furthermore, 24.2% of patients' SOFA scores were >10.

This study found that a model based on age, D-dimer, creatinine, PT, and albumin has predictive value for sepsis prognosis. It also found an association between hypoalbuminemia

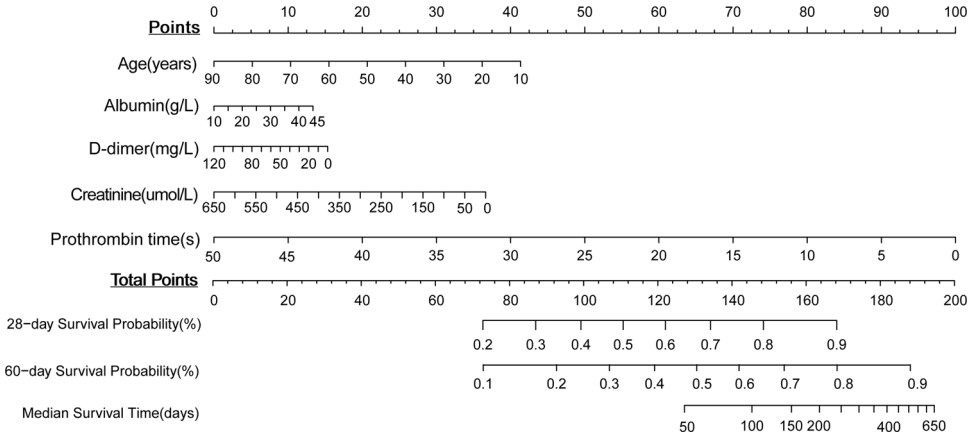

Figure 3. Nomogram based on multivariate logistic regression analysis. Based on the multivariate logistic regression analysis, five variables (including age, albumin, D-dimer, creatinine, and PT) were included in the nomogram. The five variables correspond to five lines, and the length reflects the contribution to the outcome event. An upward vertical line can be drawn from each axis to obtain the points for each variable. The sum of each variable point was calculated, and then a downward vertical line was drawn from the total points axis to obtain the 28-day and 60-day survival probabilities and median survival time. PT: Prothrombin time.

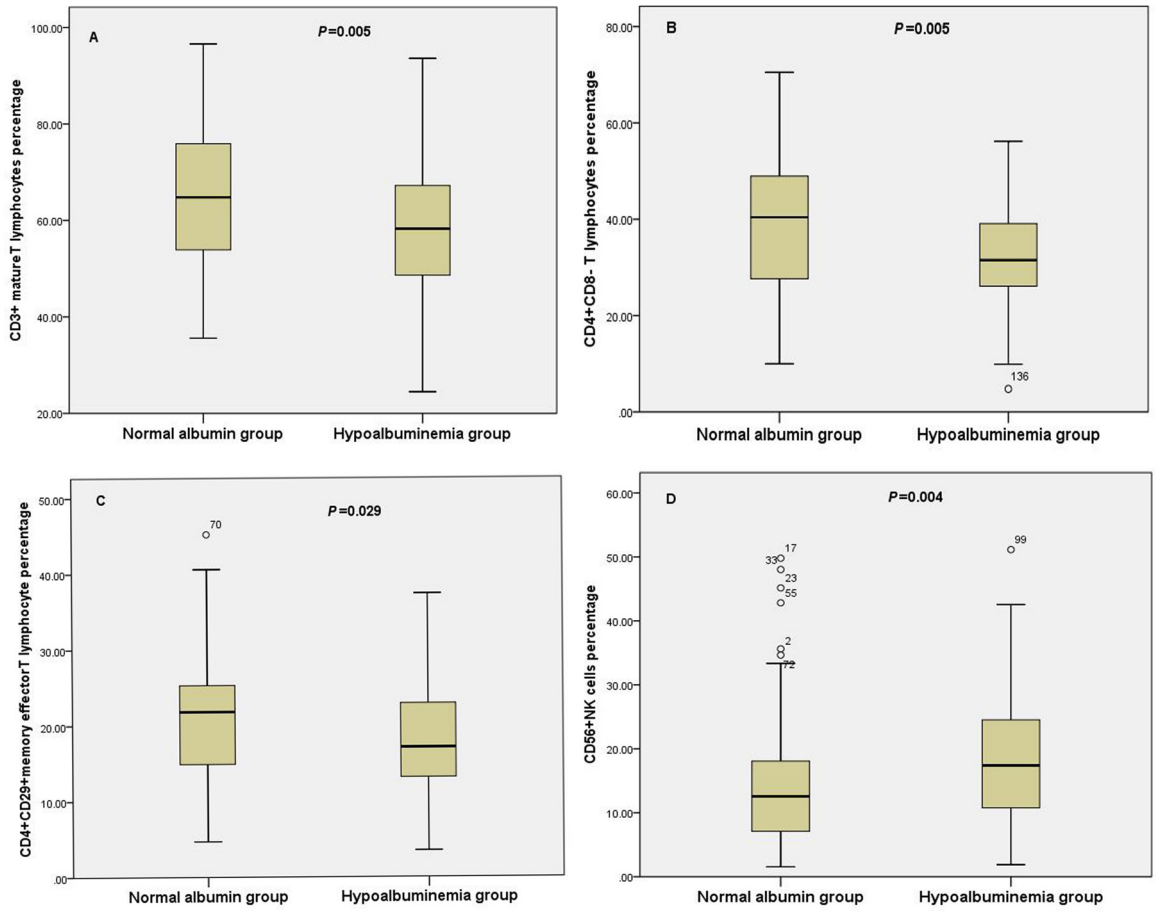

Figure 4. Comparison of immune function based on serum albumin level. A: CD3+ mature T lymphocytes; B: CD4+CD8- T lymphocytes; C: CD4+CD29+ memory effector T lymphocytes;D: CD56+ NK cells. NK: Natural killer.

and sepsis mortality. Hypoalbuminemia is a condition in which the serum albumin level is <35 g/L, and a serum albumin level <25 g/L is defined as severe hypoalbuminemia.[7] In this study, 88.9% of patients had an albumin level <35 g/L, and 30.4% of patients had severe hypoalbuminemia (albumin <25 g/L), indicating a high incidence of hypoalbuminemia in sepsis. A decreased serum albumin level (albumin <28 g/L) is not only a predictor of sepsis severity[10] but also may be closely associated with mortality. It has been reported that the mortality rate is increased when the albumin level is <25 g/L [11] and further increases when complicated by hypoglycemia.[12] When the serum albumin level is <24.5 g/L, the survival rate decreases by 63.4%. Furthermore, when the serum albumin level is <14.5 g/L, the survival rate decreases by 76.4%. If the albumin level shows a gradual decline, the survival rate drops by 70.6%.[13] The present multivariate logistic regression analysis revealed the relationship between serum albumin and mortality. Serum albumin is a protective predictor of death, as the risk of death decreases with increasing albumin level. These results are in accordance with those found in the literature.[14]

More importantly, this study found that hypoalbuminemia is associated with immunosuppression in sepsis patients. The T lymphocyte and memory effector T lymphocyte levels were decreased in sepsis patients with hypoalbuminemia. Persistent malnutrition is a high-risk factor for immunosuppression, and serum albumin level is an essential indicator for evaluating patient nutrition. One study reported that the function of NK cells, dendritic cells, and monocytes was decreased following viral infection, and the gene expression spectrum of intestinal epithelial cells was altered in a malnourished pig model.[15] Another report demonstrated the relationship between nutritional status and in-hospital infection in elderly patients, where poor nutritional status was a risk of in-hospital infection due to hypoproteinemia and immune system impairment.[16] In addition, the activity of NK cells is reduced in elderly patients with hypoproteinemia.[17] However, the mechanisms by which hypoproteinemia aggravates immune impairment are rarely reported.

T lymphocyte depletion is an important cause of immunosuppression in sepsis patients. Apoptosis of T lymphocytes plays an important role in the loss of this cell population in patients with sepsis.[18] Apoptosis leads to significant loss of immune cells including $CD4^+$ and $CD8^+$ T cells, B cells, and follicular dendritic cells in sepsis patients, resulting in immunosuppression. Another study found that both $CD4^+$ and $CD8^+$ T lymphocytes were significantly reduced in autopsies of septic patients.[19] Mechanically, apoptosis may be induced via the death receptor and mitochondrial pathways in sepsis.[18] Immunodeficiency is common in sepsis or septic shock, and is associated with an increased risk of short-term mortality.[20] The present study analyzed the immune indexes of 140 sepsis patients and found that $CD3^+$

mature, $CD4^+CD8^-$, and $CD4^+CD29^+$ memory effector T lymphocytes were significantly decreased in the hypoalbuminemia group compared with the normal albumin group.

In addition, the incidence of acute kidney injury in patients with septic shock is 40–45%, [21] and the mortality rate increases 6–8 times [22] or 3–5 times [23] when sepsis patients present with acute kidney injury. The change in serum creatinine within 24 h after admission is associated with mortality, and an increase of 0.3 mg/mL of creatinine has a predictive value for sepsis-related death.[24] This study showed that a high serum creatinine level was associated with an increased risk of death, which is in accordance with the literature. Creatinine is also a risk factor for the prognosis of sepsis in the prediction model herein.

Despite many valuable clinical indexes for sepsis patients found in this study and the establishment of a prediction model based on these data, some limitations should be noted. First, this study only involved in 545 sepsis patients and a large sample size study is needed in the future. Second, this is a retrospective study, and a prospective study is needed to validate the prediction model. Third, this study found that hypoalbuminemia is associated with immunosuppression in sepsis patients, and further work should be done to explore more valuable findings to advance the prevention and treatment of sepsis in the future.

Conclusions

The risk factors for 28-day sepsis mortality include age, D-dimer, creatinine, PT, and albumin. A decreased albumin level exacerbates immunosuppression in patients with sepsis. This study established a prediction model based on these indicators, which showed a good degree of calibration and differentiation. This model may provide good predictive value for clinical sepsis prognosis.

Ethical approval

This study was approved by the Ethics review board of the Shanghai General Hospital (approval no. 2020KY216). Given the observational retrospective nature of this study, written informed consent from each patient was not required. Patient data were anonymized and unidentifiable. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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