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Risk prediction model for acute kidney injury in elderly sepsis patients based on MIMIC-IV database

FANG Chuntian*, LIU Dongmei

**Department of Nephrology, the 940th Hospital of Joint Logistics Support Force of PLA, Lanzhou, Gansu 730050, China*

Corresponding author: LIU Dongmei, E-mail: liudongmeilz@163. com

Abstract: Objective To investigate the risk factors for acute kidney injury (AKI) in elderly septic patients, construct a predictive model for AKI in elderly septic patients, and validate the predictive value of the model. Methods A retrospective cohort study was conducted using the data from hospitalized elderly septic patients collected in the Medical Information Mart for Intensive Care-IV 2.2 (MIMIC-IV 2.2) database. Demographic, clinical and laboratory data were collected. The patients were randomly divided into a training set and a validation set at a 7:3 ratio. Feature selection was performed in the training set using the least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation, followed by logistic regression analysis to establish a predictive model for AKI in elderly septic patients and a nomogram. The model was then validated in the validation set. The predictive value of the model was evaluated using the receiver operating characteristic (ROC) curve and the clinical impact curve (CIC) . Results A total of 5 792 elderly septic patients was included, of which 4 888 developed AKI (incidence rate: 84.4%) . Multivariate logistic regression analysis revealed that mechanical ventilation (*OR*=2.115, 95%*CI*:1.722-2.598), congestive heart failure (*OR*=2.237, 95%*CI*:1.771-2.824), body mass index (BMI) (*OR*=1.108, 95%*CI*:1.09-1.13), activated partial thromboplastin time (APTT) (*OR*=1.010, 95%*CI*:1.004-1.017), lactic acid level (*OR*=1.114, 95%*CI*:1.018-1.225), Acute Physiology Score (APS) (*OR*=1.025, 95%*CI*:1.020-1.031), arterial partial pressure of oxygen (PaO_2) (*OR*=1.003, 95%*CI*:1.002- 1.004), and urine output (*OR*=0.942, 95%*CI*:0.932- 0.951) were independent influencing factors for the development of AKI ($P<0.05$) . A static nomogram for predicting AKI in elderly septic patients was constructed based on these eight variables. In the training set, the area under the ROC curve (AUC) of the nomogram for predicting the occurrence of AKI in sepsis patients was 0.803 (95%*CI*:0.786-0.821), with a sensitivity of 0.733 and specificity of 0.726, and an optimal cut-off value of 0.829, indicating that the model had moderate discriminatory ability. The Hosmer-Lemeshow test showed good calibration of the predictive model ($P=0.976$). The CIC also demonstrated that the model had good clinical utility. Conclusion Urine output, congestive heart failure, BMI, APTT, lactate, PaO_2, APS, and mechanical ventilation are the main influencing factors for AKI in elderly septic patients. The predictive model for AKI in elderly septic patients, based on these factors, can help clinicians identify high-risk patients early and provide timely interventions.

Keywords: Elderly; Sepsis; Acute kidney injury; Medical Information Mart for Intensive Care-IV 2.2 database; Nomogram; Acute Physiology Score; Activated partial thromboplastin time; Congestive heart failure; Mechanical ventilation

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and is a leading cause of mortality in critically ill patients [1]. Approximately 49.89 million sepsis cases and 11 million sepsis-related deaths are reported annually, accounting for 19.7% of all global deaths [2]. Acute kidney injury (AKI) is recognized as a common and complex clinical complication of sepsis, affecting up to 60% of septic patients [3]. Compared to non-AKI patients, sepsis-associated acute kidney injury (SA-AKI) is closely associated with poorer prognosis, prolonged intensive care unit (ICU) stay, reduced quality of life, and increased risk of death [4]. With the global population aging, currently about 700 million people are aged 65 years or older, representing 9% of the total population, and this proportion is projected to increase to 17% by 2050 [5]. Age is considered an independent risk factor for mortality in both sepsis and AKI [6]. Patients over 65 years old have a significantly worse prognosis for AKI compared to younger patients [7]. Elderly SA-AKI patients are critically ill, and the early identification of elderly septic patients at high risk for AKI is crucial for influencing outcomes and prognosis. Previous research using the Medical Information Mart for Intensive Care (MIMIC)-III database developed a prediction model for AKI in 15,726 septic patients, which demonstrated good predictive accuracy with a C-index of 0.711 (95%*CI*: 0.702-0.721) [8]. This study aims to utilize the MIMIC-IV database to develop and validate a prediction model for AKI occurrence in elderly septic patients, intending to assist clinicians in the early identification of high-risk patients and potentially improve patient outcomes.

1 Materials and Methods

1.1 Data Source

The data for this study were sourced from MIMIC-IV version 2.2 [9], jointly developed by the MIT and Beth Israel Deaconess Medical Center. All patient data in this study were anonymized, thus obviating the need for informed consent and ethical approval statements. The researcher of this study passed the Collaborative Institutional Training Initiative program exam and obtained certification (Certificate ID: 12871705).

1.2 Inclusion and Exclusion Criteria

(1) Inclusion Criteria: ① First ICU admission; ② Age ≥ 65 years; ③ Diagnosed with sepsis according to the Sepsis-3.0 criteria; ④ ICU length of stay ≥ 48 hours.

(2) Exclusion Criteria: ① Occurrence of AKI prior to ICU; ② History of chronic kidney disease or kidney transplantation; ③ History of immunodeficiency diseases such as AIDS; ④ Data missingness exceeding 20%.

1.3 Data Extraction and Study Endpoint

Data were extracted from the MIMIC-IV v2.2 database using Navicat Premium 16.0 software, including:

(1) Demographic data: Age, gender, body mass index (BMI), type of hospital admission, and comorbidities. (2) Vital signs within the first 24 hours of ICU admission: Temperature, heart rate, respiratory rate, mean arterial pressure (MAP), urine output, oxygen saturation. (3) Laboratory test results within the first 24 hours of ICU admission: Including complete blood count, blood biochemistry, coagulation profile, arterial blood gas analysis, etc. (4) Scores within the first 24 hours of ICU admission: Acute Physiology Score (APS), Sequential Organ Failure Assessment (SOFA), Glasgow Coma Scale (GCS). (5) Treatment within the first 24 hours of ICU admission: mechanical ventilation, renal replacement therapy (RRT).

Additionally, multiple imputation was used to handle missing data. Variables with more than 20% missing values were excluded. The study outcome was the occurrence of AKI within 7 days in elderly septic patients. AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

1.4 Statistical Methods

Data analysis was performed using R software (version 4.4.2). The Shapiro-Wilk test was used to assess the normality of continuous variables. Non-normally distributed data are presented as $M(P_{25},P_{75})$ and compared using the Mann-Whitney *U* test. Categorical data are presented as *n*(%) and compared using the Chi-square test. A *P*-value < 0.05 was considered statistically significant. The study subjects were randomly divided into a training set and a validation set in a 7:3 ratio. The Least Absolute Shrinkage and Selection Operator (LASSO) regression with 10-fold cross-validation was used for preliminary variable dimensionality reduction. Univariate and multivariate logistic regression were used to construct the prediction model. The model was built on the training set and validated on the validation set. The discriminative ability of the model was assessed using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). The clinical impact curve (CIC) was used to evaluate the clinical utility.

2 Results

2.1 Clinical Baseline Data

A total of 5,792 elderly septicemia patients who were hospitalized were included, among which 4,888 patients (84.39%) developed AKI within 7 days. The patients had a median age of 76.00 (range: 70.00 to 83.00) years. A total of 95 patients (1.64%) received continuous renal replacement therapy within 24 hours, and 2,986 patients (51.55%) received mechanical ventilation within 24 hours. There were no statistically significant differences between the baseline data of the training and validation groups (except for urine output, red blood cell count, hemoglobin, 24-hour GCS score, and 24-hour SOFA score) (*P*>0.05). See **Table 1**.

Tab.1 Comparison of baseline characteristics between training set and validation set for elderly sepsis patients [$M(P_{25},P_{75})$]

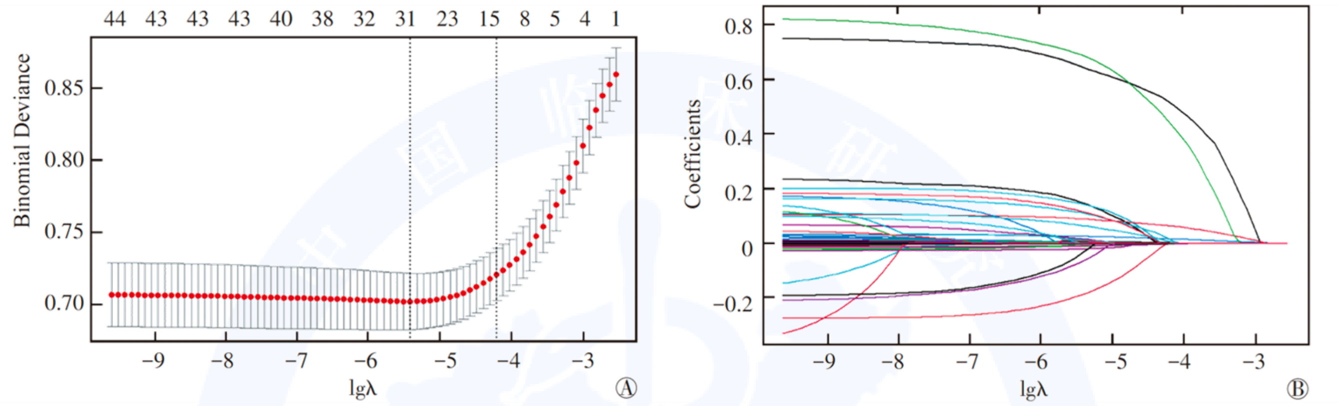
Variable	Training set (*n*=4 054)	Validation set (*n*=1 738)	$\chi^2/Z/t$ value	*P* value
SA-AKI [*n*(%)]	3 429(84.58)	1 459(83.95)	0.374	0.541
Male [*n*(%)]	2 121(52.32)	888(51.09)	0.732	0.392
Age (years)	76.00(70.00,83.00)	76.00(70.00,83.00)	1.726	0.189
BMI (kg/m²)	27.34(23.56,31.61)	27.12(23.46,31.67)	0.059	0.809
Underlying Disease [*n*(%)]				
CHF	1 315(32.44)	579(33.31)	0.425	0.514
Peripheral Vascular Disease	584(14.41)	232(13.35)	1.123	0.289
Chronic Lung Disease	1 213(29.92)	502(28.88)	0.628	0.428
Diabetes	1 153(28.44)	481(27.68)	0.352	0.553
Chronic Liver Disease	353(8.71)	166(9.55)	1.062	0.303
Malignant Tumor	697(17.19)	315(18.12)	0.732	0.392
Hypertension	2 611(64.41)	1 161(66.80)	3.073	0.480
Temperature (°C)	36.83(36.57,37.15)	36.83(36.57,37.15)	0.139	0.709
Heart Rate (bpm)	83.90(74.86,95.63)	83.80(75.12,94.99)	0.034	0.854
Respiratory Rate (breaths/min)	19.08(16.85,22.00)	18.93(16.80,22.09)	0.615	0.433
MAP (mmHg)	74.50(69.41,81.16)	74.48(69.20,81.16)	0.024	0.877
SpO_2 (%)	97.36(95.85,98.61)	97.42(95.95,98.73)	1.460	0.227
PaO_2 (mmHg)	150.50(97.00,236.00)	149.00(97.00,237.88)	0.150	0.699
Oxygenation Index (mmHg)	240.00 (172.80,314.00)	237.00 (165.44,316.63)	0.587	0.444
Blood Glucose (mg/dL)	133.97(116.50,161.69)	133.82(117.76,159.11)	0.011	0.917
Blood Lactate (mmol/L)	1.85(1.35,2.65)	1.85(1.35,2.60)	<0.001	0.991
Urine Output (mL)	1 415.00 (900.00,2 098.75)	1 475.00 (940.00,2 168.75)	4.619	0.032
Laboratory Indicators				
WBC (×10⁹/L)	12.10(8.95,15.97)	12.10(8.90,16.10)	0.440	0.507
RBC (×10¹²/L)	3.48(3.11,3.96)	3.46(3.07,3.90)	6.144	0.013
Platelet (×10⁹/L)	180.00(130.68,245.46)	179.25(130.75,245.33)	<0.001	0.996
Hemoglobin (g/L)	10.50(9.35,11.80)	10.33(9.20,11.70)	6.270	0.012
ALT (u/L)	28.00(17.00,63.00)	27.00(16.50,56.50)	1.824	0.177
ALP (u/L)	78.00(58.00,115.00)	78.00(59.00,117.50)	0.602	0.438
AST (u/L)	44.00(27.00,102.00)	43.00(27.00,98.50)	0.265	0.606
BUN (mg/dL)	20.50(15.00,31.00)	20.50(15.00,30.50)	0.488	0.485
SCr (mg/dL)	0.95(0.75,1.30)	0.95(0.75,1.30)	0.358	0.550
INR	1.30(1.15,1.50)	1.30(1.15,1.50)	0.016	0.899
PT (s)	14.30(12.80,16.65)	14.35(12.80,16.70)	0.035	0.852
APTT (s)	31.60(27.55,40.30)	31.80(27.60,40.45)	0.417	0.518
24-hour SOFA	3.00(2.00,4.00)	3.00(2.00,4.00)	3.971	0.046
24-hour APS	53.00(39.00,72.00)	52.00(38.00,71.00)	0.508	0.476
24-hour GCS	15.00(15.00,15.00)	15.00(15.00,15.00)	7.554	0.006
Treatment within 24 hours [*n*(%)]				
RRT	70(1.73)	25(1.44)	0.627	0.429
Mechanical Ventilation	2 089(51.53)	897(51.61)	0.003	0.955

2.2 Preliminary Screening of AKI Characteristics in Elderly Sepsis Patients

Variables to be included were dimension-reduced using LASSO regression to extract important predictive factors (**Figure 1**). Nine variables were found to be closely associated with the development of AKI in elderly septicemia patients, including congestive heart failure (CHF), temperature, BMI, arterial oxygen partial pressure (PaO_2) blood lactate, urine output, activated partial thromboplastin (APTT), APS, and mechanical ventilation.

2.3 Univariate and Multivariate Logistic Regression Analysis

The results of univariate analysis showed that all 9 variables included in the LASSO regression analysis were independent risk factors for the development of AKI in elderly septicemia patients (P<0.01). These variables were all included in a multivariate logistic regression analysis. The results indicated that urine output, concomitant CHF, BMI, PaO_2, blood lactate, APTT, APS score, and mechanical ventilation were independent risk factors for AKI in elderly septicemia patients (P<0.05). See **Table 2**.



Note: (A) Lasso regression cross-validation plot. (B) Lasso regression variable selection path plot.

Fig.1 LASSO regression feature dimensionality reduction diagram

Tab.2 Univariable and multivariable logistic regression analysis of AKI in elderly patients with sepsis

Variable	Univariable logistic regression analysis				Multivariable logistic regression analysis			
	β	*SE*	*OR*(95%*CI*)	*P* value	*β*	*SE*	*OR*(95%*CI*)	*P* value
APS score	0.028	0.002	1.029 (1.024, 1.033)	<0.001	0.025	0.003	1.025 (1.020, 1.031)	<0.001
Mechanical Ventilation	0.882	0.092	2.416 (2.017, 2.893)	<0.001	0.749	0.105	2.115 (1.722, 2.598)	<0.001
BMI	0.084	0.008	1.087 (1.071, 1.104)	<0.001	0.102	0.009	1.108 (1.089, 1.127)	<0.001
APTT	0.016	0.003	1.016 (1.010, 1.022)	<0.001	0.01	0.003	1.010 (1.004, 1.017)	0.001
MAP	-0.027	0.004	0.973 (0.965, 0.982)	<0.001				
blood lactate	0.273	0.043	1.314 (1.212, 1.433)	<0.001	0.108	0.047	1.114 (1.018, 1.225)	0.022
PaO_2	0.003	0.001	1.003 (1.001, 1.004)	<0.001	0.003	0.001	1.003 (1.002, 1.004)	<0.001
urine output	-0.05	0.004	0.951 (0.942, 0.961)	<0.001	-0.06	0.005	0.942 (0.932, 0.951)	<0.001
CHF	0.766	0.107	2.150 (1.751, 2.659)	<0.001	0.805	0.119	2.237 (1.771, 2.824)	<0.001

2.4 Nomogram Prediction Model Construction

A nomogram was constructed based on the results of the multivariate logistic regression analysis. See **Figure 2**. For each indicator, a vertical line is drawn to the scoring axis to obtain the score. The scores are then summed to give a total score. The corresponding probability of AKI occurrence in septicemia patients is obtained by drawing a vertical line down from the total score. This model can be used to predict the risk of AKI in elderly septicemia patients in clinical settings.

2.5 Evaluation and Internal Validation of the Nomogram Model

In both the training and validation sets, the AUC of the nomogram was 0.803 (95% *CI*: 0.786–0.821) and 0.779 (95% *CI*: 0.753–0.804), respectively. See **Figure 3.** This indicates that the nomogram model has good discrimination. The calibration curve of the prediction model shows a good consistency between the predicted and observed outcomes in both the training and internal validation sets. The Hosmer-Lemeshow test showed P-values of 0.976 and 0.079, both greater than 0.05, indicating no significant difference. The CIC curve was used to evaluate the clinical utility of the nomogram. The CIC curve demonstrates that the prediction model provides greater net benefit than both the "all intervention" or "no intervention" strategies. See Figures 3B and 3C.

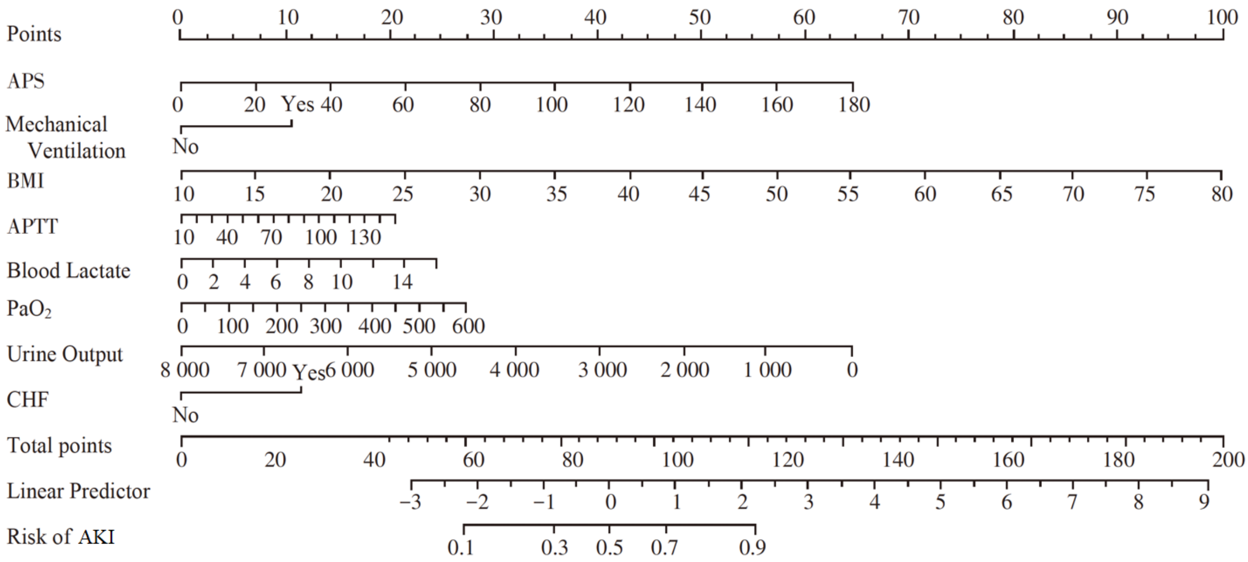
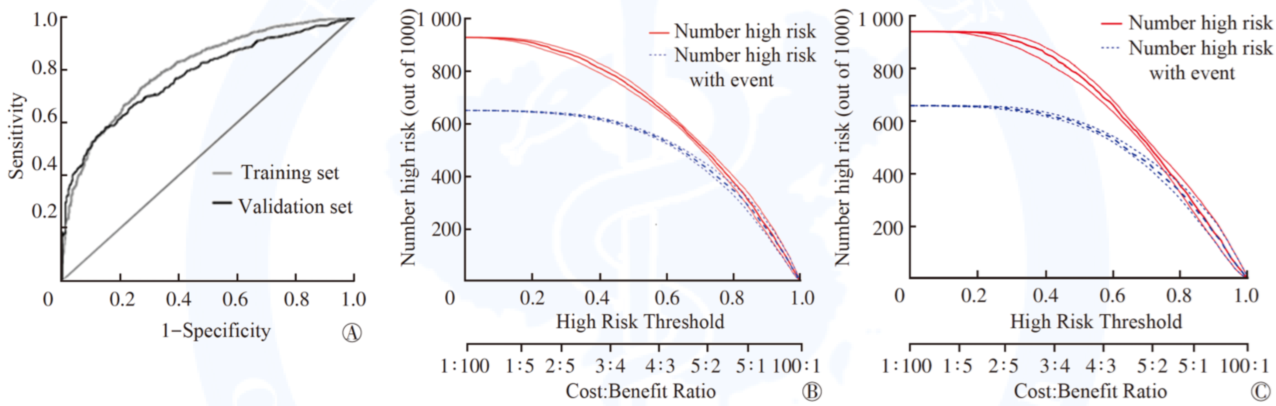


Fig.2 Nomogram for predicting AKI in elderly sepsis patients



Note: A, ROC of nomogram; B, CIC of training set; C, CIC of validation set.

Fig.3 ROC and CIC of the nomogram for SA-AKI in elderly sepsis patients

3 Conclusion

AKI is common in critically ill patients and is closely associated with adverse outcomes [10]. In the elderly, the structure and function of various organs and tissues gradually degenerate, compounded by a high prevalence of underlying diseases, making them highly susceptible to multiple organ dysfunction following sepsis [11]. Early identification of elderly septic patients at high risk for AKI and initiating active treatment play a crucial role in improving prognosis. Constructing disease prediction models is an effective management strategy for septic patients [12]. This study developed a nomogram model to predict the risk of AKI in elderly septic patients. The model incorporates eight variables: APS, mechanical ventilation, BMI, APTT, blood lactate, PaO_2, urine output, and CHF, which can be used to assess the risk of AKI development in this population.

Urine output, as a direct reflection of renal function, often serves as an early signal of inadequate renal perfusion or functional impairment. In the context of CHF, the heart fails to pump blood effectively to the kidneys. To maintain internal environmental stability, the kidneys initiate a series of compensatory mechanisms. When cardiac function continues to deteriorate and these compensatory mechanisms can no longer offset the insufficient renal perfusion, AKI can be triggered. Jiang *et al.* [13] found that CHF is a risk factor for AKI in critically ill patients, which is consistent with the findings of this study. During the pathophysiology of sepsis, systemic inflammatory responses can lead to vascular endothelial dysfunction, microcirculatory disturbances, and hemodynamic changes [14]. These alterations reduce effective renal perfusion and decrease the glomerular filtration rate. CHF can exacerbate these effects, consequently leading to a decrease in urine output.

BMI, an indicator of nutritional status and overall health, significantly influences the risk of mortality and organ damage in septic patients, whether it is increased or decreased. Some studies have indicated that obese septic patients are more prone to developing AKI compared to patients with normal weight [15]. Yue *et al.* [16] also found that BMI values were significantly higher in SA-AKI patients than in those with sepsis alone, further supporting that obesity may contribute to AKI in septic patients.

APS is part of the acute physiological score within the APACHE II scoring system, including parameters such as temperature, MAP, heart rate, respiratory rate, and PaO_2 [17]. Research has shown that a high APS score is a risk factor for the progression of sepsis to chronic critical illness [18]. Patients with chronic critical illness often have multiple organ dysfunction, including AKI. Pérez-Fernández *et al.* [19] also found that APS was associated with 90-day mortality in SA-AKI patients.

PaO_2, lactate, and the use of mechanical ventilation all reflect the body's oxygenation status. When PaO_2 falls below the normal range and cannot be improved through oxygen delivery via a mask, mechanical ventilation becomes necessary for oxygen support. Lactate levels represent the hypoxic state within the internal environment; previous studies have shown that elevated lactate levels are a risk factor for increased incidence of SA-AKI [20]. Gong *et al.* [21] found that when lactate levels were ≥ 2.75 mmol/L, the risk of AKI in septic patients increased by 1.772 times (*OR*=2.772). Hypoxia leads to an increased incidence of SA-AKI in elderly patients. The reason may be that a hypoxic state inhibits aerobic metabolism in renal cells and increases anaerobic metabolism, leading to a series of pathophysiological changes such as intracellular acidosis and reduced ATP production [22], ultimately triggering AKI.

Coagulation dysfunction is a common systemic manifestation in septic patients, often presenting as prolonged APTT and abnormalities in platelet morphology and count. The hypercoagulable state can lead to microthrombus formation, further aggravating renal injury and systemic multi-organ damage [23]. One study showed that elevated APTT is an independent risk factor for AKI, and the APTT value has certain predictive value for the short-term mortality risk in SA-AKI patients [24], which aligns with the results of this study.

This study has several limitations. First, it is a single-center retrospective study lacking external validation, which may limit its clinical generalizability. Second, regarding the handling of missing data, this study used multiple imputation for continuous variables and nearest neighbor imputation for ordinal data, which might introduce dataset errors. Finally, there is the issue of included clinical indicators; due to the absence of some variables, not all potential risk factors could be incorporated.

In summary, the risk prediction model developed in this study demonstrates good discriminatory ability for identifying AKI within 7 days in elderly septic patients. It incorporates eight variables that are readily available in hospital settings. Clinicians can use this model to calculate the individual risk of AKI in elderly septic patients. The visualization of the prediction model via a nomogram makes it easier to apply in clinical practice.

Author contributions

FANG Chuntian was responsible for the study conception, design and implementation, manuscript writing, data collection and analysis, quality control and review of the article and is the guarantor for the overall content. LIU Dongmei was responsible for the design and implementation, revised the manuscript.

Conflict of Interest None

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·论　著·

基于MIMIC-Ⅳ数据库的老年脓毒症患者急性肾损伤风险预测模型

方春天[1]，　刘冬梅[2,3]

1. 中国人民解放军联勤保障部队第九四〇医院肾内科，甘肃 兰州 730050；
2. 中国人民解放军联勤保障部队第九四〇医院重症医学科，甘肃 兰州 730050；
3. 西北民族大学医学部，甘肃 兰州 730050

摘要：目的　探讨老年脓毒症患者发生急性肾损伤（AKI）的危险因素，构建老年脓毒症患者发生AKI的预测模型并验证模型的预测价值。**方法**　以美国重症监护医学信息数据库-Ⅳ 2.2（MIMIC-Ⅳ 2.2）中收录的住院老年脓毒症患者数据进行回顾性队列研究。收集患者人口学、临床和实验室数据。按7∶3随机分为训练集和验证集。在训练集中使用10折交叉验证的最小绝对收缩和选择算法（LASSO）回归进行特征选择，然后进行logistic回归分析建立老年脓毒症并发AKI的预测模型并绘制列线图，并在验证集中验证。通过受试者工作特征曲线（ROC）、临床影响曲线（CIC）评价预测模型的预测价值。**结果**　共纳入5 792例老年脓毒症患者，其中4 888例发生AKI（发生率84.4%）。多因素logistic回归分析显示，机械通气（*OR*=2.115，95%*CI*：1.722~2.598）、充血性心力衰竭（*OR*=2.237，95%*CI*：1.771~2.824）、身体质量指数（BMI）（*OR*=1.108，95%*CI*：1.09~1.13）、活化部分凝血活酶时间（APTT）（*OR*=1.010，95%*CI*：1.004~1.017）、乳酸水平（*OR*=1.114，95%*CI*：1.018~1.225）、急性生理学评分（APS）（*OR*=1.025，95%*CI*：1.020~1.031）、动脉血氧分压（PaO_2）（*OR*=1.003，95%*CI*：1.002~1.004）、尿量（*OR*=0.942，95%*CI*：0.932~0.951）是AKI发生的独立影响因素（*P*<0.05）。结合以上8个变量绘制老年脓毒症患者发生AKI预测模型的静态列线图。训练集中列线图预测脓毒症患者发生AKI的ROC曲线下面积（AUC）为0.803（95%*CI*：0.786~0.821），灵敏度为0.733，特异度为0.726，最佳截断值为0.829，提示该模型区分度尚可；Hosmer-Lemeshow检验显示，预测模型有较好的校准能力（*P*=0.976）。CIC曲线亦证明该模型具有良好的临床效用。**结论**　尿量、充血性心力衰竭、BMI、APTT、乳酸、PaO_2和APS以及机械通气是老年脓毒症患者发生AKI的主要影响因素，基于上述因素构建的老年脓毒症并发AKI的预测模型能够帮助临床医生尽早识别高危患者，并及时干预。

关键词：老年；脓毒症；急性肾损伤；美国重症监护医学信息数据库-Ⅳ；列线图；急性生理学评分；活化部分凝血活酶时间；充血性心力衰竭；机械通气

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Risk prediction model for acute kidney injury in elderly sepsis patients based on MIMIC-Ⅳ database

FANG Chuntian*，LIU Dongmei

**Department of Nephrology，the 940th Hospital of Joint Logistics Support Force of PLA，Lanzhou，Gansu 730050，China*

Corresponding author：LIU Dongmei，E-mail：liudongmeilz@163.com

Abstract：Objective　To investigate the risk factors for acute kidney injury（AKI）in elderly septic patients，construct a predictive model for AKI in elderly septic patients，and validate the predictive value of the model. **Methods**　A retrospective cohort study was conducted using the data from hospitalized elderly septic patients collected in the Medical Information Mart for Intensive Care database-Ⅳ 2.2（MIMIC-Ⅳ 2.2）. Demographic，clinical and laboratory data were collected. The patients were randomly divided into a training set and a validation set at a 7∶3 ratio.

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通信作者：刘冬梅，E-mail：liudongmeilz@163.com

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QR code for English version

Feature selection was performed in the training set using the least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation, followed by logistic regression analysis to establish a predictive model for AKI in elderly septic patients. A nomogram was draw and the model was then validated in the validation set. The predictive value of the model was evaluated using the receiver operating characteristic (ROC) curve and the clinical impact curve (CIC). **Results** A total of 5 792 elderly septic patients was included, of which 4 888 developed AKI (incidence rate: 84.4%). Multivariate logistic regression analysis revealed that mechanical ventilation (OR=2.115, 95%CI:1.722-2.598), congestive heart failure (OR=2.237, 95%CI: 1.771-2.824), body mass index (BMI) (OR=1.108, 95%CI: 1.09-1.13), activated partial thromboplastin time (APTT) (OR=1.010, 95%CI: 1.004-1.017), lactic acid level (OR=1.114, 95%CI: 1.018-1.225), Acute Physiology Score (APS) (OR=1.025, 95%CI: 1.020-1.031), arterial partial pressure of oxygen (PaO_2) (OR=1.003, 95%CI: 1.002-1.004), and urine output (OR=0.942, 95%CI: 0.932-0.951) were independent influencing factors for the development of AKI (P<0.05). A static nomogram for predicting AKI in elderly septic patients was constructed based on these eight variables. In the training set, the area under the ROC curve (AUC) of the nomogram for predicting the occurrence of AKI in sepsis patients was 0.803 (95%CI: 0.786-0.821), with a sensitivity of 0.733 and specificity of 0.726, and an optimal cut-off value of 0.829, indicating that the model had moderate discriminatory ability. The Hosmer-Lemeshow test showed good calibration of the predictive model (P=0.976). The CIC also demonstrated that the model had good clinical utility. **Conclusion** Urine output, congestive heart failure, BMI, APTT, lactate, PaO_2, APS, and mechanical ventilation are the main influencing factors for AKI in elderly septic patients. The predictive model for AKI in elderly septic patients, based on these factors, can help clinicians identify high-risk patients early and provide timely interventions.

Keywords: Elderly; Sepsis; Acute kidney injury; Medical Information Mart for Intensive Care database - Ⅳ; Nomogram; Acute Physiology Score; Activated partial thromboplastin time; Congestive heart failure; Mechanical ventilation

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脓毒症是一种危及生命的器官功能障碍，由宿主对感染的反应失调引起，是危重患者死亡的主要原因[1]。每年报告约4 890万例脓毒症病例和1 100万例脓毒症相关死亡，占所有死亡的19.7%[2]。急性肾损伤(acute kidney injury，AKI)被认为是脓毒症的一种常见和复杂的临床并发症，影响了高达60%的脓毒症患者[3]。与非AKI患者相比，脓毒症相关急性肾损伤(sepsis associated acute kidney injury，SA-AKI)与预后较差、重症监护室(intensive care unit，ICU)住院时间延长、生活质量下降和死亡风险升高密切相关[4]。随着世界人口老龄化，目前约有7亿人年龄在65岁及以上，占总人口的9%，预计到2050年，这一比例将增加到17%[5]。年龄被认为是脓毒症和AKI死亡的独立风险因素[6]。与年轻患者相比，65岁以上患者的AKI预后明显变差[7]。老年SA-AKI患者病情危重，早期识别高风险AKI的老年脓毒症患者对结局以及预后的影响至关重要。有研究使用美国重症监护医学信息数据库(Medical Information Mart for Intensive Care，MIMIC)-Ⅲ，在15 726例脓毒症患者中建立了AKI的预测模型，该模型显示了较好的预测准确性，其C-index为0.711(95%CI:0.702~0.721)[8]。本研究拟利用MIMIC-Ⅳ数据库构建老年脓毒症患者并发AKI的预测模型并进行验证，以期为临床医生早期发现高危患者，并改善患者预后提供参考。

1 资料与方法

1.1 *数据来源* 本研究数据来源于美国麻省理工学院与贝斯以色列女执事医疗中心联合开发的MIMIC-Ⅳ 2.2[9]。这项研究中所有患者都是匿名的，不需要知情同意和伦理批准声明。研究者通过了协作机构培训计划项目考试并获得了证书(证书编号:12871705)。

1.2 *纳入和排除标准* (1)纳入标准:①首次入ICU;②年龄≥65周岁;③以Sepsis3.0诊断标准诊断为脓毒症;④ICU住院时间≥48 h。(2)排除标准:①入ICU前发生AKI;②存在慢性肾脏病、肾移植病史;③存在艾滋病等免疫缺陷病病史;④数据缺失值超过20%。

1.3 *数据提取和研究终点* 在MIMIC-Ⅳ2.2数据库中利用Navicat Premium 16.0软件获取以下数据。(1)人口学信息:年龄、性别、身体质量指数(body mass index，BMI)、入院类型以及合并症。(2)入ICU后24 h内的生命体征:体温、心率、呼吸频率、平均动脉压(mean arterial pressure，MAP)、尿量、血氧饱和度

等。（3）入ICU后24 h内实验室化验结果：包括血常规、血生化、凝血指标、动脉血气分析等。（4）入ICU后24 h内评分：急性生理学评分（Acute Physiology Score，APS）、序贯器官衰竭评估（Sequential Organ Failure Assessment，SOFA）评分、格拉斯哥昏迷量表（Glasgow Coma Scale，GCS）评分。（5）入ICU后24 h内治疗情况：机械通气、肾脏替代治疗。另外，缺失值的插补采用多重插补的方式，缺失值超过20%的变量被剔除在外。研究结局为老年脓毒症患者7 d内发生AKI的事件，使用改善全球肾脏病预后组织（Kidney Disease：Improving Global Outcomes，KDIGO）标准确定患者在住院期间是否发生AKI。

1.4 统计学方法 采用R 4.4.2软件进行数据分析。采用Shapiro-Wilk法对计量资料进行正态性检验，符合正态分布的计量资料以 $\bar{x}\pm s$ 表示，比较采用独立样本 t 检验；不符合正态分布的计量资料以 $M(P_{25},P_{75})$ 表示，采用Mann-Whitney U 检验；计数资料以例（%）表示，采用 χ^2 检验比较。$P<0.05$ 为差异有统计学意义。将研究对象按照7∶3的比例随机分为训练集和验证集。采用10折交叉验证的最小绝对收缩和选择算法（least absolute shrinkage and selection operator，LASSO）回归将变量初步降维处理。采用单因素与多因素logistic回归构建预测模型。在训练集上建立模型，在验证集上进行验证。通过受试者工作特征（receiver operating characteristic，ROC）曲线和曲线下面积（area under the curve，AUC）判断模型的区分度，采用临床影响曲线（clinical impact curve，CIC）评估其临床实用性。

2 结 果

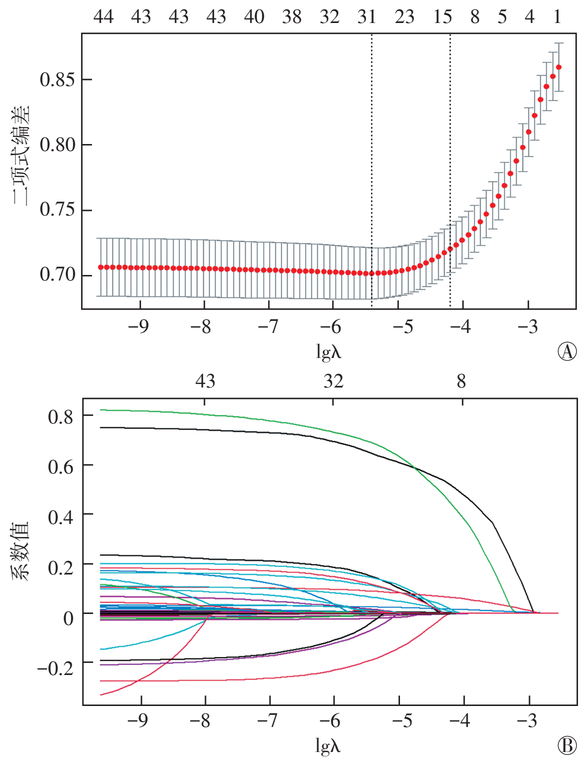
2.1 临床基线资料 共纳入5 792例住院的老年脓毒症患者，其中4 888例（84.39%）患者7天内发生了AKI。患者年龄为76.00（70.00~83.00）岁，有95例（1.64%）患者24 h内进行了连续性肾脏替代治疗，有2 986例（51.55%）患者24 h内进行了机械通气治疗。其中训练集与验证集患者基线资料（除尿量、红细胞计数、血红蛋白及24 h GCS评分、24 h SOFA评分）比较差异均无统计学意义（$P>0.05$）。见表1。

2.2 老年脓毒症患者发生AKI特征 初步筛选将纳入的变量用LASSO回归降维处理，提取出重要的预测因素，结果见图1。有9个变量与老年脓毒症患者发生AKI密切相关，分别为合并充血性心力衰竭（congestive heart failure，CHF）、体温、BMI、动脉血氧分压、血乳酸、尿量、APTT、APS评分与机械通气治疗。

2.3 单因素和多因素logistic回归分析 单因素分析的结果表明上述LASSO回归分析纳入的9个变量均属于老年脓毒症患者发生AKI的影响因素（$P<0.01$），将其全部纳入多因素logistic回归分析中，结果显示尿量、合并CHF、BMI、动脉血氧分压、血乳酸、APTT、APS评分、机械通气是老年脓毒症患者发生AKI的独立影响因素（$P<0.05$）。见表2。

2.4 列线图预测模型的构建 根据上述多因素logistic回归分析结果构建列线图。见图2。根据每一项指标，垂直划线到评分轴上，从而得到分值，最后将分值相加得到总分，总分向下的垂直线对应脓毒症患者发生AKI的概率数值，用于临床预测收住老年脓毒症患者发生AKI的风险。

2.5 列线图模型的评价和内部验证 在训练集和验证集中，列线图的AUC分别为0.803（95%CI：0.786~0.821）和0.779（95%CI：0.753~0.804）。见图3A。证明此列线图模型具有良好的区分度。该预测模型的校准曲线显示在训练集和内部验证集的预测和观察之间具有良好的一致性，Hosmer-Lemeshow检验显示 P 值为0.976和0.079，均大于0.05，不具有显著性。CIC曲线被用来评估该列线图的临床实用性。CIC曲线显示，该预测模型可以获得比“全部干预”或“不干预”策略更大的净收益。见图3B、3C。



注：A为惩罚项的交叉验证图；B为惩罚参数的不同值上绘制LASSO回归系数。

图1 LASSO回归特征降维图

Fig.1 LASSO regression feature dimensionality reduction diagram

表1 训练集和验证集老年脓毒症患者基线特征比较 ［$M(P_{25},P_{75})$］

Tab.1 Comparison of baseline characteristics between training set and validation set for elderly sepsis patients ［$M(P_{25},P_{75})$］

变量	训练集(n=4 054)	验证集(n=1 738)	χ^2/Z/t值	P值
SA-AKI[例(%)]	3 429 (84.58)	1 459 (83.95)	0.374	0.541
男性[例(%)]	2 121 (52.32)	888 (51.09)	0.732	0.392
年龄(岁)	76.00 (70.00,83.00)	76.00 (70.00,83.00)	1.726	0.189
BMI(kg/m²)	27.34 (23.56,31.61)	27.12 (23.46,31.67)	0.059	0.809
基础疾病[例(%)]				
CHF	1 315 (32.44)	579 (33.31)	0.425	0.514
周围血管疾病	584 (14.41)	232 (13.35)	1.123	0.289
慢性肺疾病	1 213 (29.92)	502 (28.88)	0.628	0.428
糖尿病	1 153 (28.44)	481 (27.68)	0.352	0.553
慢性肝脏病	353 (8.71)	166 (9.55)	1.062	0.303
恶性肿瘤	697 (17.19)	315 (18.12)	0.732	0.392
高血压	2 611 (64.41)	1 161 (66.80)	3.073	0.480
体温(℃)	36.83 (36.57,37.15)	36.83 (36.57,37.15)	0.139	0.709
心率(次/分)	83.90 (74.86,95.63)	83.80 (75.12,94.99)	0.034	0.854
呼吸频率(次/分)	19.08 (16.85,22.00)	18.93 (16.80,22.09)	0.615	0.433
MAP(mmHg)	74.50 (69.41,81.16)	74.48 (69.20,81.16)	0.024	0.877
血氧饱和度(%)	97.36 (95.85,98.61)	97.42 (95.95,98.73)	1.460	0.227
动脉血氧分压(mmHg)	150.50 (97.00,236.00)	149.00 (97.00,237.88)	0.150	0.699
氧合指数(mmHg)	240.00 (172.80,314.00)	237.00 (165.44,316.63)	0.587	0.444
血糖(mg/dL)	133.97 (116.50,161.69)	133.82 (117.76,159.11)	0.011	0.917
血乳酸(mmol/L)	1.85 (1.35,2.65)	1.85 (1.35,2.60)	< 0.001	0.991
尿量(mL)	1 415.00 (900.00,2 098.75)	1 475.00 (940.00,2 168.75)	4.619	0.032
实验室指标				
白细胞计数(×10⁹/L)	12.10 (8.95,15.97)	12.10 (8.90,16.10)	0.440	0.507
红细胞计数(×10¹²/L)	3.48 (3.11,3.96)	3.46 (3.07,3.90)	6.144	0.013
血小板计数(×10⁹/L)	180.00 (130.68,245.46)	179.25 (130.75,245.33)	<0.001	0.996
血红蛋白(g/L)	10.50 (9.35,11.80)	10.33 (9.20,11.70)	6.270	0.012
ALT(u/L)	28.00 (17.00,63.00)	27.00 (16.50,56.50)	1.824	0.177
碱性磷酸酶(u/L)	78.00 (58.00,115.00)	78.00 (59.00,117.50)	0.602	0.438
AST(u/L)	44.00 (27.00,102.00)	43.00 (27.00,98.50)	0.265	0.606
尿素氮(mg/dL)	20.50 (15.00,31.00)	20.50 (15.00,30.50)	0.488	0.485
血肌酐(mg/dL)	0.95 (0.75,1.30)	0.95 (0.75,1.30)	0.358	0.550
国际标准化比值	1.30 (1.15,1.50)	1.30 (1.15,1.50)	0.016	0.899
凝血酶原时间(s)	14.30 (12.80,16.65)	14.35 (12.80,16.70)	0.035	0.852
APTT(s)	31.60 (27.55,40.30)	31.80 (27.60,40.45)	0.417	0.518
24 h SOFA评分	3.00 (2.00,4.00)	3.00 (2.00,4.00)	3.971	0.046
24 h APS评分	53.00 (39.00,72.00)	52.00 (38.00,71.00)	0.508	0.476
24 h GCS评分	15.00 (15.00,15.00)	15.00 (15.00,15.00)	7.554	0.006
24 h 内治疗[例(%)]				
肾脏替代治疗	70 (1.73)	25 (1.44)	0.627	0.429
机械通气	2 089 (51.53)	897 (51.61)	0.003	0.955

注：ALT为丙氨酸氨基转移酶；AST为门冬氨酸氨基转移酶；APTT为活化部分凝血酶原时间。

表2 老年脓毒症患者发生AKI的单因素和多因素logistic回归分析

Tab.2 Univariable and multivariable logistic regression analysis of AKI in elderly patients with sepsis

变量	单因素分析				多因素分析			
	β	SE	OR (95%CI)	P值	β	SE	OR (95%CI)	P值
APS评分	0.028	0.002	1.029 (1.024~1.033)	<0.001	0.025	0.003	1.025 (1.020~1.031)	<0.001
机械通气	0.882	0.092	2.416 (2.017~2.893)	<0.001	0.749	0.105	2.115 (1.722~2.598)	<0.001
BMI	0.084	0.008	1.087 (1.071~1.104)	<0.001	0.102	0.009	1.108 (1.089~1.127)	<0.001
APTT	0.016	0.003	1.016 (1.010~1.022)	<0.001	0.010	0.003	1.010 (1.004~1.017)	0.001
MAP	−0.027	0.004	0.973 (0.965~0.982)	<0.001				
血乳酸	0.273	0.043	1.314 (1.212~1.433)	<0.001	0.108	0.047	1.114 (1.018~1.225)	0.022
动脉血氧分压	0.003	0.001	1.003 (1.001~1.004)	<0.001	0.003	0.001	1.003 (1.002~1.004)	<0.001
尿量	−0.050	0.004	0.951 (0.942~0.961)	<0.001	−0.060	0.005	0.942 (0.932~0.951)	<0.001
CHF	0.766	0.107	2.150 (1.751~2.659)	<0.001	0.805	0.119	2.237 (1.771~2.824)	<0.001

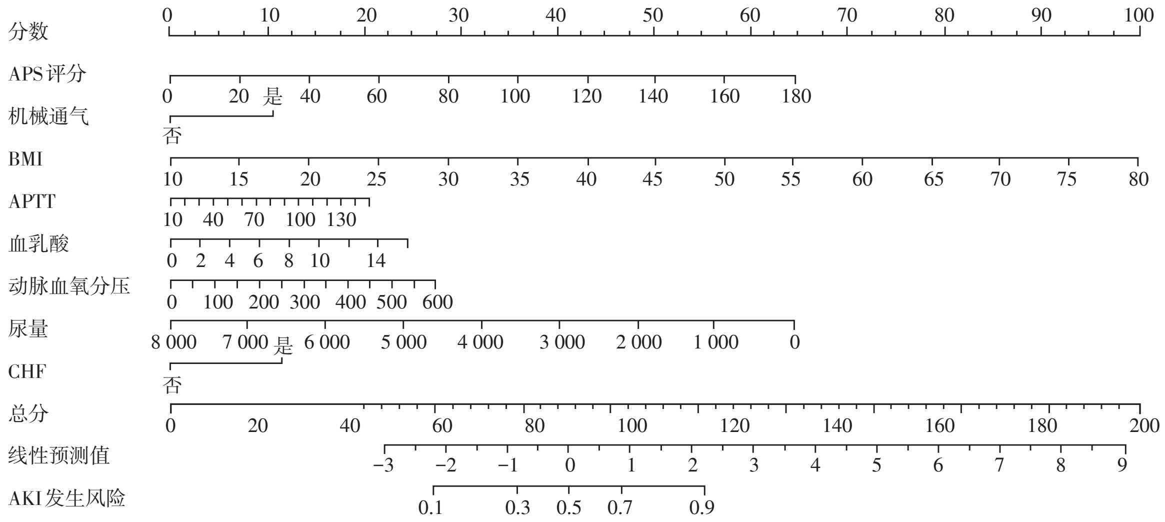
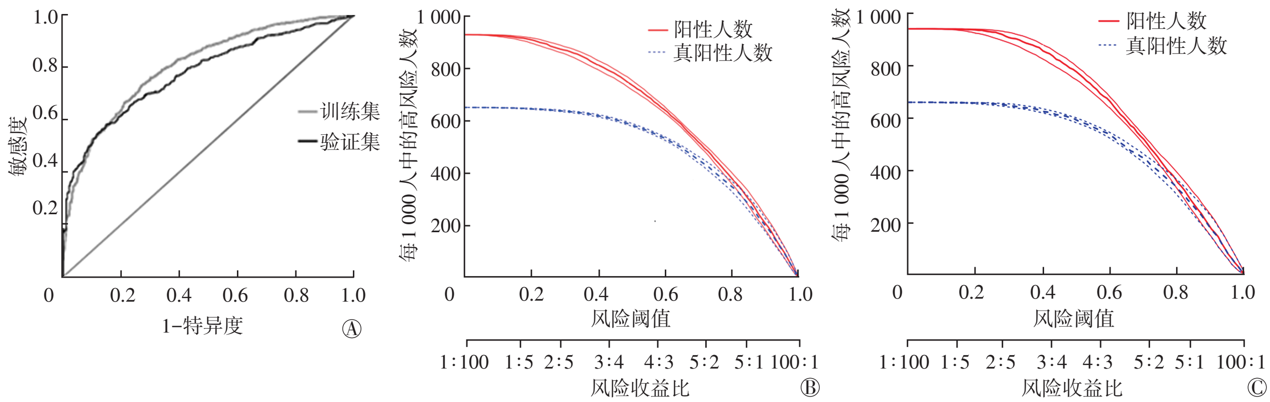


图 2　预测老年脓毒症患者发生 AKI 的列线图

Fig.2　Nomogram for predicting AKI in elderly sepsis patients



注：A 为列线图的 ROC 曲线结果；B 为训练集的 CIC 曲线结果；C 为验证集的 CIC 曲线结果。

图 3　老年脓毒症并发 AKI 列线图模型的 ROC 曲线及 CIC 曲线

Fig.3　ROC and CIC of the nomogram for SA-AKI in elderly sepsis patients

3　讨　论

AKI 在危重患者中很常见，与不良预后密切相关[10]。老年人各器官组织的结构和功能逐渐退化，加之基础疾病多，发生脓毒症后极易并发多脏器功能损伤[11]。早期发现高 AKI 风险的老年脓毒症患者并进行积极治疗将对改善预后发挥重要作用，构建疾病预测模型是针对脓毒症患者的一种有效管理方案[12]。本研究构建老年脓毒症患者并发 AKI 风险预测的列线图模型，模型中包含 8 个变量，分别为 APS、机械通气、BMI、APTT、血乳酸、动脉血氧分压、尿量与 CHF，可用于预测老年脓毒症患者并发 AKI 的风险。

尿量作为肾脏功能的直观反映，其减少往往是肾脏灌注不足或功能受损的早期信号。CHF 时心脏无法有效地将血液输送至肾脏，肾脏为了维持内环境稳定，会启动一系列代偿机制。当心脏功能持续恶化，代偿机制无法弥补肾脏灌注的不足时，就会引发 AKI。Jiang 等[13]发现 CHF 是重症患者发生 AKI 的危险因素，本研究结果与其一致。在脓毒症的病理生理过程中，全身性的炎症反应会引发血管内皮功能障碍、微循环障碍以及血流动力学的改变[14]。这些变化导致肾脏的有效灌注减少，肾小球滤过率下降，CHF 则会加重上述反应，进而引起尿量的减少。

BMI 作为评估身体情况和健康状态的指标，其增加或减少均会显著影响脓毒症患者的死亡风险和器官损害。有研究表明，肥胖的脓毒症患者相较于正常体重患者更容易发生 AKI[15]。Yue 等[16]也发现，SA-AKI 患者的 BMI 值显著高于仅有脓毒症的患者，也证明肥胖可能会引起脓毒症患者并发 AKI。

APS 是 APACHE Ⅱ评分中急性生理评分的一部分，包含体温、MAP、心率、呼吸频率、氧分压等[17]。有研究表明 APS 评分高是脓毒症进展为慢性危重的

危险因素[18],慢性危重患者存在多脏器功能损伤,其中就包括AKI。Pérez-Fernández等[19]也发现,APS与SA-AKI患者的90 d死亡率相关。

氧分压、乳酸、是否机械通气这三个指标都反映机体的缺氧情况。氧分压低于正常值通过面罩吸氧不能提高氧分压后,则需要机械通气给予氧气支持。乳酸代表内环境中的缺氧状态,已有研究表明乳酸水平升高是SA-AKI发病风险升高的危险因素[20]。龚春蕾等[21]发现,当乳酸≥2.75 mmol/L时,脓毒症患者发生AKI的风险增加1.772倍。既往研究提示低氧可能通过诱发肾脏能量代谢障碍与氧化应激,增加老年脓毒症患者AKI风险[22]。本研究则发现PaO_2升高反而与AKI风险增加相关,推测其反映患者病情更重、治疗强度更大,因而更易发生AKI。

凝血功能异常是脓毒症患者常见的全身表现之一,常表现为APTT延长及血小板形态和数量异常,血液高凝状态导致微血栓形成,进一步加重肾脏病变和全身多器官损伤[23]。一项研究显示APTT升高是发生AKI的独立危险因素,且APTT的值对SA-AKI患者短期死亡风险具有一定预测价值[24],本研究结果与其一致。

本研究仍存在以下几个局限性:首先是单中心回顾性研究,缺乏外部验证,会降低临床适用性。其次是缺失值的处理,本研究计量资料插补采用多重插补法,等级资料采用邻近插补法,其可能会引起数据集误差。最后是纳入的临床指标问题,由于部分指标缺失,导致危险因素纳入不全。

综上所述,本研究所构建的风险预测模型对老年脓毒症患者7 d内发生AKI有较好的识别能力,其中包含8个医院容易获得的变量,可被临床医生用来计算老年脓毒症患者发生AKI的个体风险,并且通过列线图可视化预测模型,使其更易在临床中应用。

作者贡献 方春天负责研究的构思,设计与实施,撰写论文,数据的收集与分析,文章的质量控制与审查,对文章整体负责;刘冬梅负责论文的设计与实施,论文的修订

利益冲突 无

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