

Development and Validation of a Nomogram for Predicting Acute Kidney Injury in Septic Patients

Li Zhao¹, Tuo Zhang², Xunliang Li³, Li Chen¹, Shenglin Zhou¹, Zhaoli Meng¹, Wei Fang¹, Jianle Xu⁴, Jicheng Zhang¹, Man Chen^{1,2}

¹Department of Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China; ²Department of Critical Care Medicine, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, 250021, People's Republic of China; ³Department of Intensive Care Unit, Central Hospital Affiliated to Shandong First Medical University, Jinan, 250013, People's Republic of China; ⁴Department of Statistics and Medical Records Management, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China

Correspondence: Jicheng Zhang; Man Chen, Department of Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324 Jingwu Weiqi Road, Jinan, Shandong, 250021, People's Republic of China, Email zhangjicheng2023@126.com; chenman_slyy@163.com

Purpose: Sepsis-associated acute kidney injury (S-AKI) is associated with increased morbidity and mortality. We aimed to develop a nomogram for predicting the risk of S-AKI patients.

Patients and Methods: We collected data from septic patients admitted to the Provincial Hospital Affiliated with Shandong First Medical University from January 2019 to September 2022. Septic patients were divided into two groups based on the occurrence of AKI. A nomogram was developed by multiple logistic regression analyses. The performance of the nomogram was evaluated using C-statistics, calibration curves, and decision curve analysis (DCA). The validation cohort contained 70 patients between December 2022, and March 2023 in the same hospital.

Results: 198 septic patients were enrolled in the training cohort. Multivariate logistic regression analysis showed that neutrophil gelatinase-associated lipocalin (NGAL), platelet-to-lymphocyte ratio (PLR), and vasopressor use were independent risk factors for S-AKI. A nomogram was developed based on these factors. C-statistics for the training and validation cohorts were respectively 0.873 (95% CI 0.825–0.921) and 0.826 (95% CI 0.727–0.924), indicating high prediction accuracy. The calibration curves showed good concordance. DCA revealed that the nomogram was of great clinical value.

Conclusion: The nomogram presents early and effective prediction for the S-AKI patients, and provides optimal intervention to improve patient outcomes.

Keywords: sepsis, acute kidney injury, neutrophil gelatinase-associated lipocalin, platelet-to-lymphocyte ratio, vasopressor use, nomogram

Introduction

Sepsis represents a life-threatening organ dysfunction caused by a dysregulated host response to infection,¹ with high morbidity and mortality.² Based on evidence from previous research, millions of people are suffering from sepsis every year around the world, and about one-sixth to one-third of those die of it.^{3–5} It has become one of the most challenging tasks for the healthcare system. Meanwhile, As the most common type of organ dysfunction, acute kidney injury (AKI) generally occurs in the early stage of sepsis.⁶ About two-thirds of patients with sepsis or septic shock develop AKI.⁷ Sepsis-associated acute kidney injury (S-AKI) is associated with increased mortality, longer ICU stay, ventilator use, increased hospitalization costs, and increased social burden.^{8–11} Therefore, early prediction of the high-risk population of S-AKI and helping doctors actively take appropriate preventive measures are of great practical significance for clinical practice.

At present, the diagnosis of AKI is mainly based on oliguria or elevated serum creatinine levels. However, the sCr level does not accurately reflect the renal injury in the early stage, which is influenced by tubular creatinine secretion and non-renal factors.^{12,13} At the same time, some departments cannot obtain urine output. For these reasons, some potential

markers for the early diagnosis of AKI have been under study in recent years., such as NGAL, uKIM-1, [TIMP-2]* [IGFBP7],^{14–16} however, due to the high cost and requirements of detection technology, these biomarkers have not been widely used in clinical practice. The evidence has shown that single biomarkers have certain deficiencies in the early prediction of S-AKI, with varying sensitivity and specificity.

A nomogram is a statistical tool for predicting individual-specific outcomes by transforming complex regression equations into visual graphs, helping clinicians identify high-risk patients.

Currently, most studies on predictive models of AKI risk are single-center and lack external validation, making it difficult to be widely generalized in the clinic.^{17–19} As a result, the goal of this study is to develop and validate an effective nomogram for early detection of S-AKI patients and prompt intervention measures.

Materials and Methods

This prediction model study is reported following the TRIPOD checklist.²⁰

Study Design and Participants

In this retrospective study, we included 553 consecutive patients with sepsis admitted to four intensive care units in Provincial Hospital Affiliated with Shandong First Medical University from January 2019 to September 2022. The Declaration of Helsinki guidelines were followed during the whole study. All enrolled patients agreed to participate in this study, and signed the informed consent form. According to whether AKI occurred within 7 days after diagnosis of sepsis, patients were divided into two groups: S-AKI group (n = 96) and Non-SAKI group (n = 102). The S-AKI group comprised sepsis patients who developed AKI during the first week. The inclusion criteria were as follows: (1) age ≥ 18 years old; (2) meeting the diagnostic criteria of Sepsis 3.0; (3) The length of ICU stay was > 24 h and the patient data were complete. The exclusion criteria were as follows: (1) Patients diagnosed with AKI before being admitted to ICU; (2) Patients with end-stage renal disease or current hemodialysis, or acute kidney injury induced by other causes except sepsis, or kidney transplantation; (3) Patients during pregnancy and lactation; (4) Patients with hematological disorders; (5) Patients who were hospitalized for less than 24h or died within 24h; (6) Patients with immunosuppressive or autoimmune disease, or long-term use of immunosuppressive agents; (7) Patients with malignancies; (8) Missing information. (Figure 1) The patients in the validation cohort were enrolled from January 2023 to March 2023 in the same hospital.

Definition

Sepsis was defined according to the standards of Sepsis 3.0,²¹ which means SOFA scores ≥ 2 points in cases of clear or suspected infection within 24 hours of admission. AKI was defined, per KDIGO guideline, as a rise in serum creatinine ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 h or an increase in creatinine levels ≥ 1.5 times from baseline within 7 days. Baseline creatinine was defined as the lowest serum creatinine value in the last 6 months before the onset of AKI, or the lowest value in patients who had not measured and were without dialysis during their hospitalization. S-AKI was defined as the occurrence of AKI within 7 days of sepsis onset.^{22,23}

Data Collection

Patient's baseline data were collected within 24h after being diagnosed with sepsis as follows: general characteristics including age, gender, smoking history, drinking history, hypertension, diabetes mellitus, cardiovascular disease, MAP, heart rate, temperature, APACHE II score, SOFA score. Laboratory data including WBC, RBC, Hb, NEUT%, LYM#, PLR, Cr, BUN, UA, NGAL, PT, APTT, FIB, D-D, ALT, AST, ALB, IL-6, PCT, Lac. Serum NGAL was measured by Latex Immunoturbidimetric Assay (the kits were purchased from Zhongtuo Biological Co., LTD., China). After venous blood samples were collected, the serum was obtained by centrifugation, and the operation was detected in strict accordance with the instructions of the kit. The therapeutic strategy includes mechanical ventilation, vasopressor use, hospital length of stay, and ICU stay. All variable data were obtained from the electronic medical record system of our hospital.

Outcomes

The primary outcome was the occurrence of S-AKI.

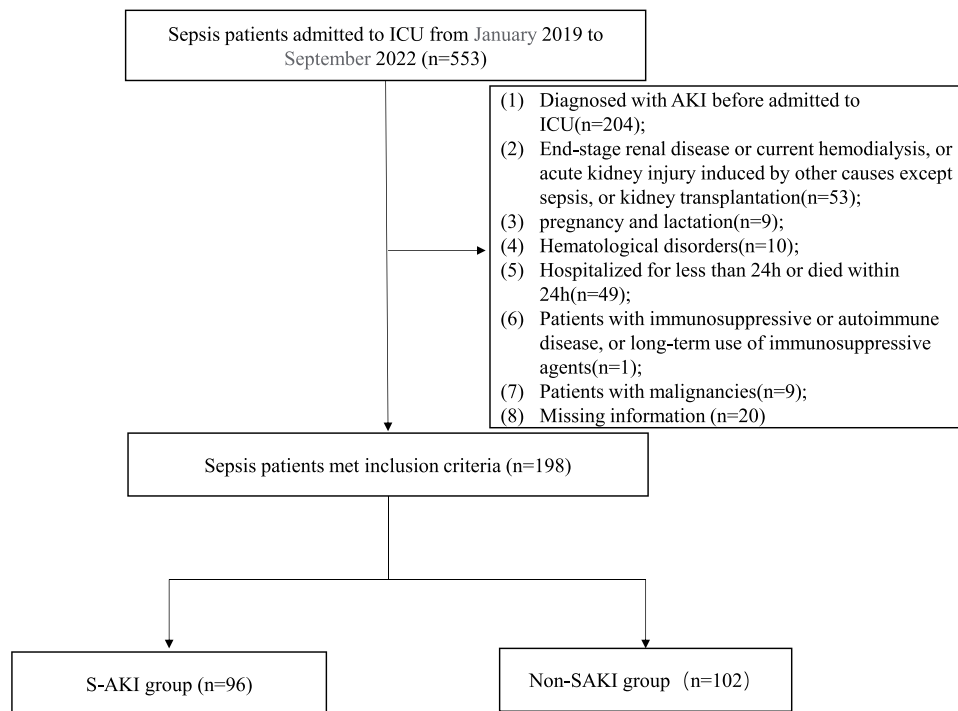


Figure 1 The flowchart of the study.

Statistical Analysis

Statistical analysis was done using SPSS 26.0 (IBM, Chicago, IL, USA) and R software (version 3.1.4; <http://www.Rproject.org>). The Confidence Intervals for One Proportion method of PASS 2021 software was used to calculate the sample size. The Shapiro–Wilk method was utilized to examine the normal distribution of continuous data. Continuous variables that conformed to normal distribution were compared using independent samples *t*-test and were expressed as mean \pm SD or median, Mann–Whitney *U*-test was used to determine the non-normally distributed variables, and they were presented as median (2nd–4th quartile), while Categorical variables were compared using Chi-square tests and expressed in frequencies and percentages (%). Through the comprehensive evaluation of the univariate and multivariate regression analyses, we finally selected the statistically significant indicators. Based on the multivariable logistic analysis, we constructed a nomogram for S-AKI. The concordance index (C-statistics) was used to evaluate the discriminative ability of the model. We evaluated the calibration of the model by calibration plots. Moreover, the decision curve analysis (DCA) was adopted to evaluate the clinical benefits and utility of the nomogram. In addition, the established nomogram was subjected to 1000 bootstraps resamples for internal validation and external validation to assess its predictive accuracy, the C-statistics was derived based on the regression analysis. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Patient Clinical Characteristics

The characteristics of the patients in the training and external validation cohorts are shown in [Table 1](#), including demographic characteristics, vital signs, and laboratory examinations. According to the inclusion and exclusion criteria, 198 patients were ultimately enrolled in the training cohort, among which 96 (48.5%) were S-AKI ([Supplementary Table 1](#)). 70 patients were eligible for inclusion in the external validation cohort, of which 52 (67.5%) were S-AKI.

Construction of the Nomogram

We used univariate and multivariate analyses to screen the prognostic factor. The univariate analysis revealed that RBC ($p=0.034$), PLR ($p<0.001$), Cr ($p = 0.002$), BUN ($p = 0.150$), UA ($p= 0.137$), NGAL ($p<0.001$), AST ($p=0.163$), IL-6

Table 1 Baseline Clinical and Laboratory for Training and External Validation Cohort

Characteristic	Training Cohort (N=198)	External Validation Cohort (N=77)	P
Age (years)	65(55,75)	66(52,76)	0.474
Gender n,(%)			0.637
Male	133(67.2)	54(70.1)	
Female	65(32.8)	23(29.9)	
Smoking history n,(%)			0.010*
Yes	79(39.9)	18(23.4)	
No	119(60.1)	59(76.6)	
Drinking history n,(%)			0.049*
Yes	82(41.4)	22(28.6)	
No	116(58.6)	55(71.4)	
Hypertension n,(%)			0.299
Yes	84(42.4)	38(49.4)	
No	114(57.6)	39(50.6)	
Diabetes mellitus n,(%)			0.666
Yes	59(29.8)	25(32.5)	
No	139(70.2)	52(67.5)	
Cardiovascular disease n,(%)			<0.001*
Yes	3(1.5)	14(18.2)	
No	195(98.5)	63(81.8)	
MAP(mmHg)	79(73,89)	84(72,93)	0.919
Heart rate (bpm)	97±16	98±21	0.200
T (°C)	37.2(36.7,37.7)	37.0(36.5,37.8)	0.902
Laboratory tests			
WBC (× 10 ⁹ /L)	11.95(7.54,15.95)	9.75(5.90,15.76)	0.195
RBC(×10 ¹² /L)	3.22(2.76,3.80)	3.01(2.50,4.09)	0.032*
Hb(g/L)	97(83,113)	95(75,125)	0.107
PLT(×10 ⁹ /L)	123(75,179)	116(67,183)	0.392
NEUT% (%)	88.50(82.70,92.43)	91.20(85.35,94.95)	0.728
LYM#(×10 ⁹ /L)	0.86(0.58,1.19)	0.71(0.36,1.07)	0.077
PLR	155(120,173)	174(158,188)	<0.001*
NLR	11.50 (7.46,18.69)	12.25 (8.17,21.52)	0.352
Cr(μmol/L)	68.80(52.53,98.55)	97.60(64.24,175.71)	<0.001*
BUN(mmol/L)	9.50(6.20,14.60)	12.30(8.40,18.90)	0.012*
UA(μmol/L)	211(138,321)	263(146,374)	0.032*
NGAL(ng/mL)	109(85,196)	149(125,166)	<0.001*
PT(s)	15.75(14.10,18.15)	15.70(14.70,18.45)	0.055
APTT(s)	41.10(34.38,50.83)	40.10(34.85,47.90)	0.366
Fib(g/L)	3.82(2.68,5.21)	4.42(3.29,5.93)	0.297
D-D(mg/L)	4.17(2.14,9.04)	3.56(1.76,8.27)	0.675
ALT(U/L)	30(15,75)	26(15,44)	0.159
AST(U/L)	39(21,119)	34(25,78)	0.025*
ALB(g/L)	30.7(27.0,34.5)	29.3(26.0,32.7)	0.755
IL-6(pg/mL)	112.9(57.43,313.33)	101.0(40.86,371.45)	0.036*
PCT(ng/mL)	1.98(0.51,10.32)	2.06(0.36,18.31)	0.076
PH	7.41(7.34,7.47)	7.43(7.35,7.48)	0.359
Lac(mmol/L)	1.7(1.1,3.1)	2.4(1.4,3.5)	0.001*
APACHE II score	19(13,25)	23(13,28)	0.359
SOFA score	7(5,11)	8(6,11)	0.013*

(Continued)

Table 1 (Continued).

Characteristic	Training Cohort (N=198)	External Validation Cohort (N=77)	P
Mechanical ventilation, n (%)			0.018*
Yes	158(79.8)	51(66.2)	
No	40(20.2)	26(33.8)	
Vasopressors use, n (%)			0.297
Yes	134(67.7)	47(61.0)	
No	64(32.3)	30(39.0)	
Hospital stay (days)	15(8,25)	12(5,21)	0.033*
ICU stay (days)	10(5,18)	9(4,15)	0.783
AKI, n(%)			0.004*
Yes	96(48.5)	52(67.5)	
No	102(51.5)	25(32.5)	

Note: *P < 0.05.

Abbreviations: MAP, mean arterial pressure; T, temperature; WBC, white blood cell; RBC, red blood cell; Hb, Hemoglobin; NEUT%, neutrophil percentage; LYM#, Lymphocytes; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; NGAL, neutrophil gelatinase-associated lipocalin; PT, partial thromboplastin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; D-D, D-Dimer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; IL-6, interleukin-6; PCT, serum procalcitonin; Lac, Lactate; APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment.

(p=0.051), Lac (p=0.074), SOFA score (p=0.015), mechanical ventilation (p<0.001), vasopressors use (p<0.001), hospital length of stay (p=0.633) were significant risk factors. Further multivariate regression analysis indicated that the variables included in the prediction model were PLR (p<0.001), NGAL (p<0.001), and vasopressors use (p<0.001) (Table 2). A nomogram was further generated to visualize the model (Figure 2).

Assessment and Validation of Nomogram

We assessed the ability of our final model to discriminate patients using C-statistics. The nomogram for predicting S-AKI in the training cohort had a C-statistic of 0.873 (95% CI: 0.825–0.921). The C-statistic remained stable in external validation (AUC=0.826 [95% CI 0.727–0.924]) (Figure 3).

Table 2 Univariate and Multivariate Analyses of Risk Factors for S-AKI

Variables	Univariate Analysis		Multivariate Analysis	
	OR(95% CI)	P	OR(95% CI)	P
RBC($\times 10^{12}/L$)	1.487(1.029–2.147)	0.034*	1.270(0.701,2.303)	0.431
PLR	1.011(1.005–1.017)	<0.001*	1.015(1.007–1.023)	<0.001*
Cr($\mu\text{mol}/L$)	10.10(1.004–1.016)	0.002*	1.000(0.991,1.009)	0.991
BUN(mmol/L)	1.028(0.990–1.067)	0.150		
UA($\mu\text{mol}/L$)	1.001(1.000–1.003)	0.137		
NGAL(ng/mL)	1.020(1.014–1.026)	<0.001*	1.023(1.016–1.030)	<0.001*
AST(U/L)	1.000(1.000–1.001)	0.163		
IL-6(pg/mL)	1.000(1.000–1.000)	0.051		
Lac(mmol/L)	1.080(0.993–1.175)	0.074		
SOFA score	1.098(1.019–1.183)	0.015*	1.137(0.962–1.344)	0.131
Mechanical ventilation (%)	4.221(1.886–9.446)	<0.001*	2.053(0.530–7.951)	0.298
Vasopressors use (%)	3.971(2.067–7.628)	<0.001*	6.302(2.616–15.181)	<0.001*

Note: *P < 0.05.

Abbreviations: RBC, red blood cell; PLR, platelet-to-lymphocyte ratio; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; NGAL, neutrophil gelatinase-associated lipocalin; AST, aspartate aminotransferase; IL-6, interleukin-6; Lac, lactate; SOFA, Sequential Organ Failure Assessment; OR, odds ratio; CI, confidence interval.

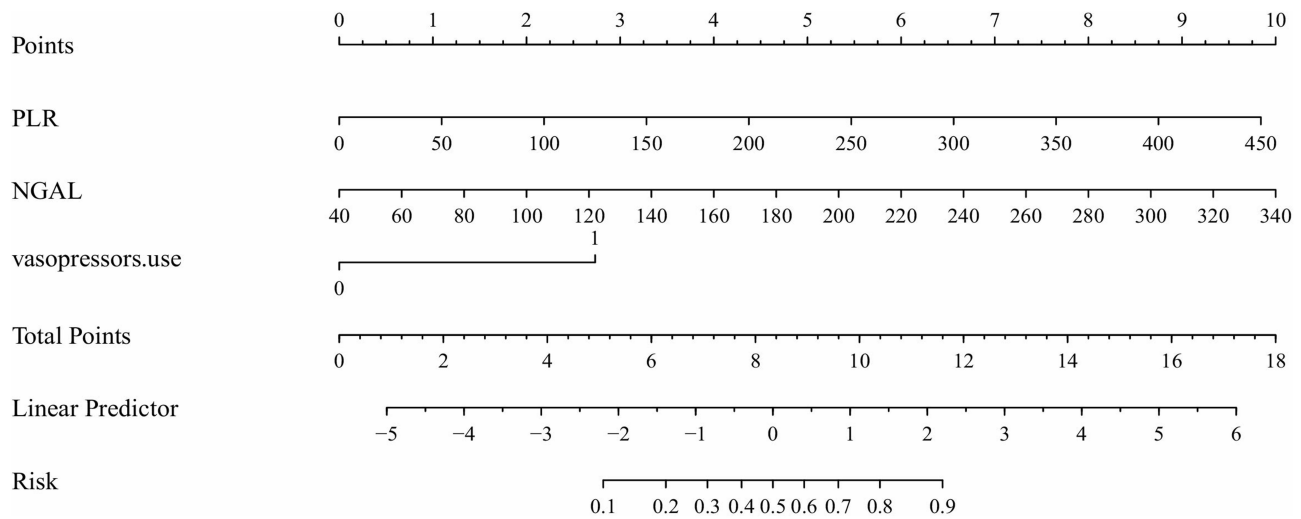


Figure 2 Nomogram to predict the risk of S-AKI.

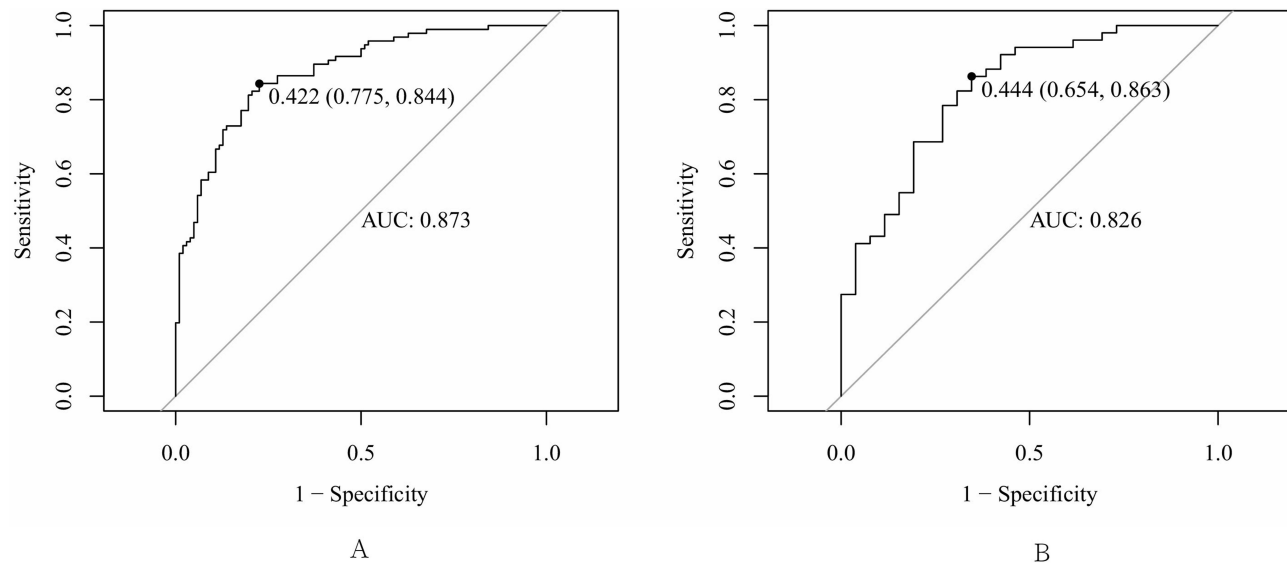


Figure 3 The verification ROC curve of internal validation of sepsis-associated AKI prediction model, the area under the curve was 0.873, the training cohort (A), the external validate cohort (B).

The nomogram was further internally validated. The calibration curves of the nomogram showed high consistencies between the predicted and observed values (Figure 4). To assess the clinical utility of the model, we conducted a decision curve analysis. As shown in Figure 5, the DCA demonstrated that the nomogram had superior overall net benefit within the wide and practical ranges of threshold probabilities, indicating high potential for clinical utility.

Discussion

We collected the clinical data of septic patients in our hospital retrospectively. Three variables (NGAL, PLR, vasopressors use) were identified by multivariable logistic regression and were incorporated into the nomogram for the identification of S-AKI patients. This nomogram had an excellent diagnostic performance (AUC: 0.873, sensitivity: 84.4%, and specificity: 77.5%). Furthermore, the study validated the model by internal and external data, and it also showed high discrimination ability and promising benefits in both datasets.

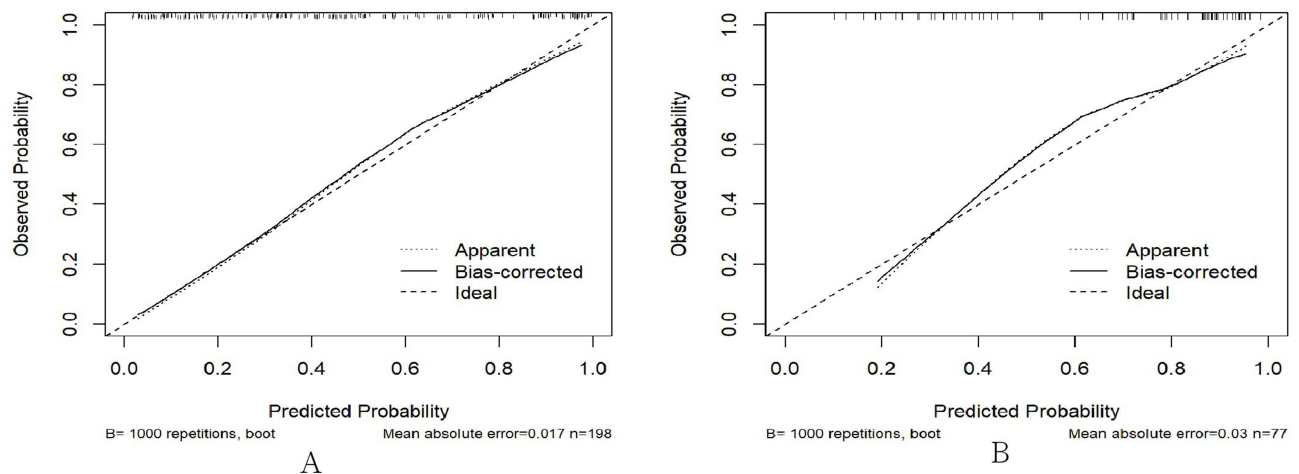


Figure 4 Calibration curves of a prediction model to predict the risk of S-AKI, the training cohort (A), the external validate cohort (B).

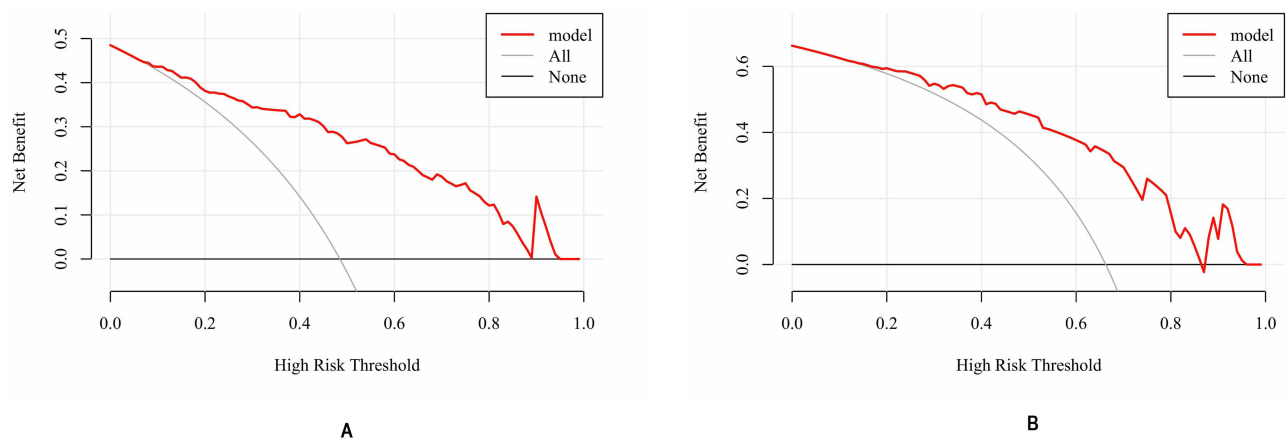


Figure 5 DCA curves of the prediction model to predict S-AKI, the training cohort (A), the external validate cohort (B).

Septic patients need to predict AKI in the early stage. In this study, we indicated that the serum NGAL had a significant difference between the S-AKI group and the Non-S-AKI group. Moreover, previous studies have demonstrated that serum NGAL in people with AKI was significantly higher than those without AKI before sepsis occurred within 72 hours, and exhibit different optimal cut-off values.²⁴ A comprehensive analysis also has shown that serum NGAL is a useful biomarker for diagnosing AKI with sepsis.²⁵ In this study, we advanced the onset of AKI to within 24 hours of the diagnosis of sepsis. However, a model of renal transplantation reported that the elevation of serum NGAL was not caused by tubular injury.²⁶ Since the pathophysiologic mechanism of S-AKI is still unclear, the predictive value of serum NGAL in the early stage of S-AKI needs to be further studied. In addition, we also need to pay more attention to determining the accuracy and optimal cut-off value of serum NGAL in predicting acute kidney injury in sepsis. At the same time, Other markers of renal injury may also be helpful in predicting AKI. When septic shock patients progress to AKI, integrating urinary [TIMP-2] \times [IGFBP7] into the staging of AKI helps distinguish patients with different outcomes.²⁷ An increase in proenkephalin A 119–159 at admission is associated with adverse renal outcomes, AKI, and worsening renal function in septic patients, but its predictive ability needs to be evaluated in comparison with serum NGAL, urinary TIMP-2, IGFBP7, etc.²⁸ Interestingly, obesity as a body fat marker may also increase the risk of early S-AKI,²⁹ expect to find more sensitive factors of kidney damage.

PLR is the ratio of platelet count to absolute lymphocyte count, which has been shown to correlate with the inflammatory response in sepsis,^{30–32} but little research has been done on it in S-AKI, and it still needs to be studied in depth. In this study, PLR was analyzed as an indicator, and it was found that PLR was an independent risk factor for S-AKI. As we all know, sepsis-associated excessive inflammation and clotting response in endothelial cells induces platelet activation. These activated platelets further aggravate coagulation dysfunction and systemic inflammation.^{33,34} When sepsis occurs, the immune system responds to the injury and apoptosis acts on injury-induced immunosuppression, with activated lymphocytes migrating to the site of inflammation and resulting in reduced lymphocyte count. Clinical studies have shown that lymphocyte counts decline as sepsis progresses, and persistent lymphocytopenia increases mortality in patients with sepsis.³⁵ Based on these theories, PLR was analyzed as an indicator in this study, and it was found that PLR was an independent risk factor for S-AKI. Therefore, PLR is a promising biomarker that can be easily applied to clinical practice to help predict the occurrence of S-AKI. Additionally, similar inflammatory markers include NLR, which has been shown to be associated with AKI progression and mortality, but the relationship between NLR and S-AKI was not found in this study, which may be affected by population heterogeneity.³⁶ Based on this, we hope that our study will provide a new idea for the discovery of pathophysiological mechanisms of S-AKI.

Apart from the biomarker, clinical therapy in sepsis also indicates that the disease may be more severe. This study found that the early use of vasopressors was associated with the occurrence of S-AKI. When S-AKI patients present with mean arterial pressure lower than 65 mmHg, perfusion to vital systemic organs is reduced, which can exacerbate tissue ischemia and hypoxia. In theory, vasopressors, as the first choice, can alleviate acute kidney injury during hypotension. However, the study demonstrated that the use of vasopressors can increase the risk of AKI.³⁷ According to the sepsis sheep model, vasopressor administration can be beneficial to a temporary recovery of renal function, but it may be more susceptible to increased underlying renal medullary hypoxia.^{38,39} However, another study in an animal model showed that restoring mean arterial pressure with vasopressin improved renal function more persistently than norepinephrine, meanwhile, it did not exacerbate medulla ischemia and hypoxia, and decrease mesenteric blood flow below baseline.⁴⁰ The difference in results may be related to the different types of vasopressors. This also suggests to clinicians that the optimal combination of vasopressors is different for individuals, and different vasopressors may respond differently to different phenotypes of shock. Unfortunately, our study was not designed to further compare the effects of different vasopressor agents on patients with S-AKI, and we will further refine the data in the future to find more accurate results. It is worth considering whether the conclusions obtained from animal studies are consistent with humans. Thus, A further prospective study is needed to clarify those issues.

To provide clinicians with an easy-to-use tool, we developed a nomogram that includes all three of these factors. Compared with other models on the early prediction of S-AKI, our model involves relatively few comprehensive metrics, which can be obtained in a short period and at less expense. We also validated our model internally and externally, showing sufficient discriminative power and better predictive performance. In other words, it can be used at the bedside to facilitate the assessment of S-AKI and reduce the burden on both doctors and patients. It has the potential to mitigate the risks associated with chronic renal insufficiency and mortality caused by septic AKI, thereby enhancing patient quality of life and improving long-term prognosis.⁴¹

There are some limitations to this study. First, as a retrospective, single-center study, it was inevitable to have potential bias. Second, the study included only one part of China's population, and the results cannot be extended to other groups yet, there are significance differences between the training and external validation cohort in various variables, which may affect the accuracy of the nomogram validation and cause bias. Thirdly, urine volume may not be reliable due to the use of diuretics, so urine volume was not a diagnostic criterion in this study, which may reduce the overall incidence of AKI. Given these limitations, we are now planning to expand the sample size of S-AKI patients, further, based on the current findings, exploring markers with clinical practicability and improving the model to optimize the prediction of S-AKI.

Conclusion

In this study, an early prediction model for S-AKI was developed and externally validated. Data on the three independent factors included in the model are easy and fast to obtain: NGAL, PLR, and vasopressor. With sufficient performance and discrimination, the novel nomogram might help clinicians identify the risk of S-AKI and carry out necessary interventions to improve patient outcomes and reduce social and family burdens.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author Man Chen.

Ethics Approval and Consent to Participate

This study received approval from the Human Research Ethics Committee of the Provincial Hospital Affiliated with Shandong First Medical University (No. 2023-071).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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