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*Original Article*

# Risk factors and predictive nomogram for multi-organ failure in patients with acute kidney failure combined with severe sepsis

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**Abstract:** Objectives: To identify independent risk factors for multiple organ failure (MOF) and construct a clinically applicable predictive nomogram. Methods: We retrospectively analyzed 418 patients with acute kidney failure (AKF) and severe sepsis treated between January 2020 and September 2024. Demographic data, clinical features, and laboratory parameters were collected. Patients were randomly assigned to a training cohort (n=293) and a validation cohort (n=125). Independent risk factors for MOF were identified using logistic regression analysis, and a nomogram was subsequently developed. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), calibration curves, and decision curve analysis (DCA). Results: Five independent predictors of MOF were identified: abdominal infection, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, neutrophil count (NEU), lactate (Lac), and heparin-binding protein (HBP). The nomogram showed good discrimination, with an AUC of 0.756 (95% CI: 0.701-0.811) in the training cohort and 0.816 (95% CI: 0.743-0.889) in the validation cohort. Calibration curves demonstrated good agreement between predicted and observed outcomes, and DCA indicated a favorable net clinical benefit. Conclusions: A nomogram incorporating abdominal infection, APACHE II score, NEU, Lac, and HBP effectively predicts the risk of MOF in AKF patients with severe sepsis. This model may aid in early risk stratification and clinical decision-making.

**Keywords:** Sepsis, acute renal failure, multiple organ failure, nomogram

## Introduction

Acute kidney failure (AKF) is a common and severe clinical condition often associated with systemic diseases such as severe sepsis [1]. In such cases, the kidneys are among the primary organs affected by sepsis, and the associated systemic inflammatory response significantly increases the risk of AKF [1]. The pathogenesis involves the release of inflammatory mediators, recruitment of immune cells, and the onset of a so-called "cytokine storm" [2], which can induce systemic inflammation, microcirculatory dysfunction, alterations in renal hemodynamics, and tubular injury. Furthermore, the accumulation of endogenous toxins and an exaggerated immune response also contribute to AKF progression. Studies have shown that 25% to 75% of patients with acute kidney injury (AKI) also present with severe sepsis [3]. The duration and severity of AKF are key prognostic indicators in septic patients [4]. The coexistence of AKF and severe sepsis often leads to critical illness and high mortality, posing a significant clinical challenge.

Sepsis is defined as a systemic inflammatory response syndrome triggered by infection [5]. It can adversely affect multiple organ systems, leading to cellular necrosis, metabolic derangement, and organ dysfunction. In addition to AKF, the development of multiple organ failure (MOF) is a major complication that further worsens prognosis and compromises treatment outcomes. The systemic inflammatory cascade in sepsis is a principal driver of MOF, with renal failure frequently preceding the onset of multi-organ involvement [6]. The incidence and severity of organ dysfunction are influenced by various factors, including age,

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comorbidities, immune status, and the infecting pathogen [7]. Mortality rates in septic patients have been shown to correlate with the number of failing organs: <4 organ failures correspond to <50% mortality, 5-7 organ failures correspond to >50% mortality, and ≥7 organ failures result in nearly 100% mortality [8].

With advances in medical research, an increasing number of clinical prediction models have been developed. These models typically integrate statistical techniques to analyze multiple risk factors, offering high practical value. Among them, nomograms serve as intuitive visual tools that present complex prediction models in an easy-to-use graphical format [9].

Given that AKF is a common complication of severe sepsis, preventing the progression to MOF is essential to improving treatment outcomes and reducing mortality. However, a review of the current literature reveals a lack of robust studies focusing specifically on MOF prediction in this population. Therefore, this study aims to identify key risk factors for MOF in patients with AKF and severe sepsis and to develop a reliable and user-friendly nomogram for clinical risk assessment. It is hoped that this model will support personalized treatment strategies and inform clinical decision-making.

## Materials and methods

### *Study subjects*

This retrospective study included 418 patients diagnosed with AKF combined with severe sepsis, treated between January 2020 and September 2024. Among them, 293 were assigned to the training cohort and 125 to the external validation cohort. The inclusion criteria were as follows: (a) patients meeting the diagnostic criteria for severe sepsis/septic shock according to the Chinese Guidelines for the Treatment of Severe Sepsis/Septic Shock [10]; (b) patients meeting the diagnostic criteria for AKF [11]; and (c) patients with an AKF and sepsis duration of less than 72 hours at the time of admission. The exclusion criteria included: (a) a history of chronic kidney disease (CKD) or end-stage renal disease; (b) severe cardiovascular disease, liver disease, malignancy, or other organ dysfunction; (c) pre-existing infections or inability to receive effective anti-infective treatment; and (d) incomplete clinical data. This study was approved by the Ethics Committee of Guang'an People's Hospital.

### *Data collection*

General demographic and clinical data were collected. Demographic variables included age, sex, body mass index (BMI), education level, residence (urban/rural), and marital status. Clinical data included sepsis etiology, urine output, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, lactate dehydrogenase (LDH), serum creatinine (Scr), blood urea nitrogen (BUN), D-dimer (D-D), N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP), platelet (PLT), neutrophil (NEU), estimated glomerular filtration rate (eGFR), lactate (Lac), and heparin-binding protein (HBP).

### *Nomogram and clinical validation*

The training cohort of 293 patients was used to construct the predictive model. A nomogram was developed based on multivariate logistic regression analysis. The model's discrimination was assessed using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Model calibration was evaluated using calibration plots and the Hosmer-Lemeshow goodness-of-fit test; a $P$ value > 0.05 was considered indicative of good model fit. Internal validation was performed via bootstrapping with 1,000 resamples.

Additionally, a separate cohort of 125 patients admitted between February 2023 and September 2024 was used as an external validation cohort for prospective clinical validation of the nomogram.

### *Statistical analysis*

To ensure data integrity and accuracy, all data were verified prior to analysis. Continuous variables following a normal distribution were expressed as mean ± standard deviation (SD) and compared using independent-samples t tests. Categorical variables were expressed as percentages and compared using the chi-square test or Fisher's exact test, as appropriate. MOF occurrence was treated as the dependent variable. Variables with P<0.05 in univariate analysis were entered into a multivariate logistic regression model to identify independent risk factors. The nomogram was constructed using R software (version 4.2.2), and internal validation was performed with 1,000 bootstrap resamples.

**Table 1.** Comparison of baseline and clinical data between the training and validation groups

| Variables | Training group (n=293) | Validation group (n=125) | $t/x^2$ | *P* |
|---|---|---|---|---|
| Age (year, Mean ± SD) | 52.25±5.71 | 53.08±5.62 | 1.367 | 0.172 |
| Sex [n (%)] | | | | |
| Male | 175 | 75 | 0.003 | 0.959 |
| Female | 118 | 50 | | |
| BMI (kg/m$^2$, Mean ± SD) | 24.24±3.22 | 24.15±3.09 | | |
| Educational level [n (%)] | | | | |
| College degree or above | 40 | 21 | 2.662 | 0.264 |
| High school or secondary vocational school | 85 | 27 | | |
| Junior high school or below | 168 | 77 | | |
| Place of Residence [n (%)] | | | | |
| Rural area | 190 | 89 | 1.594 | 0.207 |
| Urban area | 103 | 36 | | |
| Marital status [n (%)] | | | | |
| Married | 203 | 88 | 0.681 | 0.712 |
| Unmarried | 54 | 25 | | |
| Widowed | 36 | 12 | | |
| Cause of sepsis [n (%)] | | | | |
| Abdominal infection | 120 | 53 | 0.075 | 0.784 |
| Pulmonary infection | 80 | 35 | 0.021 | 0.884 |
| Urinary system | 61 | 20 | 1.303 | 0.254 |
| Other infections | 32 | 17 | 0.608 | 0.436 |
| Urine volume (mL/d, Mean ± SD) | 1478.68±426.71 | 1444.94±433.06 | 0.737 | 0.462 |
| APACHE II score (Mean ± SD) | 18.47±3.94 | 18.81±6.28 | 0.669 | 0.504 |
| LDH (U/L, Mean ± SD) | 594.83±81.48 | 595.88±95.15 | 0.115 | 0.901 |
| Scr (μmol/L, Mean ± SD) | 106.78±15.21 | 106.66±15.72 | 0.073 | 0.942 |
| BUN (mmol/L, Mean ± SD) | 7.07±3.27 | 7.22±3.12 | 0.435 | 0.664 |
| D-D (μg/L, Mean ± SD) | 817.18±164.52 | 824.23±171.08 | 0.396 | 0.692 |
| NT pro-BNP (ng/mL, Mean ± SD) | 3975.97±517.20 | 3985.77±524.47 | 0.177 | 0.860 |
| CRP (mg/L, Mean ± SD) | 152.44±20.28 | 155.10±31.17 | 1.035 | 0.301 |
| PLT (×10$^9$, Mean ± SD) | 187.86±35.24 | 182.73±42.88 | 1.274 | 0.203 |
| NEU (%, Mean ± SD) | 67.08±10.49 | 69.35±12.39 | 1.926 | 0.056 |
| eGFR [mL/(min·1.73 m$^2$), Mean ± SD] | 72.30±9.12 | 73.94±8.45 | 1.720 | 0.086 |
| Lac (mmol/L, Mean ± SD) | 5.13±1.79 | 5.43±1.97 | 1.522 | 0.129 |
| HBP (ng/mL, Mean ± SD) | 71.15±12.87 | 73.35±18.03 | 1.411 | 0.159 |

Abbreviation: SD, standard deviation; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; LHD, lactate dehydrogenase; Scr, serum creatinine; BUN, blood urea nitrogen; D-D, D-Dimer; NT pro-BNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; PLT, platelet; NEU, neutrophil; eGFR, estimated glomerular filtration rate; Lac, lactic acid; HBP, heparin-binding protein.

## Results

### *Comparison of general characteristics between the training and validation two groups*

A total of 418 patients with AKF combined with severe sepsis were included in this study. There were no statistically significant differences in baseline characteristics or laboratory parameters between the training cohort and the external validation cohort (P>0.05) (**Table 1**).

### *Univariate analysis*

Patients in the training cohort were divided into two groups: those who developed MOF (n=153) and those who did not (n=140). Baseline characteristics and laboratory findings for both groups are presented in **Table 2**. There were no significant differences between the two groups in age, sex, BMI, education level, place of residence, marital status, pulmonary or urinary tract infections, other infections, urine vol-

**Table 2.** Univariate and multivariate analysis of the baseline characteristics in the training cohort

| Variables | Univariate analysis | | Multivariate analysis | | | | |
|---|---|---|---|---|---|---|---|
| | $t/x^2$ value | *P* value | B | SE | *P* | OR | 95% CI |
| Age | 0.929 | 0.354 | | | | | |
| Sex | 0.744 | 0.388 | | | | | |
| BMI | 0.689 | 0.492 | | | | | |
| Educational level | 0.216 | 0.897 | | | | | |
| Place of Residence | 1.374 | 0.241 | | | | | |
| Marital status | 1.925 | 0.382 | | | | | |
| Abdominal infection | 12.128 | <0.001 | 0.888 | 0.315 | 0.005 | 2.430 | 1.310-4.506 |
| Pulmonary infection | 3.163 | 0.075 | | | | | |
| Urinary system | 1.230 | 0.267 | | | | | |
| Other infections | 3.119 | 0.074 | | | | | |
| Urine volume (mL/d) | 1.849 | 0.066 | | | | | |
| APACHE II score | 10.134 | <0.001 | 0.148 | 0.034 | <0.001 | 1.159 | 1.086-1.238 |
| LDH (U/L) | 2.265 | 0.024 | | | | | |
| Scr (μmol/L) | 1.642 | 0.102 | | | | | |
| BUN (mmol/L) | 1.151 | 0.251 | | | | | |
| D-D (μg/L) | 1.470 | 0.143 | | | | | |
| NT pro-BNP (ng/mL) | 0.957 | 0.339 | | | | | |
| CRP (mg/L) | 3.240 | 0.001 | | | | | |
| PLT ($\times 10^9$) | 1.260 | 0.209 | | | | | |
| NEU (%) | 4.317 | <0.001 | 0.051 | 0.016 | 0.001 | 1.052 | 1.020-1.085 |
| eGFR [mL/(min·1.73 $m^2$)] | 1.230 | 0.220 | | | | | |
| Lac (mmol/L) | 5.249 | <0.001 | 0.372 | 0.093 | <0.001 | 1.450 | 1.209-1.740 |
| HBP (ng/mL) | 8.359 | <0.001 | 0.087 | 0.014 | <0.001 | 1.090 | 1.061-1.121 |

Abbreviation: SE, standard error; OR, odds ratio; CI, confidence interval; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; LHD, lactate dehydrogenase; Scr, serum creatinine; BUN, blood urea nitrogen; D-D, D-Dimer; NT pro-BNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; PLT, platelet; NEU, neutrophil; eGFR, estimated glomerular filtration rate; Lac, lactic acid; HBP, heparin-binding protein.

ume, Scr, BUN, D-D, NT pro-BNP, PLT, or eGFR (all P>0.05).

In contrast, patients who developed MOF had significantly higher rates of abdominal infection ($x^2$=12.128, P<0.001), as well as elevated APACHE II scores (t=10.134, P<0.001), LDH (t=2.265, P=0.024), CRP (t=3.240, P=0.001), NEU (t=4.317, P<0.001), Lac (t=5.249, P< 0.001), and HBP (t=8.359, P<0.001).

*Multivariate analysis*

Variables with P<0.05 in the univariate analysis were included in the multivariate logistic regression model. The final analysis identified five independent predictors of MOF: abdominal infection, APACHE II score, NEU, Lac, and HBP (**Table 2**). The regression equation was as follows: log(P) = 0.888 × abdominal infection + 0.148 × APACHE II score + 0.051 × NEU + 0.372 × Lac + 0.087 × HBP - 17.405. The AUCs for each individual factor were 0.605, 0.694, 0.627, 0.673, and 0.748, respectively. The combined prediction model achieved an AUC of 0.850 (**Figure 1**).

*Nomogram construction*

A nomogram model for predicting the risk of MOF in patients with AKF and severe sepsis was constructed using R software based on five independent predictors (**Figure 2**). The risk probability of MOF can be $P = \frac{1}{1 + e^{-Log(P)}}$ calculated using the logistic regression model equation. Points are assigned based on the specific values of each variable listed. Each indicator is vertically aligned with its corresponding value on the bottom score line. The total score is the sum of the points for all indicators, and this score is located on the total score scale (Axis

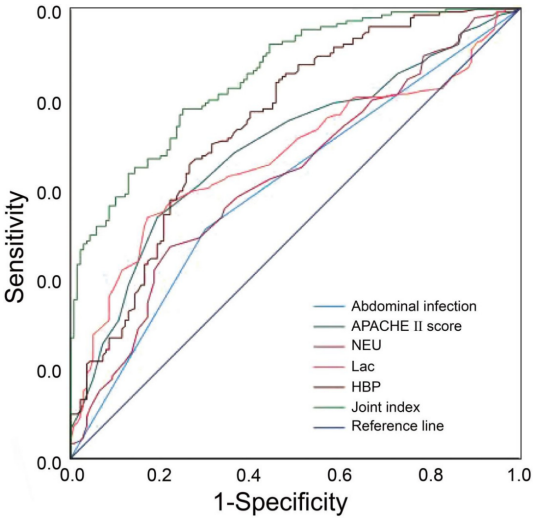


**Figure 1.** ROC analysis of risk factors and joint indicators. Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II; NEU, neutrophil; Lac, lactic acid; HBP, heparin-binding protein.

7). The total score is then projected vertically towards Axis 8, and a line is drawn downwards to determine the likelihood of the patient developing MOF.

*Internal validation*

Internal validation of the nomogram was performed by bootstrapping with 1,000 resamples from the training cohort. The calibration curve closely matched the ideal reference line (Hosmer-Lemeshow P=0.924) (**Figure 3A**). The AUC of the model was 0.756 (95% CI: 0.701-0.811), indicating good discrimination (**Figure 3B**). Decision curve analysis (DCA) showed a net benefit with a steep slope approaching 1, further supporting the clinical value of the model (**Figure 3C**).

*External validation*

External validation was conducted on 125 patients in the validation cohort. The calibration curve demonstrated good agreement with the ideal curve (Hosmer-Lemeshow P=0.238) (**Figure 4A**). The model yielded an AUC of 0.816 (95% CI: 0.743-0.889) in this cohort (**Figure 4B**). DCA also demonstrated substantial net clinical benefit (**Figure 4C**). Furthermore, predictive performance of the model in this cohort showed an accuracy of 79.20%, sensitivity of 82.86%, and specificity of 74.55% (**Table 3**).

## Discussion

This retrospective study analyzed baseline data from 418 patients with AKF and severe sepsis using a broad range of clinical indicators. Both univariate and multivariate logistic regression analyses were performed to identify risk factors for the development of MOF, leading to the construction of a predictive nomogram using R software. The model identified five independent predictors of MOF: abdominal infection, APACHE II score, NEU, Lac, and HBP, with the combined model demonstrating high predictive accuracy. The following section discusses each of these factors in greater detail.

Abdominal infections are pathophysiologically complex and often progress rapidly. Without timely assessment, these infections can lead to multi-organ dysfunction and, ultimately, death [12]. A large prospective cohort study by Arvaniti et al. reported that sepsis-related intra-abdominal infections were significantly associated with increased mortality, particularly in patients over 40 years old [13]. Our findings are consistent with this, confirming that intra-abdominal infection is an independent predictor of MOF in patients with AKF and severe sepsis.

The intestinal epithelium normally provides a crucial barrier against toxins and microbial invasion [14]. However, sepsis frequently compromises this barrier, causing mucosal injury and endothelial dysfunction, which increases vascular permeability [15]. Intra-abdominal infections, such as peritonitis or intestinal perforation, can trigger a systemic inflammatory response, allowing large quantities of bacteria, endotoxins, and other harmful agents to enter the bloodstream. These substances can directly stimulate renal endothelial and tubular epithelial cells, activating systemic immune responses and amplifying inflammation, thereby accelerating kidney damage and the development of MOF [16]. Once the intestinal barrier is disrupted, translocation of gut-derived bacteria further amplifies the systemic inflammatory cascade [17].

In addition, abdominal infections are often associated with metabolic derangements. When combined with the impaired renal excretory function typical of AKF in sepsis, the resulting toxin accumulation can further compromise the

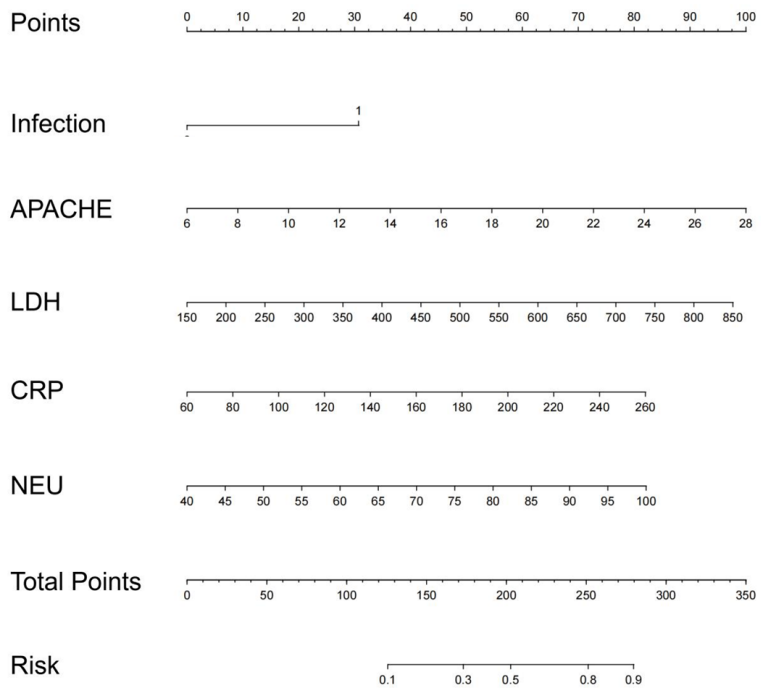


**Figure 2.** Nomogram prediction model. Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II; LHD, lactate dehydrogenase; CRP, C-reactive protein; NEU, neutrophil.

liver, heart, and other organs. Therefore, for patients with AKF and sepsis due to abdominal infection, early identification of high-risk individuals and enhanced organ function monitoring are essential. Personalized treatment strategies should be implemented to reduce the risk of MOF and improve clinical outcomes.

The findings of this study demonstrated that an elevated APACHE II score was associated with an increased probability of MOF in patients with AKF and severe sepsis. The APACHE II score provides a comprehensive assessment of the patient's systemic physiological status. Tekin et al. reported that in a study of 202 elderly patients with sepsis, the APACHE II score was significantly correlated with mortality and could be effectively used to predict it [18]. Abnormalities in physiological parameters often reflect a systemic inflammatory response, with elevated inflammatory mediators in the circulation. This leads to vasodilatation and hypovolemia, exacerbating ischemia and perfusion insufficiency in organs sensitive to blood flow, such as the kidneys and heart, which are prone to metabolic disorders and functional failure [19]. Additionally, Zhao et al. demonstrated that a high APACHE II score indicates severe maloxygenation, leading to systemic hypoxia, pulmonary edema, and impaired gas exchange. This worsens the burden on the lungs and causes metabolic imbalances (e.g., pH, lactic acid, and electrolytes), which further increases the risk of concurrent MOF. A common disturbance in critically ill patients is metabolic or respiratory acidosis, which impairs cardiomyocyte function and disrupts sodium-calcium exchanger activity. This results in calcium ion accumulation and decreased myocardial contractility [20, 21].

Elevated NEU is another independent factor influencing MOF development in AKF patients with severe sepsis. NEUs, as the body's primary defense against infection, play a critical role in sepsis diagnosis and differentiation [22]. Sepsis triggers a systemic inflammatory response that activates and migrates NEUs [23]. In the context of AKF and severe sepsis, excessive NEU activation drives tissue damage and MOF. This occurs through the release of oxygen free radicals by NEUs, which damage local and systemic tissues, especially renal endothelial and tubular cells. Furthermore, the increased expression of adhesion molecules during inflammation promotes NEU adhesion to blood vessel walls, leading to microvascular embolism and microcirculatory disturbances. These disturbances impair organ perfusion, worsening renal and other organ ischemia and injury [24]. Flora et al. found that activated NEUs release neutrophil extracellular traps (NETs) to capture and destroy microorganisms. However, excessive NET formation can promote platelet aggregation and endothelial cell coagulation, leading to fibrin production and microthrombosis [25].

Lac is a metabolite produced under anaerobic conditions and serves as a key indicator of hypoxic tissue damage [26]. Wu et al. reported that Lac is an independent prognostic factor for sepsis, consistent with our findings [26]. In sepsis, mitochondrial ATP production is reduced,

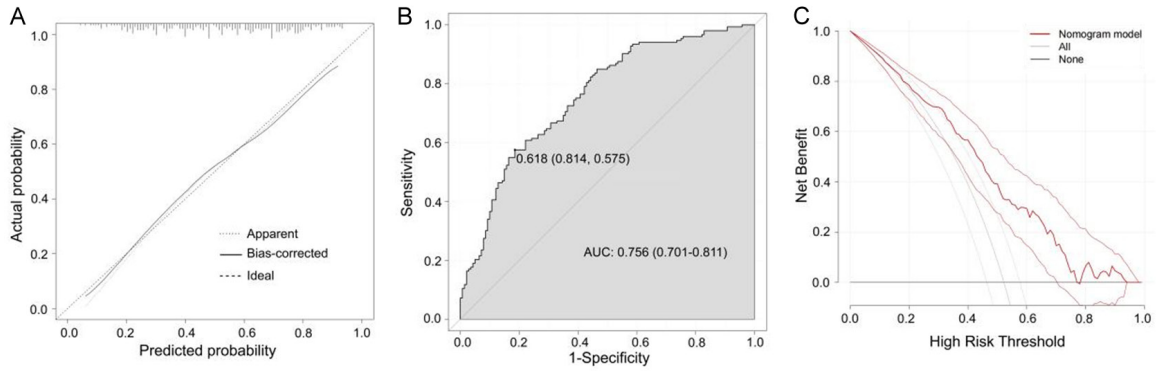


**Figure 3.** Internal validation of the predictive model. A. Calibration curve analysis; B. ROC analysis; C. DCA. Abbreviation: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

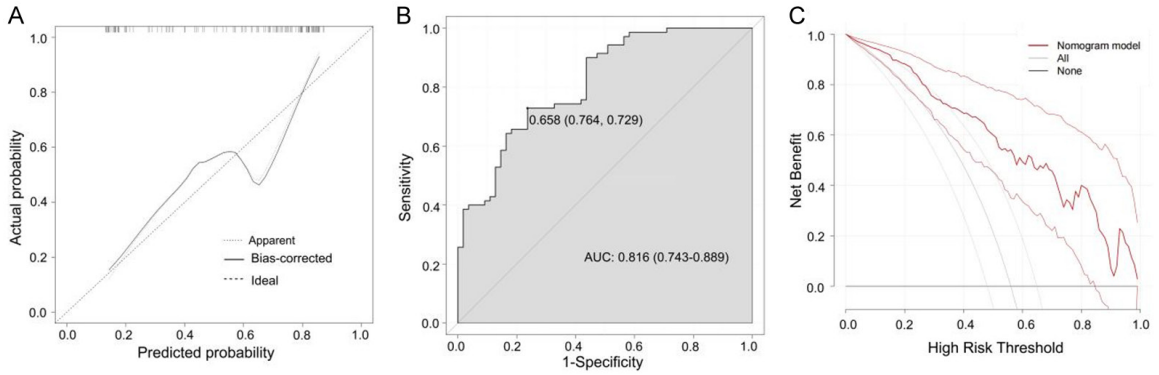


**Figure 4.** External validation of the predictive model. A. Calibration curve analysis; B. ROC analysis; C. DCA. Abbreviation: ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.

**Table 3.** Clinical validation of the nomogram

| Prediction result | Gold standard | | Total |
|---|---|---|---|
| | MOF | No MOF | |
| MOF | 58 | 14 | 72 |
| No MOF | 12 | 41 | 53 |
| Total | 70 | 55 | 125 |

Abbreviation: MOF, multiple organ failure.

prompting cells to rely more on anaerobic glycolysis, increasing lactate production [27]. In patients with AKF and severe sepsis, impaired lactate clearance results in accumulation, causing metabolic acidosis, which exacerbates organ oxygen deficiency, a key contributor to MOF [28]. Elevated lactate directly affects myocardial function by increasing cardiac workload, reducing oxidative metabolism, and impairing pumping function, raising the risk of heart failure. As lactate levels rise, lung oxygenation worsens, potentially leading to acute respiratory distress syndrome [29].

HBP, an inflammatory mediator secreted by neutrophils, plays a critical role in pathogen elimination and is involved in the progression of infection. Elevated serum HBP levels reflect infection severity and can predict patient outcomes [30]. Research has shown that elevated HBP is closely associated with MOF in severe sepsis [31]. Liu et al. found that elevated HBP levels not only reflect inflammation severity but also damage vascular endothelium, causing capillary leakage, microvascular thrombosis, and tissue edema, which exacerbate organ damage [32]. Moreover, elevated HBP promotes renal fibrosis [32, 33]. In AKF patients with severe sepsis, this cascade contributes to worsened renal failure and increases the risk of MOF. In the liver, elevated HBP exacerbates inflammation, leading to liver failure, while in the heart, it impairs endothelial function, disrupts cardiac microvasculature, and impedes recovery, elevating the risk of heart failure [34, 35].

However, the study has limitations. First, its retrospective nature may introduce unknown confounding factors. Second, the model was not externally validated, and its predictive accuracy requires validation with a larger cohort.

In conclusion, this study successfully developed a nomogram model based on five indicators to predict MOF occurrence in AKF patients with severe sepsis. The model demonstrated high predictive efficacy, with AUC values exceeding 0.7 in both the modeling and validation cohorts. Close monitoring of APACHE II score, NEU, Lac, and HBP levels is recommended to detect MOF early, allowing for timely interventions.

## Disclosure of conflict of interest

None.

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