A novel risk prediction nomogram to predict 30-day mortality in older patients with sepsis

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Research Article

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Abstract

**Background:** Sepsis is a common clinical disease with a high mortality rate, and the prognosis of older patients with sepsis varies. The purpose of this study was to determine the prognostic factors in older patients with sepsis and to establish a prognostic model for predicting short-term mortality in older adults with sepsis, as early intervention is recommended to reduce case fatality rate.

**Methods:** We reviewed 426 older patients with sepsis and collected their demographic details, clinical information, and data on biological markers for the first time within 24 hours of hospital admission. At the same time, we calculated a Nutrition Risk Screening (NRS-2002) score. In a 7:3 ratio, these patients were randomly divided into a training group (n = 298) and validation group (n = 128). The lasso regression model was used to reduce data dimensions and select features. To construct a prognostic signature, Cox regression analysis was used, based on which a nomogram was developed, and its predictive accuracy was evaluated. The discrimination, calibration, and clinical usefulness of the nomogram were assessed using calibration curves and decision curve analysis (DCA).

**Results:** Albumin (ALB) level, blood urea nitrogen (BUN) level, lactic acid level, and NRS-2002 score were independent risk factors that affected the 30-day prognosis of older patients with sepsis ($P \leq 0.05$). The area under the receiver operating characteristic (ROC) curve (AUC) values of the nomogram of the training and validation groups were 0.772 (95% CI, 0.734–0.812) and 0.730 (95% CI, 0.695–0.766), respectively. The calibration curves fit well in the two groups.

**Conclusions:** We developed and validated a prognostic nomogram model based on ALB, BUN, and lactic acid levels and NRS-2002 score for older patients with sepsis. This model can help clinicians timely assess the early risk of death in older patients with sepsis and accordingly take proactive measures.

**Background**

The progression of sepsis is rapid, accompanied by multiple organ dysfunction, followed by organ failure, which is the direct cause of death. It is characterised by a high incidence of disability and mortality [1–3]. The age of the patient is an independent predictor of mortality [4]; 60% of sepsis occurs in patients aged 65 years and older [5], and immunocompromised older patients often have a variety of chronic diseases. They are prone to repeat infections by a variety of pathogenic and opportunistic microorganisms, and therefore, the mortality rate of older patients with sepsis is generally high [6, 7]. Physical injuries, psychosocial and financial difficulties, and other factors make older adults vulnerable to nutritional deficiencies in the face of an ageing global population [8, 9]. The prevalence of malnutrition is 32.9–76% higher in older hospitalised patients than in younger patients [10–12], and malnutrition is associated with a high risk of morbidity and mortality. A screening tool (NRS-2002) for assessing the nutritional risk and disease severity, particularly in the critically ill, is recommended for hospitalised patients (ESPEN, SCCM, ASPEN) [13].
Several screening tools have been used to predict mortality in patients with suspected sepsis, including the Modified Early Warning Score (MEWS), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II). Many commonly used biomarkers in sepsis have also been shown to be used as outcome predictors in patients with sepsis. However, these prognostic indicators have limitations regarding early diagnosis or accuracy, and none of them has been shown to be the best predictor of the risk of death in patients with sepsis. Prognostic nomograms are efficient statistical tools suggested as a new standard for predicting the survival of an individual patient [14]. Compared with traditional methods, a nomogram can predict patient risk more quickly, conveniently, and accurately. Currently, there are few relevant models to predict the prognosis of older patients with sepsis. Accurate and reliable prediction models are conducive to reminding clinicians to take correct and effective treatment on time and improve the clinical prognosis of patients.

Therefore, we examined the clinical characteristics and factors that affect survival and prognosis of older patients with sepsis, then selected meaningful clinical trial indicators, and further improved the prognosis of these patients in our retrospective study.

Methods

Study design and patients

As shown in Fig. 1, 426 patients admitted to The Third Affiliated Hospital of Anhui Medical University from June 1, 2018, to June 30, 2022, were selected. Inclusion criteria: (1) age ≥ 65 years; (2) met the latest diagnostic criteria for sepsis [15]. Exclusion criteria: (1) patients with advanced malignant tumours, blood system diseases, severe heart failure, and autoimmune diseases; (2) patients with human immunodeficiency virus infection and long-term use of immunosuppressants; (3) patients whose family members relinquished treatment or left the hospital against medical advice. Three of seven training data points were randomly divided between calibration data (n = 128) and training data (n = 298). Informed consent was waived because the study was conducted retrospectively and no interventions were applied. The ethics committee of our organisation approved this study, which was compliant with medical ethics standards (No: 2022-013-01).

Data Collection

We collected the general data (sex and age) of the patients, and the following laboratory indicators were taken within the first 24 hours after admission: blood routine test, liver function, renal function, procalcitonin (PCT), high-sensitivity-c-reactive protein (hCRP), prothrombin time (PT), D-dimer and blood gas indicators, and the 30-day clinical outcomes (survival or death) were recorded for all selected patients. The missing values from 20% of the individuals were removed and the remaining values were imputed by sampling the multivariate normal distribution.
Nutritional Screening

The NRS-2002 questionnaire is a straightforward tool used to screen patients for malnutrition, which was used in our study by physicians to evaluate nutritional abnormalities in patients [13]. The questionnaire was completed within 24 hours of admission.

Statistical analysis

SPSS 25.0 statistical software was used for statistical analysis. Normally distributed data were displayed as mean and standard deviation (±s). Intergroup comparisons were conducted by performing independent sample t-tests. The enumeration data were presented as percentages, and comparisons between groups were made using the χ² test. Non-normally distributed variables were presented as median (interquartile range), and the Mann-Whitney U-test was used to compare the groups.

Lasso regression analyses were performed with the R package glmnet (4.2.1). Multivariate data analysis was performed using the Cox regression model based on the variables with significant differences in univariate analysis. Risk scores were calculated for each patient, who were divided into low-risk (> median) and high-risk groups (≥ median) according to the median risk score. A nomogram was derived using the rms package in the R software, which incorporates all independent prognostic factors. We measured the discriminating ability of the model both in the modelling group and the validation group on the basis of its ROC curve and the area under the curve. To test the calibration performance and clinical utility of the calibration curve, DCA and calibration curve were performed.

Results

Baseline characteristics

A total of 426 patients were recruited to the study after the exclusion criteria were applied. Of these, 251 patients were male and 175 were female, 94 patients died, and the fatality rate was 22.07%. Two groups were randomly selected in this study: 298 comprised the training set (70%) and 128 the validation set (30%). The recruitment process is illustrated in Fig. 1. No significant differences were found between the two groups in terms of age, sex distribution, or biomarkers (P > 0.05) (Table 1). In general, the distribution of the predictor variables in the training set and the validation set was the same, indicating that the training set and the validation set grouping was completely random, therefore avoiding the uneven distribution bias.
<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Training set (n = 298)</th>
<th>Validation set (n = 128)</th>
<th>F/ χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>172/126</td>
<td>79/49</td>
<td>0.59</td>
<td>0.45</td>
</tr>
<tr>
<td>Age (years)</td>
<td>80.04 ± 8.91</td>
<td>79.85 ± 8.86</td>
<td>0.66</td>
<td>0.25</td>
</tr>
<tr>
<td>hLOS (days)</td>
<td>24.03 ± 8.35</td>
<td>25.39 ± 9.31</td>
<td>1.86</td>
<td>0.16</td>
</tr>
<tr>
<td>WBC, 10⁹/L</td>
<td>10.51 ± 6.87</td>
<td>11.32 ± 6.84</td>
<td>0.63</td>
<td>0.29</td>
</tr>
<tr>
<td>NEU (%)</td>
<td>80.71 ± 13.63</td>
<td>82.81 ± 13.87</td>
<td>1.35</td>
<td>0.66</td>
</tr>
<tr>
<td>RBC, 10¹²/L</td>
<td>3.48 ± 0.86</td>
<td>3.52 ± 0.93</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>HGB, g/L</td>
<td>104.39 ± 24.35</td>
<td>108.72 ± 25.09</td>
<td>1.21</td>
<td>0.66</td>
</tr>
<tr>
<td>MCHC, g/L</td>
<td>315.88 ± 38.06</td>
<td>323.34 ± 23.99</td>
<td>2.31</td>
<td>0.07</td>
</tr>
<tr>
<td>PLT, 10⁹/L</td>
<td>161.13 ± 85.66</td>
<td>171.77 ± 102.58</td>
<td>3.18</td>
<td>0.85</td>
</tr>
<tr>
<td>PDW, %</td>
<td>16.14 ± 1.42</td>
<td>16.47 ± 1.68</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>hCRP, mg/L</td>
<td>52.70(19.53,114.26)</td>
<td>59.73(18.52,122.90)</td>
<td>0.65</td>
<td>0.82</td>
</tr>
<tr>
<td>Cr, umol/L</td>
<td>71(49.40,101)</td>
<td>75.20(58.60,75.20)</td>
<td>1.34</td>
<td>0.52</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>7.13(4.73,10.28)</td>
<td>7.3(5.13,11.31)</td>
<td>1.06</td>
<td>0.26</td>
</tr>
<tr>
<td>ALB, g/L</td>
<td>32.69 ± 5.32</td>
<td>32.32 ± 6.14</td>
<td>4.04</td>
<td>0.55</td>
</tr>
<tr>
<td>ALT, u/L</td>
<td>38.32 ± 9.40</td>
<td>58.93±</td>
<td>3.82</td>
<td>0.12</td>
</tr>
<tr>
<td>TB, umol/L</td>
<td>17.25 ± 3.76</td>
<td>18.55 ± 5.78</td>
<td>2.40</td>
<td>0.43</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>3.99 ± 0.62</td>
<td>3.94 ± 0.59</td>
<td>0.44</td>
<td>0.41</td>
</tr>
<tr>
<td>Ca⁺, mmol/L</td>
<td>2.12 ± 0.17</td>
<td>2.10 ± 0.15</td>
<td>0.87</td>
<td>0.63</td>
</tr>
<tr>
<td>PCT, ng/mL</td>
<td>1.40(0.77,4.30)</td>
<td>1.43(1.11,5.42)</td>
<td>1.13</td>
<td>0.86</td>
</tr>
<tr>
<td>Lac, mmol/L</td>
<td>1.91 ± 1.38</td>
<td>1.99 ± 1.65</td>
<td>0.86</td>
<td>0.59</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>213(169.25,292)</td>
<td>201.51(156,277.25)</td>
<td>0.58</td>
<td>0.74</td>
</tr>
<tr>
<td>NRS</td>
<td>2.97 ± 1.52</td>
<td>2.64 ± 1.49</td>
<td>1.32</td>
<td>0.36</td>
</tr>
<tr>
<td>PT, s</td>
<td>12.67 ± 3.94</td>
<td>13.42 ± 5.87</td>
<td>0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>FIB, g/L</td>
<td>3.81 ± 1.89</td>
<td>4.88 ± 2.35</td>
<td>9.11</td>
<td>0.26</td>
</tr>
<tr>
<td>D-D, mg/L</td>
<td>2.88 ± 0.98</td>
<td>2.45 ± 0.76</td>
<td>0.05</td>
<td>0.61</td>
</tr>
</tbody>
</table>
Feature Selection

Due to the many research variables included, the reliability of the single factor analysis result is poor due to a certain correlation between different variables. Therefore, 25 variables in the training set were selected using lasso regression. When selecting the optimal lambda parameters, 10-fold cross-validation is used. The lambda value is obtained when the cross-validation error is at a minimum and is the optimal value of the model (Fig. 2). The number of variables corresponding to the non-zero regression coefficient at this time was counted. The results of the lasso regression showed that the seven variables, namely NRS, blood urea nitrogen (BUN), albumin (ALB), lactic acid (Lac), white blood cells (WBC), mean corpuscular hemoglobin concentration (MCHC) and PCT, were closely related to the prognosis of patients with sepsis.

Multivariate Cox Regression

Multivariate Cox analysis was performed according to the independent variables screened by lasso regression. After the diagnosis of sepsis in older patients, Lac, BUN, and ALB levels and NRS-2002 score were independent risk factors associated with mortality within 30 days ($P < 0.05$, Table 2). Kaplan-Meier analysis showed a significant difference in survival rate between the high-risk group and the low-risk group ($P < 0.001$), and the risk score of patients was inversely proportional to the survival rate of patients with sepsis (Fig. 3).

![Table 2](image)

Establishment And Verification Of Nomogram Model
We developed a nomogram based on the four independent risk factors (Fig. 4). Lines were drawn from each characteristic to the axis of its corresponding point. Based on the nomogram, patients receive a total point by adding each of the multiple parameters together, and those with a higher total point were expected to have a worse outcome. Next, the ROC curve, calibration curve, and DCA curve of the prediction model were generated. The AUC of the training sets and validation sets were 0.772 (95% CI, 0.734–0.812) and 0.730 (95% CI, 0.695–0.766), respectively. Calibration curves were used to assess whether observed results and predicted probabilities were in agreement. DCA was applied to confer clinical validity of the nomograms, which confirmed our expectations. (Fig. 5)

Discussion

Sepsis is a life-threatening infection, and there is still no definitive conclusion regarding the analysis of prognostic factors of sepsis in older patients [16]. Many scoring systems are available to evaluate the severity of sepsis in patients, such as SIRS, SOFA, qSOFA, and APACHE II scores [17, 18]. However, these scores not only need to monitor the basic vital signs of patients but also need to test many physiological and biochemical indicators. The process is complex and laborious. The study aimed to construct a prediction model that could have an immediate impact on treatment decisions. It is our hope that this model will not only increase working efficiency but will also provide clinicians with more safe and effective treatment options.

Previous studies have shown that death due to sepsis in patients is strongly associated with some biological indicators, such as PCT, hCRP, renal insufficiency, Lac level, and ALB level [19–23]. Based on previous studies and clinical experience, this study included variables that were straightforward to collect and may have an impact on prognosis, combined with the nutritional status of the patients, and obtained an independent risk factor for poor outcomes after analysis. Anaerobic metabolism produces Lac, and the resultant hyperlactataemia often indicates that patients with sepsis have circulatory or respiratory failure. Lac level ≥ 4.0 mmol/l is related to an increase in mortality at 28 days in approximately 30% of patients with acute illness. A prospective cohort study involving 126 patients, who were diagnosed with severe sepsis or septic shock, found that lactic acidosis can more accurately predict hospital mortality in patients [24]. Therefore, Lac levels can be considered a good predictor of mortality risk with critical illness. Our results matched that of former studies. Therefore, dynamic monitoring of the blood lactate level was significant in evaluating the severity of illness and determining prognosis. BUN is the metabolic outcome of protein metabolism and is excreted by the kidney. When protein is degenerated or glomerular filtration rate decreases, the BUN level will increase. Therefore, the level of BUN can reflect protein catabolism in the body and is also a sign of kidney damage [25]. At the same time, BUN is one of the common indicators of kidney function in the clinical laboratory. Patients with sepsis have significantly increased protein catabolism and tend to have acute kidney injury. All these factors can lead to an increase in the BUN level. Another study showed that the BUN level was an independent predictor of mortality in patients with sepsis [26]. This study also showed that mortality at 30 days increased gradually in older people with sepsis as BUN levels increased.
Malnutrition is one of the major causes of death in patients with sepsis[27]. Those with sepsis are in a state of severe stress and in a hypercatabolic state, accompanied by organ dysfunction and decreased immunity, making older patients more susceptible to malnutrition. These factors lead to a poor prognosis[28]. The NRS-2002 combines information about a person’s nutritional status with clinical disease information. It is a widely used nutritional screening tool for adult inpatients, which can effectively identify critical illnesses with a high nutritional risk. It is not only more sensitive and specific but also more convenient for evaluating malnutrition-related mortality and adverse clinical outcomes of hospitalised patients[29]. Those diagnosed with sepsis are in an imbalanced inflammation-immune state and often show excessive inflammatory reactions. Lipids are peroxidised, proteins are oxidised, and carbohydrates are expended, which increase the risk of malnutrition[30]. Disordered metabolic pathways are critically starved of energy caused by the infection, and this can result in poor clinical outcomes[31]. However, limited data are available regarding NRS-2002 and sepsis[32].

The findings of this study show that the nutritional risk score is an independent risk factor for short-term mortality in older patients with sepsis. With an increase in the nutritional score, the mortality rate of the patients increased significantly in this study. Taking into account the operability of NRS-2002, the screening for malnutrition is now widely recommended for hospitalised patients. Clinicians can quickly evaluate the nutritional risk of these patients, and if they want to optimise sepsis care and prevent iatrogenic malnutrition, targeted nutritional treatment is needed for patients with sepsis. Similarly, some studies have shown that a decreased ALB level is an independent predictor of mortality in patients with sepsis or septic shock, which matches the findings of our study[33]. The mechanism is related to the decrease in colloidal osmotic pressure caused by sepsis, resulting in lower effective circulating volume, decreased ability to bind and transport substances, attenuated antioxidant action, and coagulation dysfunction. Therefore, patients diagnosed with sepsis, especially those at a high risk of undernutrition, should receive individualised nutritional intervention strategies in time, as increasing the level of ALB can improve clinical outcomes.

In conclusion, we analysed the basic data and laboratory indicators of 426 older patients with sepsis in the hospital. This study showed that the indicators ALB, BUN, and Lac levels and NRS-2002 tested for the first time after admission were independent risk factors for poor short-term prognosis (30-day mortality) of older patients with sepsis. We also established a nomogram to predict the prognosis of patients. Practically, there are uncommon models that use nutritional screening scores combined with biomarkers as prognostic factors for older patients with sepsis. The relevant indicators included in this model are convenient and easy to obtain. This model is simple and convenient to evaluate the condition of patients with acute and critical illnesses and provides a reference for clinicians to evaluate the prognosis of patients with sepsis and develop effective interventions.

However, this study also had some shortcomings. First, this study was a single-centre retrospective study, and the number of cases included was relatively small; Only clinical indicators were collected within 24 hours after admission and dynamic change analysis of indicators was not carried out, which could not accurately reflect changes in the patient’s condition. Secondly, compared with the prospective clinical
design, incomplete case data limited this study, and some meaningful indicators could not be included in
the study, such as brain natriuretic peptide levels. Considering the lack of a retrospective analysis to
confirm the clinical predictive value of the nomogram constructed in this study, and to provide clinicians
with an accurate, reliable, simple, and easy predictive model, the study results needs to be further
confirmed by a larger sample-sized study that is a reasonably designed, high-quality prospective study, to
obtain a more valuable predictive model for the prognosis of older patients with sepsis.

Conclusions

A nomogram was validated to predict the prognoses of older patients with sepsis. NRS-2002 and
biomarkers were incorporated into the model for evaluation. Attention must be paid to older patients with
sepsis and hypoproteinaemia, malnutrition, high urea nitrogen levels, and high lactataemia, because they
have a higher risk of mortality.

Abbreviations

hLOS: hospital length of stay; WBC: white blood cell; NEU: neutrophil percent; RBC: red blood cell count;
HGB: hemoglobin; MCHC: mean corpuscular hemoglobin concentration; PLT: platelets; PDW: platelet
distribution width; hCRP: high-sensitivity C-reactive protein; Cr: creatinine; BUN: blood urea nitrogen; ALB:
albumin; ALT: alanine transaminase; TB: total bilirubin; PCT: procalcitonin; LDH: lactic dehydrogenase;
NRS: Nutrition Risk Screening; PT: prothrombin time; FIB: fibrinogen; D-D: D dimer; NRS: Nutrition Risk
Screening; DCA: decision curve analysis; AUC: area under the curve; ROC: receiver operating characteristic;
MEWS: Modified Early Warning Score; SOFA: Modified Early Warning Score; APACHE II: Acute Physiology
and Chronic Health Evaluation II.

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration
and was approved by the Human Ethics Committee of Binhu Hospital of Hefei. Written informed consent
was obtained from individual or guardian participants.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon
reasonable request.

Competing interests
The authors have no conflicts of interest to report

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Authors' contributions

Fang Li conceived the study and wrote the manuscript; Wei-Feng Zhou analyzed data; Min Pan critically revised the manuscript for important intellectual content; Shu Wang created the figures; All authors read and approved the final manuscript.

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References


Figures
Figure 1

Flowchart illustrating the research process.
Figure 2

Results of lasso regression analysis (a-b). The trajectory of each independent variable, the horizontal axis represents the log value of the independent variable lambda, and the vertical axis represents the coefficient of the independent variable. The tuning parameter (\( \lambda \)) was calculated based on the partial likelihood deviation with ten-fold cross-validation. The dotted vertical lines are drawn at the optimal values by minimum criteria and 1-SE criteria.
<table>
<thead>
<tr>
<th>Variables</th>
<th>HR(95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS</td>
<td>1.229(1.031-1.465)</td>
<td>0.022</td>
</tr>
<tr>
<td>BUN</td>
<td>1.027(1.004-1.050)</td>
<td>0.023</td>
</tr>
<tr>
<td>ALB</td>
<td>0.909(0.863-0.958)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lac</td>
<td>1.250(1.049-1.491)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Figure 3

Forest plot illustrates the results of multivariate Cox analysis (a). Survival analysis of the low-risk group and the high-risk group (b). Distribution of risk scores (c).
Figure 4

The nomogram for predicting the risk of death in older patients with sepsis in 30 days. (A: NRS; B: BUN; C: ALB; D: Lac)
Figure 5

The calibration curve of the prognostic risk model(a-b). ROC curves for the prognostic risk model for patients with sepsis(c). The DCA curve of the prognostic risk model(d).