

Development and Validation of a Risk Prediction Model of One-year Survive Rate in Vancomycin-Associated Acute Kidney Injury

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Research Article

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Running title: Qin et al. one-year survive rate model of VA-AKI patients in ICU

Abstract

Objectives

Acute kidney injury (AKI) represents a major complication of vancomycin administration, leading to high rates of mortality and treatment failure. This study aimed to construct a risk scoring system for one-year mortality in vancomycin-associated acute kidney injury.

Methods

Patients diagnosed as vancomycin associated acute kidney injury in the Medical Information Mart for Intensive Care IV (MIMIC-IV) (version 2.0) database, were identified for analysis. Using all-subsets regression and multivariate Cox regression analysis, we identified potential predictors of one-year mortality in vancomycin-associated acute kidney injury and developed a risk score by plotting nomogram.

Results

12946 patients were included in the analysis; 9064 and 3882 patients in the training and validation set were randomly divided at a 7:3 ratio, respectively. The predictive factors identified by all-subsets regression and Cox regression analysis were age, BMI, BUN, respiratory rate, infection, AKI stage 2 and 3 and cancer. With the incorporation of these factors, our model had well-fitted calibration curves and achieved good C-indexes of 0.755 (95%CI: 0.747, 0.763) and 0.749 (95%CI: 0.738, 0.761) in predicting one-year

survive rate in the training and validation set, respectively.

Conclusions

The established model in this study is a simplified score system, which provides a robust tool for the prediction of one-year survive rate in AKI patients after receiving vancomycin treatment.

Keywords: vancomycin, acute kidney injury, prediction model, survive rate

Introduction

Vancomycin is commonly used to treat methicillin-resistant staphylococcus aureus (MRSA) infections[1]. Vancomycin associated acute kidney disease (VA-AKI) is a major adverse drug reaction with an incidence rate of 15%. What is more, it reaches up to 40% in critically-ill patients[2]. Partial patients need renal replacement therapy, which is associated with prolonged hospitalization, greater incidence of end-stage kidney disease, higher health care costs, and increased mortality[3].

Risk factors of VA-AKI have been extensively studied. Age, intensive care unit (ICU) admittance, dose, cirrhosis, mechanical ventilation, length of therapy, hypertension, hyperuricemia, concomitant medications, heart failure, shock, vasopressor drugs are possible predictive factors of VA-AKI[4-9]. However, there are limited data about risk factors of one-year mortality in vancomycin-associated acute kidney injury.

By integrating multiple possible factors, risk prediction models can be developed to help clinicians to make significant clinical decisions. Forecasting future event, risk prediction models have been extensively applied and make great clinical benefits. Therefore, we

attempted to explore clinical predictors of VA-AKI and constructed a risk prediction model of one-year survive rate in VA-AKI patients.

Methods

Data Source

Medical Information Mart for Intensive Care (MIMIC) IV are openly available US-based critical care database. MIMIC IV includes integrated, detailed clinical dataset from all patients admitted to the ICU of Beth Israel Deaconess Medical Center in Boston, MA from 2008 to 2019. Basic information, vital signs, diagnoses, laboratory results, imaging examinations, and others were well recorded. In addition, international classification of diseases, 9th revision (ICD-9) and 10th revision (ICD-10) was named for precise diseases, when patients were discharged. Since data included in our study was based on the date from publicly available database, IRB approval was waived.

Study Population

Patients who received vancomycin treatment for ≥ 48 h occur AKI during the period of ICU stay were eligible. The definition of VA-AKI was the happens of AKI during vancomycin therapy or within 7 days after the withdrawal of vancomycin. Patients were excluded: 1). they had chronic kidney disease (CKD), were receiving dialysis or receipted kidney transplantation; 2). duration in ICU less than one day; 3). they were admitted to ICU more than once.

Patients were divided into two sets: derivation set and validation set. The Model was developed in the training set and independently validated in the validation set. The

inclusion and exclusion criteria were the same in the two sets.

Baseline data

The pgAdmin PostgreSQL (version 1.22.1) tool was used to extract the raw data of VA-AKI patients during their ICU admission. R software (version 4.2) was used for the data processing.

The primary outcome was one-year overall survive rate in VA-AKI patients. AKI was defined as Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guidelines[10]. AKI was diagnosed if the serum creatinine (SCr) increased by $26.5\mu\text{mol/L}$ within 48 h, or SCr rose to 1.5 times of the baseline value within 7 days or urine volume $< 0.5\text{ ml/kg/h}$ for 6 hours.

Statistical analysis

Categorical data were presented as number and percentage, compared using the chi-squared test. Continuous data were valued as mean plus/minus standard deviation or median, compared using Student's t-test or Mann-Whitney U test. Potential risk factors were assessed using all-subsets regression and multivariate Cox regression analysis in the training set. Based on the results of all-subsets regression and multivariate Cox regression analysis, a nomogram was developed using the rms package of R, version 4.2 (<http://www.r-project.org/>). Harrell's concordance index (C index) was used to value the predictive performance of the nomogram. P value <0.05 was considered statistically significant.

Results

Baseline characteristics

As shown in Figure 1, 12946 patients diagnosed as VA-AKI were included in the study. 9064 and 3882 patients were divided in the training and validation set, respectively. And 3325 one-year death patients in training set was calculated. The basic data in the training set were shown in Table 1. In the training set, age, gender, BMI, heart rate, respiratory rate, temperature, systolic blood pressure, WBC, oxygen saturation, hemoglobin, platelets, bicarbonate, blood chlorine, anion gap, blood urea nitrogen(BUN), SCr, potassium, glucose, international standard ratio (INR), prothrombin time (PT), APTT, lactate, pH, mechanical ventilation (the first day in ICU), RRT(the first day in ICU), vasopressor use (the first day in ICU), antibiotics use (the first day in ICU), infection, AKI, hypertension, congestive heart failure, cerebrovascular disease, liver disease, chronic kidney disease, cancer, CCI (the first day in ICU), APACHE II (the first day in ICU), SOFA (the first day in ICU), duration of hospital, duration in ICU, death in hospital, were significantly different between survivors and non-survivors.

Identification of potential risk factors of one-year survive rate in VA-AKI patients

Based on the results of Table 1, laboratory and baseline variables with statistically significant differences between survivors and non-survivors were entered in the all-subsets regression. The results showed that age, BMI, BUN, respiratory rate, lactate, infection, AKI stage 2 and 3 and cancer were associated one-year overall survive rate in VA-AKI patients (Figure 2). Then the mentioned variables were entered into multivariate Cox regression analysis. Finally, multivariate Cox regression model based on the all-subsets regression displayed that the age, BMI, BUN, respiratory rate, lactate, infection, AKI stage 2 and 3

and cancer were risk factors of one-year overall survive rate in VA-AKI patients (Table 2).

A new prognostic nomogram for one-year overall survive rate in VI-AKI patients

According to multivariate Cox regression, 8 factors were found to be independently associated with VA-AKI patients one-year overall survive rate: age, BMI, BUN, respiratory rate, lactate, infection, AKI stage 2 and 3 and cancer ($P < 0.05$). And all variables were eventually integrated in the final model. As shown in Figure 3, total scores were calculated through the sum of each score of different risk factors. In this nomogram, a higher total point represented worse one-year survive rate. To further identify the predictive ability of the nomogram, the values of C-index and calibration curves were also calculated. The C-index for one-year survive rate prediction in the training and validation sets were 0.732 (95%CI: 0.699-0.765) and 0.757 (95%CI: 0.704-0.810), respectively. In the end, our results indicated our nomogram had a well accuracy ability in predicting one-year survive rate in VA-AKI patients. Moreover, the calibration curves showed that the predicted and the observed one-year survive rate had a good consistency (Figure 4).

Decision Curve Analysis of the nomogram

As shown Figure 5, as the threshold probability fluctuates between 0.01 and 0.85, the decision curve analysis of this nomogram showed good net benefit. Therefore, the model has good clinical practical value in predicting one-year overall survive rate in VA-AKI patients.

Discussion

In this study, we found that age, BMI, BUN, respiratory rate, infection, lactate, AKI stage 2 and 3 and cancer were risk factors of one-year survive rate in VA-AKI patients. Based on this, we developed and validated a risk prediction model for VA-AKI patients. To the best of our knowledge, our study is the first to attempt to develop a risk prediction model of one-year survive rate in VA-AKI patients.

Vancomycin, one of the most commonly antibiotics, is used for critically ill patients in ICU. Widespread treatment with vancomycin has been linked with an increased incidence of vancomycin-associated acute kidney injury. Though often reversible, vancomycin associated AKI may affect up to 40% of patients' treatment with vancomycin, with higher incidence of AKI[11], which lead to increased morbidity, hospital admissions, length of stay and seriously threaten patients' health and survival. And moderate degrees of AKI have been associated with increased mortality in critically ill patients[3].

Vancomycin-associated AKI occurred in about 40% of critically-ill patients[12]. Nephrotoxicity is a serious adverse event of vancomycin treatment and it is also related with 30-day hospital readmission rates and all-cause 30-day mortality[13]. Risk factors associated with vancomycin-induced nephrotoxicity were still not clearly demonstrated. Different risk factors and outcomes were reported with vancomycin-related nephrotoxicity. Risk factors, such as age, BMI, vancomycin exposure, duration of therapy, increased body weight, preexisting renal dysfunction, blood urea nitrogen (BUN) to serum creatinine ratio

greater than 20:1 at initiation of therapy, vancomycin doses greater than 4 grams in 24 hours, and higher serum vancomycin trough levels, critical illness, and concurrent nephrotoxin therapy[14-19], had been demonstrated to be related with VA-AKI. However, limited studies evaluated the long-term morbidity or mortality after VA-AKI and the possible risk factors. Outcomes associated with vancomycin-related AKI require additional research for further elucidation.

Based on large scale of patients' data, for the first time, this study found that age, BMI, BUN, respiratory rate, infection, AKI stage 2 and 3 and cancer were important prognostic factors for VA-AKI, which is consistent with the findings of other studies. For example, consider a 70-year-old man with VA-AKI stage 2, and severe pneumonia. The patient's BMI was 25 kg/m², BUN level 40 mg/dL, lactate level 2 mmol/L, respiration rate 15/min. According to Figure 3, the score of each individual parameter in this case should be based on the first row. For example, for age, the score will be approximately 60 based on an age of 70 years. And the final score is calculated as the total points for all parameters (60 (age) + 38 (BMI) + 22(BUN) + 25 (lactate) + 15 (respiration rate) + 15(infection) +13(AKI stage 2) =134). This score corresponds to a risk of one-year survival rate in VA-AKI patients of approximately 81%. It is helpful for us to identify the risk factors that affect the 1-year survival rate of VA-AKI patients early and take effective preventive measures in time.

There are also some limitations to our study. First, our study was a retrospective analysis. Second, this was a single-center study. Multicenter trials would be beneficial in identifying

the influence of the one-year survive rate while receiving vancomycin therapy. However, our results firstly used the potential risk factors to develop a scoring system and had important clinical significance.

Conclusions

In this study, to the best of our knowledge, this is the first study to propose a risk scoring system for predicting 1-year survival rate of VA-AKI patients. The application of this nomogram can help physicians in decision-making regarding treatment and management, which may in turn help reduce mortality caused by VA-AKI.

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Conflicts of Interest: No conflicts of interest need to be declared.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Study design: Fei Zhao and Li Qin; Data extraction: Xia Chen and Fei Zhao; Data analysis: Li Qin; Model development and deployment: Li Qi; Manuscript preparation: Li Qin and Fei Zhao. All authors reviewed and approved the final manuscript.

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Figure and Table

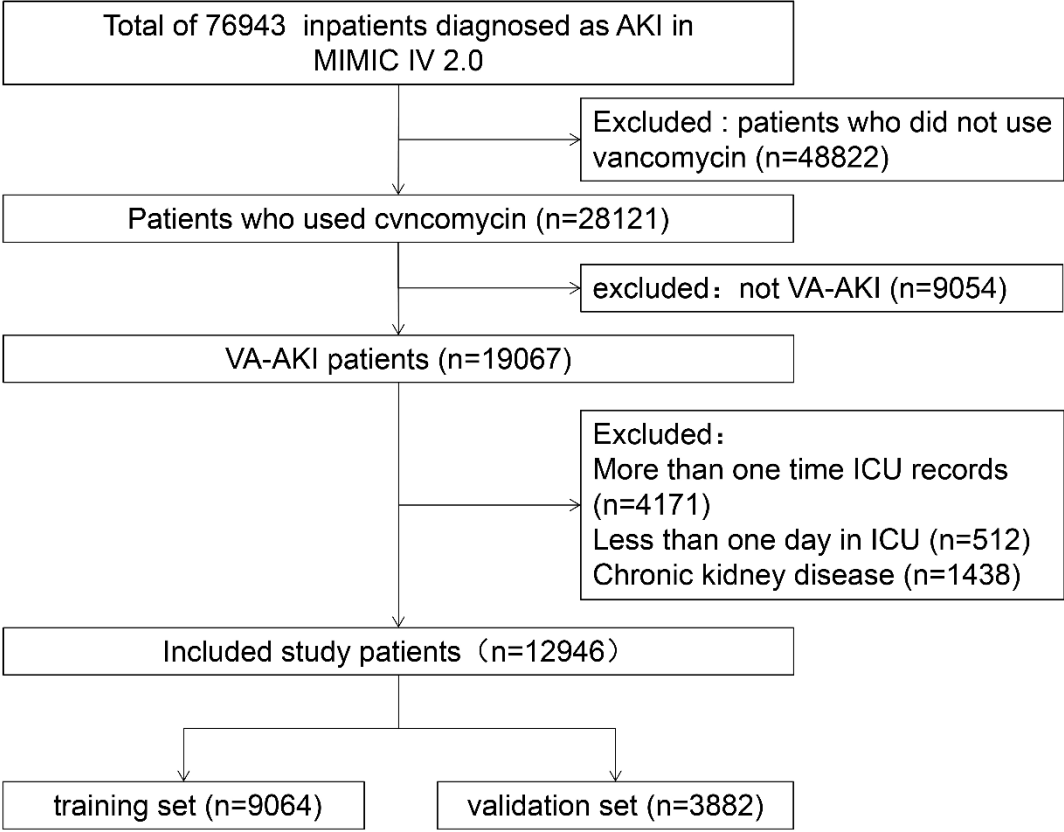


Figure 1. The flowchart of the cohort selection process.

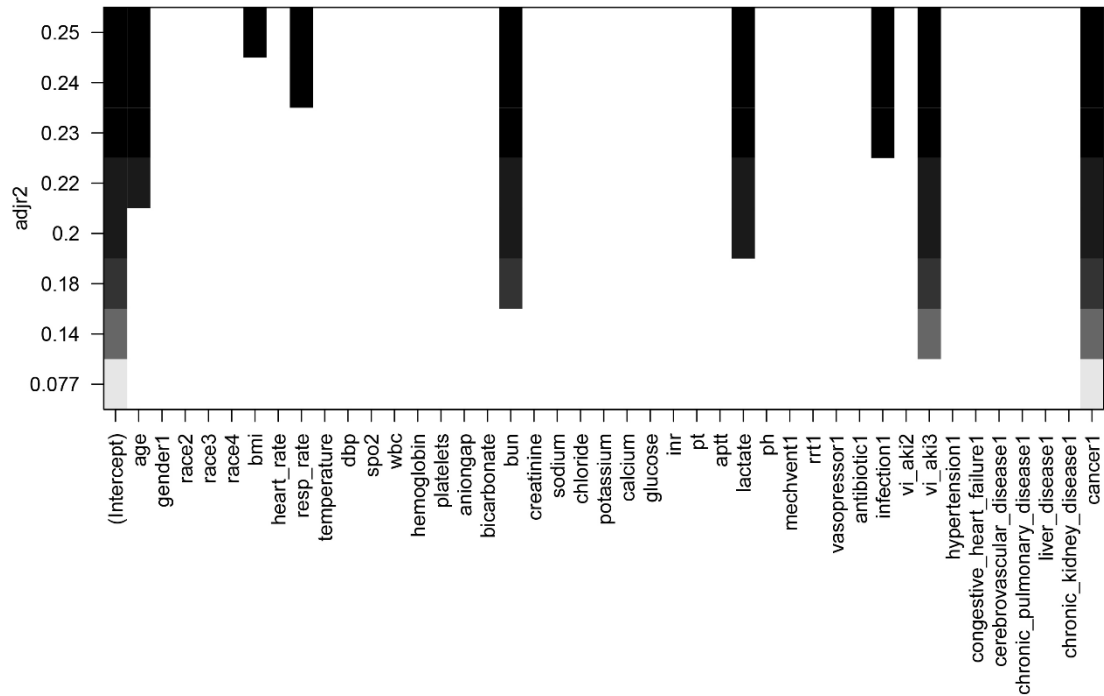


Figure 2. All-subsets regression to screen predictors for one-year overall survive rate in

VA-AKI patients.

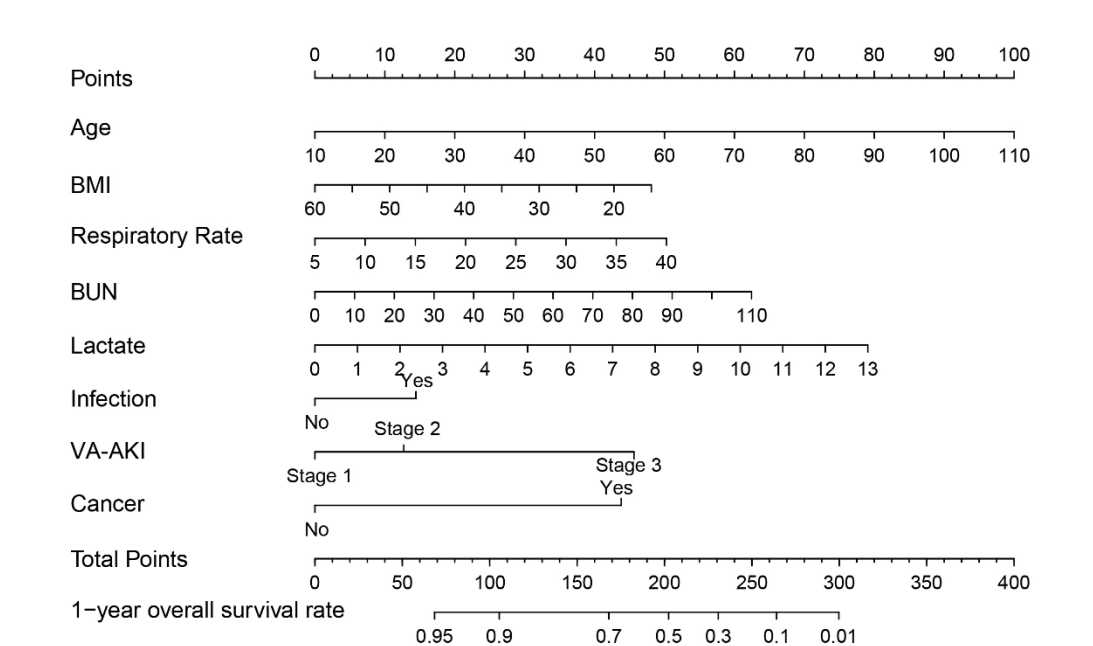


Figure 3. Predictive nomogram for one-year survive rate in VA-AKI.

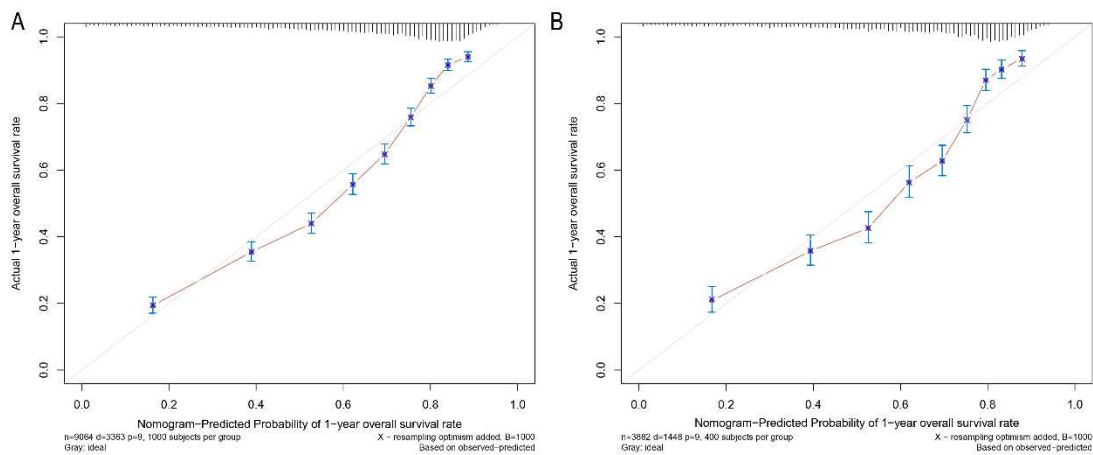


Figure 4. The calibration curve of the nomogram for predicting one-year survive rate in VA-AKI patients in the training (A) and the validation (B) sets. The dotted line represents the ideal curve. X-axis: survival rate as predicted by the nomogram; Y-axis: actual survival rate in the cohort.

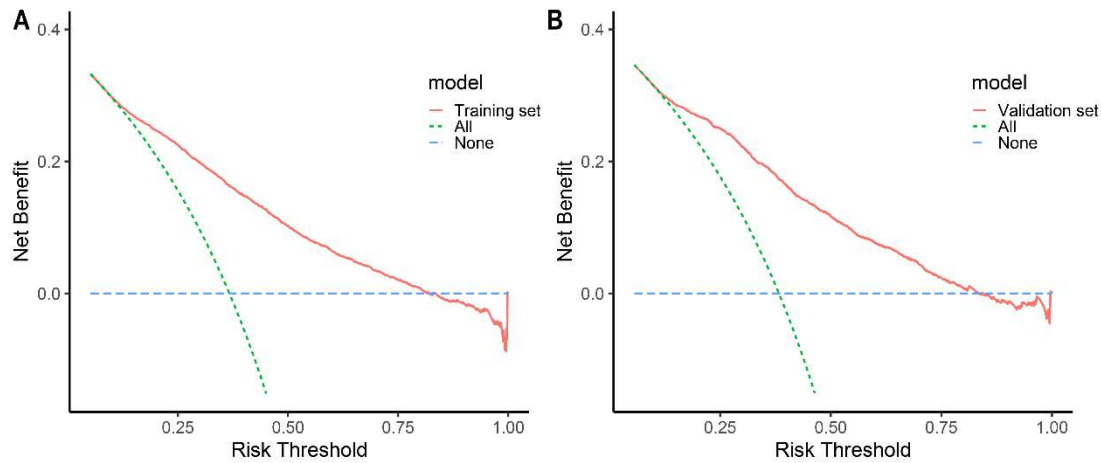


Figure 5. Decision curve for the training set cohort implicating the net benefit with the use of the nomogram. The y-axis represents the net benefit. The x-axis represents the threshold value. The red line represents the nomogram model, The blue grey line is the assumption that all patients have the outcome (deceased). A thin green line is the assumption that no patients have the outcome (deceased)

Table 1: Comparison of the demographic and clinical characteristics between survivors and non-survivors in the training set

Patient characteristics	survivors N=5739	non-survivors N=3325	<i>P value</i>
Age (years)	65.01 (15.12)	70.59 (14.98)	<0.001
Gender			<0.001
Female, n (%)	2257 (39.33%)	1478 (44.45%)	
Male, n (%)	3482 (60.67%)	1847 (55.55%)	
Ethnicity			0.006
White, n (%)	3975 (69.26%)	2207 (66.38%)	
Black, n (%)	417 (7.27%)	300 (9.02%)	
Other races, n (%)	515 (8.97%)	301 (9.05%)	
Unknown, n (%)	832 (14.50%)	517 (15.55%)	
BMI,((kg/m ²)	29.72 (7.38)	28.22 (7.50)	<0.001
Heart rate, n (%)	88.71 (19.32)	94.78 (21.24)	<0.001
Respiratory rate, n (%)	18.82 (5.91)	21.48 (6.47)	<0.001
Temperature (°C)	36.71 (0.87)	36.65 (0.96)	0.005
SBP, (mmHg)	118.31 (23.24)	118.58 (24.54)	0.609
DBP, (mmHg)	65.58 (16.81)	67.29 (18.83)	<0.001
Oxygen saturation, (%)	97.53 (3.53)	96.23 (4.35)	<0.001
WBC, (×10 ⁹ /L)	12.90 (6.73)	13.75 (8.17)	<0.001
HGB, (g/dL)	10.87 (2.34)	10.63 (2.40)	<0.001
PLT, (×10 ⁹ /L)	207.76 (107.95)	217.67 (129.90)	<0.001
Anion gap, (mEq/L)	14.47 (4.39)	16.69 (5.02)	<0.001
Bicarbonate, (mEq/L)	23.00 (4.39)	22.14 (5.78)	<0.001
BUN, (mg/dL)	22.88 (16.16)	33.40 (23.16)	<0.001

Patient characteristics	survivors N=5739	non-survivors N=3325	<i>P value</i>
SCr, (mg/dL)	1.17 (0.80)	1.50 (1.06)	<0.001
Sodium, (mg/dL)	138.21 (4.47)	137.83 (5.99)	0.002
Chloride, (mg/dL)	104.30 (6.20)	102.42 (7.16)	<0.001
Potassium, (mg/dL)	4.27 (0.74)	4.38 (0.89)	<0.001
Calcium (mg/dL)	8.28 (0.85)	8.26 (0.92)	0.285
Glucose, (mg/dL)	146.06 (65.77)	155.01 (77.37)	<0.001
INR, n (%)	1.48 (0.68)	1.74 (1.01)	<0.001
PT, (s)	16.17 (7.02)	18.81 (10.39)	<0.001
APTT, (s)	37.34 (21.53)	40.99 (25.16)	<0.001
Lactate, (mmol/l)	1.85 (1.42)	2.69 (2.37)	<0.001
pH	7.38 (0.09)	7.35 (0.11)	<0.001
Mechanical ventilation (the first day in ICU)			<0.001
0	2362 (41.16%)	1555 (46.77%)	
1	3377 (58.84%)	1770 (53.23%)	
RRT(the first day in ICU)			<0.001
0	5661 (98.64%)	3216 (96.72%)	
1	78 (1.36%)	109 (3.28%)	
Vasopressor use(the first day in ICU)			<0.001
0	2447 (42.64%)	1574 (47.34%)	
1	3292 (57.36%)	1751 (52.66%)	
Antibiotics use(the first day in ICU)			<0.001
0	657 (11.45%)	496 (14.92%)	
1	5082 (88.55%)	2829 (85.08%)	
Infection			<0.001
0	3071 (53.51%)	1116 (33.56%)	
1	2668 (46.49%)	2209 (66.44%)	
AKI			<0.001
Stage 1	1583 (27.58%)	488 (14.68%)	
Stage 2	3077 (53.62%)	1366 (41.08%)	
Stage 3	1079 (18.80%)	1471 (44.24%)	
Hypertension			0.001
0	1882 (32.79%)	1208 (36.33%)	
1	3857 (67.21%)	2117 (63.67%)	
Diabetes			0.082
0	3863 (67.31%)	2297 (69.08%)	
1	1876 (32.69%)	1028 (30.92%)	
Myocardial infarct			0.173
0	4508 (78.55%)	2652 (79.76%)	
1	1231 (21.45%)	673 (20.24%)	
Congestive heart failure			<0.001

Patient characteristics	survivors N=5739	non-survivors N=3325	<i>P value</i>
0	4003 (69.75%)	2056 (61.83%)	
1	1736 (30.25%)	1269 (38.17%)	
Cerebrovascular disease			<0.001
0	5012 (87.33%)	2753 (82.80%)	
1	727 (12.67%)	572 (17.20%)	
Chronic pulmonary disease			<0.001
0	4234 (73.78%)	2305 (69.32%)	
1	1505 (26.22%)	1020 (30.68%)	
Liver disease			<0.001
0	5040 (87.82%)	2589 (77.86%)	
1	699 (12.18%)	736 (22.14%)	
Chronic kidney disease			<0.001
0	4990 (86.95%)	2667 (80.21%)	
1	749 (13.05%)	658 (19.79%)	
Cancer			<0.001
0	5276 (91.93%)	2358 (70.92%)	
1	463 (8.07%)	967 (29.08%)	
CCI	5.20 (2.47)	7.09 (2.80)	<0.001
SOFA	6.46 (3.56)	8.57 (4.30)	<0.001
APACHEII	21.73 (6.95)	25.87 (7.72)	<0.001
Duration of in hospital, (day)	14.91 (12.80)	14.04 (14.16)	0.004
Duration of ICU, (day)	6.45 (7.44)	7.64 (7.83)	<0.001
Death in ICU, n(%)			0.000
0	5739 (100.00%)	1529 (45.98%)	
1	0 (0.00%)	1796 (54.02%)	

Abbreviations: 0,NO; 1,Yes;SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC: White blood cell count; BMI,Body Mass Indexes;HGB, hemoglobin; PLT, blood platelet; BUN, blood urea nitrogen; SCr, serum creatinine; INR, international normalized ratio; PT, prothrombin time; APTT, partial thromboplastin time; RRT, renal replacement treatment; CCI, Charlson Comorbidity Index; APACHE II, Simplified Acute Physiology Score II; SOFA, sequential organ failure assessment.

Table 2. Predictors Included in the Cox regression analysis Model

Predictors	results		
	β value	OR (95%CI)	P value
Age	0.019	1.020 (1.017-1.022)	<0.001
BMI	-0.021	0.979 (0.974-0.984)	<0.001
BUN	0.011	1.011 (1.010-1.013)	<0.001
Lactate	0.118	1.126 (1.109-1.142)	<0.001
Respiratory rate	0.028	1.028 (1.023-1.034)	<0.001
AKI			
Stage 1		Ref	
Stage 2	0.247	1.280 (1.154-1.421)	<0.001
Stage 3	0.887	2.429 (2.181-2.704)	<0.001
Infection			
No		Ref	
Yes	0.281	1.324 (1.230-1.426)	<0.001
Cancer			
No		Ref	
Yes	0.852	2.344 (2.172-2.529)	<0.001

Abbreviations: BMI,Body Mass Indexes;BUN, blood urea nitrogen;