

A Study on the Factors Influencing Mortality Risk in Sepsis-Induced Acute Kidney Injury based on Analysis of the MIMIC Database

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Abstract

Background: Sepsis-Induced Acute Kidney Injury (SA-AKI) significantly increases mortality and healthcare burdens. Identifying key mortality risk factors is crucial for improving patient outcomes.

Objectives: This study aims to pinpoint the primary factors affecting mortality in SA-AKI patients using the MIMIC-III database.

Methods: A retrospective analysis was conducted on 4,868 SA-AKI patients from the MIMIC-III database. Clinical data from the first 24 hours of ICU admission were analyzed using logistic regression to identify mortality predictors.

Results: Key mortality predictors included advanced age, severe AKI stages, low serum albumin, delayed antibiotics, high AST and bilirubin, and presence of cerebrovascular disease and cancer. Combined, these factors showed high predictive accuracy for mortality risk (AUC=0.796).

Conclusions: Early intervention and monitoring of identified risk factors can enhance survival rates in SA-AKI patients.

Keywords: Sepsis; Acute kidney injury; Mortality risk; MIMIC database.

Introduction

Sepsis is a severe clinical condition characterized by an uncontrolled systemic inflammatory response, which can potentially lead to Multiple Organ Dysfunction Syndrome (MODS) [1-3]. Among them, Sepsis-Induced Acute Kidney Injury (SA-AKI), as a common complication of sepsis, significantly increases patient mortality, extends hospital stay, and raises treatment costs [4-6]. Sepsis has an acute onset and rapid progression, often accompanied by Acute Kidney Injury (AKI). These characteristics increase the difficulty of patient management and elevate the risk of mortality [7-9].

Recent studies indicate that among deaths in sepsis patients, approximately 15% are acute, occurring early in the disease course and posing an immediate threat to life. In contrast, up to 85% of patients experience late deaths, which are often closely

associated with secondary infections acquired in the ICU [10-12]. This finding further elucidates the complexity of sepsis and its complications, underscoring the urgency of treatment. Despite numerous studies on sepsis and Sepsis-Induced Acute Kidney Injury (SA-AKI), there are currently no definitive and universally applicable treatment strategies or medications that effectively reduce their mortality and complication rates. Current treatment methods remain largely supportive, including infection source control, timely use of antibiotics, resuscitation, and supportive care for organ dysfunction [13]. Furthermore, the complexity and heterogeneity of sepsis lead to a multitude of clinical trials ending in negative outcomes.

In the past decade, various methods for predicting Acute Kidney Injury (AKI) have been explored, with the majority of studies focusing on the discovery of novel biomarkers. Numerous

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clinical predictive models have been utilized to forecast acute kidney injury associated with surgery [14-16]. Therefore, conducting an in-depth analysis and study of the factors influencing the mortality risk associated with sepsis-induced acute kidney injury is of vital practical significance for optimizing treatment plans, improving patient survival rates, and reducing the burden on the healthcare system. This study aims to utilize data from the MIMIC database, employing a retrospective research method to systematically extract clinical information related to Sepsis-Associated Acute Kidney Injury (SA-AKI). By leveraging statistical and machine learning techniques to mine and analyze these data, the study endeavors to uncover the primary factors influencing the mortality risk in patients with SA-AKI.

Material and methods

Database

The data for this study were derived from the Medical Information Mart for Intensive Care (MIMIC-III v1.4) database, a publicly accessible resource supported by the Laboratory of Computational Physiology at the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The database documents detailed information on patients who received intensive care treatment at Beth Israel Deaconess Medical Center from 2008 to 2019, encompassing data from over 40,000 patients. All data are available to qualified PhysioNet users without special permission. We conducted a detailed retrospective data analysis based on the MIMIC-III database. The use of data in this study was approved by the appropriate Institutional Review Board and followed all applicable ethical standards and data protection regulations.

Patient admission and data extraction

In this analysis, based on the ICD-9 (International Classification of Diseases, Ninth Revision) diagnostic codes of the database, all patients with S-AKI (Sepsis-Associated Acute Kidney Injury) who met the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria were included. The following were considered diagnostic criteria: an increase in serum creatinine level by more than 0.3 mg/dL within 48 hours or Scr \geq 50%. Patients younger than 18 years of age and those with ICU stays less than 48 hours were excluded.

Clinical variables and definitions

Several variables were extracted from the database, including patient demographics, vital signs, comorbidities, laboratory indices, scoring systems, and medical interventions. All data were collected within the first 24 hours after admission to the Intensive Care Unit (ICU). The average values of laboratory variables within 24 hours after ICU admission were used for analysis and included in the predictive model, taking into account that multiple variables were measured more than once. Persistent AKI was defined as lasting longer than 48 hours, in accordance with the KDIGO criteria, based on the consensus report of the Acute Dialysis Quality Initiative (ADQI) workgroup [17]. Transient AKI was defined as AKI with a duration of less than 48 hours.

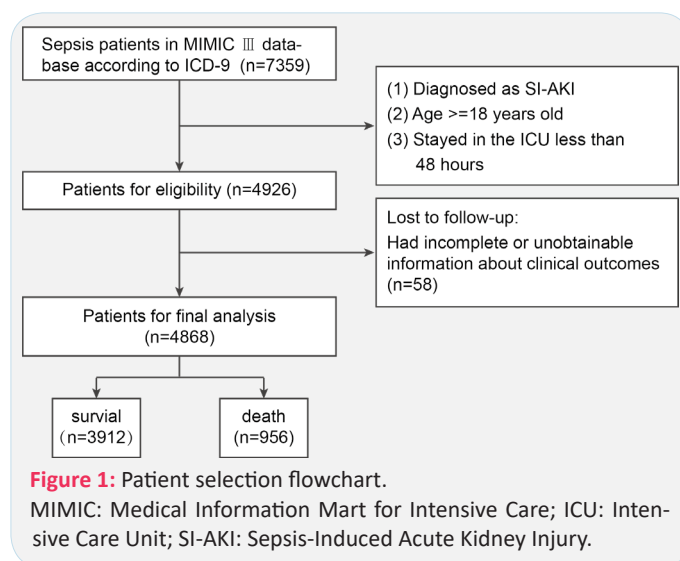
Statistical analysis

The statistical analysis was conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are presented as medians (IQR) and categorical variables as frequencies (n) with absolute numbers and percentages (%). The Mann-Whitney U test, Fisher's exact test, or the Chi-square (χ^2) test were used for intergroup comparisons when

appropriate. Initially, a univariate analysis was performed on all variables to identify factors with statistically significant effects on mortality. Subsequently, only variables that showed significant differences between groups were used in the multivariate analysis using logistic regression. Data described by OR (Odds Ratio) and CI (Confidence Interval) at 95%, with $p < 0.05$ considered to indicate statistical significance. A clinical predictive model for in-hospital mortality of persistent S-AKI was established through logistic regression and evaluated using the C-statistic and the area under the operating characteristic curve (AUC). All statistical analyses were performed using R software V.4.2.1.

Baseline characteristics

According to the ICD-9 diagnostic criteria, we identified a total of 7,359 patients diagnosed with sepsis among the admitted patients. To ensure the accuracy of the data and the validity of the analysis, we further meticulously screened these patients based on strict exclusion criteria, ultimately excluding 2,491 patients. After this series of screening processes, a total of 4,868 patients were included in our analysis. Among the 4,868 patients with AKI, there were 2,875 males (accounting for 61.4%) and 1,993 females (accounting for 38.6%), with a male-to-female ratio of 1.44:1. The average follow-up time was 26.84 ± 5.86 days. There were 956 deaths after admission to the ICU. Figure 1 provides a detailed flowchart of the patient selection process.



Comparison of clinical data between the death and survival groups

As shown in Table 1, the proportions of the following variables are higher in the non-survivor group: age, Continuous Renal Replacement Therapy (CRRT), time to antibiotics administration post-admission (Antibiotics_to_admit(h)), time to antibiotics administration post-ICU admission (Antibiotics_to_icu), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), total bilirubin, Blood Urea Nitrogen (BUN), creatinine, heart rate (beats per minute, bpm), White Blood Cell (WBC) count, neutrophil count, monocyte count, Mean Corpuscular Volume (MCV), Red Cell Distribution Width (RDW), International Normalized Ratio (INR), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), glucose (measured in mmol/L), Magnesium (Mg), Phosphorus (P), potassium, Sequential Organ Failure Assessment (SOFA) score, duration of dopamine administration (Dopamine time, in minutes), amount of dopamine administered (Dopamine amount, in mg), duration of norepinephrine administration (Norepinephrine time, in minutes), and amount

of norepinephrine administered (Norepinephrine amount, in mg). In contrast, the proportions of body weight (Weight, in kg), cerebrovascular disease, mild liver disease, myocardial infarction, peripheral vascular disease, congestive heart failure, malignant cancer, Acute Respiratory Distress Syndrome (ARDS, with a sample size of N=694), peritonitis, pneumonia, mechanical ventilation, albumin (measured in g/L), urine output rate within 6 hours (UO rate 6 hours), Systolic Blood Pressure (SBP, in mmHg), Mean Blood Pressure (MBP, in mmHg), Diastolic Blood Pressure (DBP, in mmHg), lymphocyte count, basophil count, eosinophil count, Red Blood Cell (RBC) count, Platelet (PLT) count, pH, partial pressure of oxygen (PO₂), Charlson comorbidity index, worsening of acute kidney injury (Worsen aki), and the use of dobutamine, dopamine, and norepinephrine, as well as the duration and amount of dobutamine administered

(Dobutamine time, Dobutamine amount, in mg), are lower in the non-survivor group (P<0.05).

Factors influencing all-cause death and other adverse outcomes

According to the clinical data comparison between the deceased and surviving groups in Table 1, variables with P<0.05 were included in the multivariate Cox regression analysis. The results indicated that age, Aki stage 2 day, Albumin, Antibiotic to admittime Ast, Bilirubin total, Bun, Cerebrovascular disease, Eosinophils abs, Herrat time dbp max, Hemoglobin, Lac, Malignant cancer, Mchc, Metastatic solid tumor, Mg, Ph, Platelet, Ptt, rdw, Sofa 24 hours, Wbc, Weight, diabetes and Wosen akian are independent risk factors for all-cause 28 day mortality in patients with AKI (P<0.05, as shown in Table 2).

Table 1: Data comparison between the deceased and surviving groups of patients with Acute Kidney Injury (AKI).

Parameters	Survival Group (N=3912)	Death Group (N=956)	t/ χ^2	P value
Basic characteristics				
Male/female	2335/1577	540/416	3.26	0.072
Age (year)	61.56±14.90	65.74±13.36	-7.93	<0.001
Weight (kg)	85.91±24.94	83.58±28.08	2.52	0.012
Complications				
AIDS (N=65)	57(87.7%)	8(12.3%)	2.24	0.157
Cerebrovascular Disease (N=634)	478(75.4%)	156(24.6%)	11.40	0.001
Dementia (N=111)	82(73.9%)	29(26.1%)	3.03	0.09
Diabetes with Coma (N=561)	456(81.3%)	105(18.7%)	0.341	0.61
Diabetes without Coma (N=1268)	1027(81%)	241(19%)	0.43	0.54
Mild Liver Disease (N=1036)	754(72.8%)	282(27.2%)	47.94	<0.001
Myocardial Infarct (N=910)	698(76.7%)	212(23.3%)	9.50	0.003
Peptic Ulcer Disease (N=152)	120(78.9%)	32(21.1%)	0.20	0.678
Peripheral Vascular Disease (N=569)	424(74.5%)	145(25.5%)	13.95	<0.001
COPD (N=1397)	1108(79.3%)	289(20.7%)	1.37	0.248
Congestive Heart Failure (N=1624)	1260(77.6%)	364(22.4%)	11.89	0.001
Malignant Cancer (N=633)	437(69%)	196(31%)	59.13	<0.001
Rheumatic Disease (N=184)	151(82.1%)	33(17.9%)	0.352	0.636
Paraplegia (N=230)	180(78.3%)	50(21.7%)	0.68	0.396
ARDS (N=694)	459(66.1%)	235(33.9%)	105.9	<0.001
Peritonitis (N=57)	39(68.4%)	18(31.6%)	5.21	0.029
Pneumonia (N=1148)	857(74.7%)	291(25.3%)	31.04	<0.001
Urinary Infection (N=752)	605(80.5%)	147(19.5%)	0.005	1
Mechanical Ventilation (N=2881)	2230(77.4%)	651(22.6%)	39.13	<0.001
CRRT (N=501)	247(49.3%)	254(50.7%)	341.4	<0.001
Use of antibiotics				
Antibiotics_to_admit (h)	34(13,109)	64(15,181)	-4.91	<0.001
Antibiotics_to culture (h)	24.8(10.8,50.5)	29.4(10,55.4)	-1.44	0.149
Antibiotics_to icu	15.7(5.2,66.5)	33.8(8,97)	-6.22	<0.001
Antibiotics to suspect	24.8(10.8,50.5)	29.4(10,55.4)	-1.44	0.15
Blood and biochemical indicators				
Albumin(g/L)	30.88±6.76	27.63±6.76	13.32	<0.001
ast	35(22,66)	63(29,195)	-13.09	<0.001
alt	26(16,54)	38(19,128)	-9.50	<0.001

Bilirubin total	10.26(6.84,20.52)	18.81(6.84,63.27)	-11.39	<0.001
bun	20(13,33)	33(20,55)	-15.59	<0.001
creatinine	79.56(61.88,132.6)	132.6(79.56,221)	-12.20	<0.001
UO rate 6 hours	0.54(0.4,2.87)	0.41(0.2,0.64)	-15.27	<0.001
SBP (mmHg)	147.08±23.74	146.04±25.62	7.64	<0.001
MBP (mmHg)	76.02±18.58	74.22±19.19	3.53	<0.001
DBP (mmHg)	46.01±11.17	43.08±12.63	5.16	<0.001
Heart rate (bpm)	88.69±16.52	92.51±18.17	-6.29	<0.001
WBC	10(7.2,13.78)	12.7(8.8, 18.5)	-12.16	<0.001
Neutrophils count	7.08(3.07,11.19)	8.95(4.09,11.17)	-7.62	<0.001
Lymphocytes count	1.14(0.73,1.76)	0.91(0.56,1.43)	-8.89	<0.001
Monocytes count	0.43(0.18,0.74)	0.5(0.19,0.87)	-3.59	<0.001
Basophils count	0.02(0,0.04)	0(0,0.03)	-7.74	<0.001
Eosinophils count	0.05(0,0.16)	0.01(0,0.13)	-8.32	<0.001
RBC	3.33±0.67	3.19±0.69	5.89	<0.001
MCV	91.04±7.05	92.84±8.23	-5.46	<0.001
RDW	15.66±2.45	17.22±3.12	-16.61	<0.001
PLT	226.50±145.82	180.11±130.29	9.0	<0.001
INR	1.43±0.63	1.83±1.05	-15.53	<0.001
PT	15.57±6.39	19.83±10.90	-15.78	<0.001
PTT	36.28±18.38	45.78±25.14	-13.24	<0.001
PH	7.39±0.08	7.35±0.11	10.09	<0.001
PO ₂	95(62,146.75)	88.50(63,124)	-3.23	0.001
pCO ₂	41.50±10.75	40.84±12.10	1.66	0.097
Glucose (mmol/L)	7.84±3.48	8.40±4.20	-4.21	<0.001
mg	2.07±0.35	2.14±0.38	-5.31	<0.001
p	3.54±1.33	4.14±1.84	-11.64	<0.001
potassium	4.09±0.64	4.25±0.75	-6.14	<0.001
sodium	138.72±5.07	138.71±6.63	0.05	0.96
charlson_comorbidity_index	6(3,8)	5(3,7)	-13.12	<0.001
sofa	2(0,4)	3(1,6)	-8.18	<0.001
Worsen aki (N=901)	667(74%)	234(N=26%)	28.10	<0.001
Vasoactive drug administration				
Dobutamine (N=203)	114(56.2%)	89(43.8%)	78.63	<0.001
Dopamine (N=293)	184(62.8%)	109(37.2%)	60.94	<0.001
Norepinephrine (N=2116)	1394(65.9%)	722(34.1%)	497.45	<0.001
Drug dosage and timing				
Dobutamine time (minute)	2687.5(696,5684.75)	1744(283,6972)	-0.8	0.423
Dobutamine amount (mg)	731.9(206.6,2660.4)	649.9(86.7,2483.7)	-1.32	0.187
Dopamine time (minute)	533(151,2396.8)	654(97.5,2255)	-0.84	0.402
Dopamine amount (mg)	289.3(70.9,1129.3)	400(55.6,1210.6)	-0.13	0.899
Norepinephrine time (minute)	1895.5(660.4,114.8)	3750(1661.5,7359.5)	-11.7	
Norepinephrine amount (mg)	13.4(3.8,37.3)	45.7(17,95.7)	-16.05	<0.001

Note: Bold numbers indicate significant P-values. **Abbreviation:** AIDS: Acquired Immunodeficiency Syndrome; COPD: Chronic Obstructive Pulmonary Disease; ARDS: Acute Respiratory Distress Syndrome; Antibiotics to Admit (H): Time to Antibiotic Administration After Admission (Hours); Antibiotics to Culture (H): Time to Antibiotic Administration After Culture (Hours); Antibiotics to Icu: Time to Antibiotic Administration After ICU Admission; Antibiotics to Suspect: Time To Antibiotic Administration After Suspicion of Infection; Blood And Biochemical Indicators: Hematological and Biochemical Parameters; Albumin: Serum Albumin; AST: Aspartate Transaminase; ALT: Alanine Transaminase; BUN: Blood Urea Nitrogen; SBP: Systolic Blood Pressure; MBP: Mean Blood Pressure; DBP: Diastolic Blood Pressure; WBC: White Blood Cell Count; RBC: Red Blood Cell Count; MCV: Mean Corpuscular Volume; RDW: Red Cell Distribution Width; PLT: Platelet Count; INR: International Normalized Ratio; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; PO₂: Partial Pressure of Oxygen; Pco₂: Partial Pressure of Carbon Dioxide; Mg: Magnesium; P: Phosphate; Sofa: Sequential Organ Failure Assessment (SOFA) Score.

Table 2: Multivariate Cox regression analysis of independent risk factors for 28 day all-cause mortality.

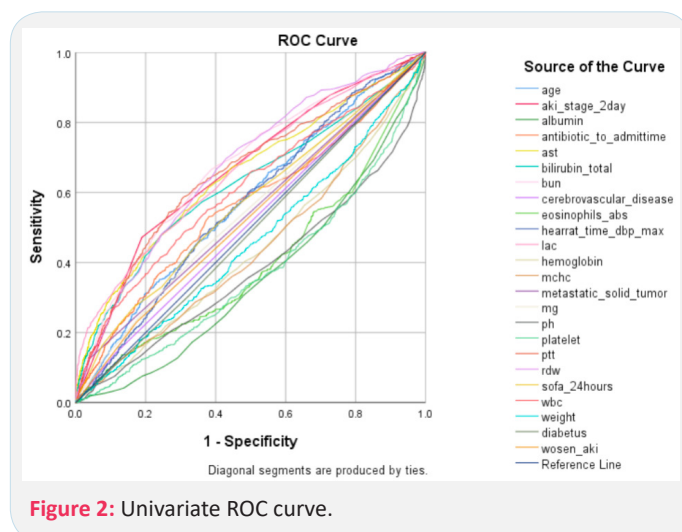
Parameters	B	SE	Wald	P value	95% CI	
					Lower Limit	Upper Limit
Age	.015	.004	11.349	0.001	1.006	1.024
Aki stage 2 day	.384	.068	32.068	<0.001	1.285	1.676
albumin	-.503	.090	30.964	0.001	.506	.722
Antibiotic to admittime	.001	.000	18.680	0.001	1.001	1.002
ast	.000	.000	6.710	0.010	1.000	1.000
Bilirubin total	.053	.014	15.413	<0.001	1.027	1.083
bun	.016	.002	41.806	<0.001	1.011	1.021
Cerebrovascular disease	.651	.167	15.222	<0.001	1.383	2.659
Eosinophils abs	-.567	.231	6.006	0.014	.360	.893
Heart rate time dbp max	.000	.000	9.264	0.002	1.000	1.000
hemoglobin	.076	.033	5.277	0.022	1.011	1.152
lac	.189	.029	41.418	<0.001	1.141	1.280
Malignant cancer	.385	.181	4.539	0.033	1.031	2.095
mchc	-.129	.039	10.906	0.001	.814	.949
Metastatic solid tumor	.896	.234	14.705	<0.001	1.550	3.872
mg	.332	.163	4.145	0.042	1.012	1.919
ph	-3.391	.630	28.967	<0.001	.010	.116
platelet	-.003	.000	32.218	<0.001	.996	.998
ptt	.010	.003	15.811	<0.001	1.005	1.015
rdw	.070	.024	8.569	0.003	1.023	1.124
Sofa 24 hours	-.041	.021	3.973	0.046	.922	.999
wbc	.038	.007	26.756	<0.001	1.024	1.054
weight	-.008	.002	11.173	0.001	.988	.997
Diabetes Mellitus	-.472	.132	12.807	<0.001	.482	.808
Wosen aki	.687	.159	18.687	<0.001	1.455	2.713

Note: The bold numbers represent the P values with significant differences. **Abbreviations:** 95% CI: 95% confidence interval; AKI: Acute Kidney Injury; B: Regression Coefficient; BE: Standard Error; Albumin: Serum Albumin; Ast: Aspartate Aminotransferase; Bun: Blood Urea Nitrogen; Heart rate time dbp max: Heart Rate at Maximum Diastolic Blood Pressure; hemoglobin; lac: Lactate; Mchc: Mean Corpuscular Hemoglobin Concentration; mg: Magnesium; ptt: Prothrombin Time; Rdw: Red Cell Distribution Width; Sofa 24 hours: Sequential Organ Failure Assessment (SOFA) Score at 24 Hours; Wbc: White Blood Cell (WBC) Count; Diabetes: Diabetes Mellitus; Wosen aki: Worsening Acute Kidney Injury.

The ROC curve analysis revealed the efficacy of both univariate and combined variables in predicting the risk of mortality

In the univariate ROC curve analysis, the Area under the Curve (AUC) for several indicators demonstrated their effectiveness in predicting the risk of death. Notably, the AUC values for aki_stage_2 day, Aspartate Aminotransferase (AST), total bilirubin (bilirubin_total), Blood Urea Nitrogen (BUN), Partial Thromboplastin Time (PTT), Red Cell Distribution Width (RDW), and White Blood Cell Count (WBC) were relatively high (Figure 2), indicating that these indicators possess a good discriminatory power in predicting the risk of mortality.

Further combined variable ROC curve analysis showed that when using combined indicators such as ALB (Albumin), AST (Aspartate Aminotransferase), BUN (Blood Urea Nitrogen), EOS (Absolute Eosinophil Count), LAC (Lactate), PH (pH value), PTT (Prothrombin Time), and RDW (Red Cell Distribution Width), the AUC value reached 0.796 (Figure 3), indicating that these combined indicators have a high accuracy in predicting the risk of mortality.



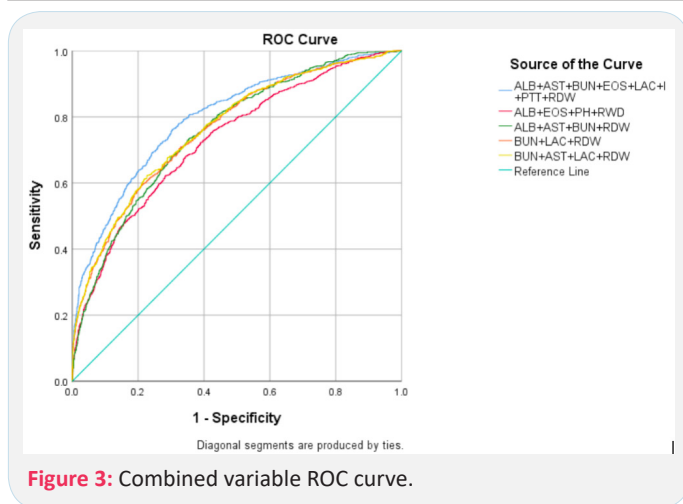


Figure 3: Combined variable ROC curve.

Discussion

This study offers a comprehensive examination of the factors influencing mortality risk in patients with Sepsis-Induced Acute Kidney Injury (SA-AKI) using data from the MIMIC-III database. Our findings underscore the complex nature of managing SA-AKI and highlight critical predictors of mortality that can guide clinical practice.

The analysis identified several significant predictors of increased mortality risk in SA-AKI patients. Advanced age emerged as a prominent risk factor, consistent with prior studies that identify age as a critical determinant in sepsis outcomes [18-20]. Patients with more severe stages of AKI exhibited worse outcomes, reinforcing the need for early and effective monitoring of kidney function [21,22]. Low serum albumin levels were strongly associated with higher mortality, indicating poor nutritional status and severe systemic inflammation [23,24]. Timely administration of antibiotics was crucial; delays were linked to worse outcomes, emphasizing the importance of prompt infection control [25,26]. Elevated AST and bilirubin levels were indicative of underlying liver dysfunction and systemic severity, contributing to higher mortality risk [27-29]. Elevated BUN levels, a marker of renal impairment and metabolic distress, were predictive of poor outcomes [30,31]. Additionally, the presence of cerebrovascular disease and malignancies was associated with increased mortality, highlighting the need for tailored care strategies for patients with complex medical histories [32].

These findings have significant implications for clinical practice in managing SA-AKI. Early intervention is crucial; prioritizing the rapid identification and management of at-risk patients can improve outcomes. This includes the swift administration of antibiotics and aggressive management of kidney function. Addressing hypoalbuminemia through nutritional support and continuous monitoring can significantly enhance survival rates. Furthermore, special attention should be given to patients with comorbid conditions like cerebrovascular diseases and malignancies, to develop effective care strategies that address their higher risk profiles [33,34].

The ROC curve analysis demonstrated that combining multiple clinical indicators substantially improves the accuracy of mortality prediction in SA-AKI patients. The combined Area under the Curve (AUC) value of 0.796 reflects the model's strong discriminatory power, suggesting its potential utility in clinical decision-making. The model's ability to accurately predict mortality risk can assist clinicians in prioritizing and managing high-risk patients more effectively [35].

While this study provides valuable insights, it has several limitations. The retrospective design may introduce selection bias and limit the ability to establish causality. Using data from a single institution might restrict the generalizability of the findings to broader populations. Moreover, variability in how clinical data were recorded and measured could affect the robustness of the predictive model. Future research should aim to validate these findings in prospective, multicenter studies and explore integrating these predictive factors into clinical decision-support systems to improve patient management and outcomes in SA-AKI.

Conclusion

This study emphasizes the importance of early, targeted interventions and continuous monitoring of critical clinical indicators to improve survival in patients with SA-AKI. The identified predictors provide a foundation for developing more effective treatment protocols and optimizing patient care strategies within the Intensive Care Unit (ICU) setting. These insights are vital for enhancing management practices and ultimately improving patient outcomes.

Declarations

Contributors: Chongyang Ye and Tianjun Yang designed the study. Chunyan Zhu, Chongyang Ye and Shijing Hu wrote the manuscript. Chongyang Ye and Tianjun Yang revised the paper.

Data availability: The experimental data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest: The authors declared that they have no conflicts of interest regarding this work.

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Ethics statements: Patient consent for publication: Not required.

Ethics approval: The data featured in this study were sourced from the MIMIC-III database, which is publicly accessible online. Before their involvement in the research, all participants had provided their consent in written form.

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