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Prognostic factors and evaluation methods of acute kidney injury among sepsis patients with pulmonary infection

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Abstract. – OBJECTIVE: Acute kidney injury (AKI) is difficult to detect in the early stages, yet is commonly associated with sepsis and infectious shock, with pulmonary infection being the most frequent culprit. This study aimed to estimate risk factors and their effects on 28-day survival among sepsis patients with pulmonary infection complicated by AKI and assessed the prognostic values of some detection indicators.

PATIENTS AND METHODS: From February 2019 to July 2021, the data of 151 patients admitted to the emergency intensive care unit (EICU) of Nanjing First Hospital with pulmonary infection complicated with sepsis were collected in this retrospective study. The patients were categorized into two groups (survivors and non-survivors) depending on the 28-day survival, compared their clinical characteristics, and analyzed the predictors of survival.

RESULTS: Cox regression analysis revealed that serum cystatin-C level, serum lactate level, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system were independent risk factors for 28-day survival. In predicting 28-day survival, the area under the receiver operating characteristic curve (ROC) for serum Cystatin-C level, serum lactate level, APACHE II score, and the three combinations was 0.74, 0.67, 0.71, and 0.86, respectively. Accordingly, the sensitivity and specificity of the three indicators of 28-day survival were 87.50% and 66.67%, respectively, which were superior to individual indicators.

CONCLUSIONS: Sepsis patients with pulmonary infection have a high risk of AKI, and multiple risk factors contribute to this risk. AKI patients may also be adversely affected by a variety of factors, including APACHE II scores, serum Cystatin-C levels, and serum lactate levels, all of which are commonly used to assess the outcomes.

Key Words:
Sepsis, Acute kidney injury, Pulmonary infection.

Introduction

Acute kidney injury (AKI) is associated with sepsis and infectious shock, and pulmonary infection is the most common. It has been reported that 64% of sepsis patients suffer from AKI, which has been associated with mortality in critical illness[1]. There has been some improvement in the treatment of AKI in recent years, however, the results are still unsatisfactory. The difficulty in detecting AKI in the early stages results in delayed diagnosis, discontinuation of nephrotoxic drugs, and the treatment of other predisposing factors, such as sepsis[2]. In order to identify early changes in the risk factors associated with the occurrence of AKI in critical illness with pulmonary infections complicated by sepsis, researchers examined the occurrence of AKI and its associated prognostic indicators.

Acute physiology and chronic health evaluation (APACHE II) is an authoritative scoring system for assessing the severity of critical illness, and the Sequential Organ Failure Assessment SOFA) score describes the occurrence and development of multiple organ dysfunction syndrome (MODS), both of which are useful tools for the prognosis of severe patients[3]. Moreover, studies[4] have indicated that there were some other indicators that could be considered to be indicators for the early prediction of AKI among sepsis patients with pulmonary infection. The present retrospective study aimed to investigate the risk factors for AKI in patients with pulmonary infections combined with sepsis, the value of each test in prognostic assessment, and an effective method for assessing these patients' prognoses after developing AKI.

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Patients and Methods

Patient Selection

From February 2019 to July 2021, 151 patients were enrolled in this retrospective study. They all were≥18 years old and suffered from sepsis with pulmonary infection in the Emergency Intensive Care Unit (EICU) of Nanjing First Hospital, including 74 patients with AKI (AKI group) and 77 patients without AKI (Non-AKI group). Meanwhile, we divided patients into two groups [survivors (n=45) and non-survivors (n=29)] according to the 28-day survival, compared their clinical characteristics, and analyzed the predictors of survival. The study was approved by the medical ethics committee of the Nanjing First Hospital.

Our inclusion criteria were as follows: (1) admission to the hospital with a diagnosis of pulmonary infection with microbiological evidence or clinical assessment of sepsis, meeting the diagnostic requirements for sepsis by the Critical Care Medicine Section of the Chinese Medical Association[5]. (2) Patients did not receive treatment for AKI prior to admission or were treated with blood purification. We excluded 10 patients who died within the first 24 h of admission, who were <18 years of age, who were on chronic dialysis, or who were diagnosed with terminal malignancy.

Data Collection

Standard demographic, clinical, and physiological data were retrieved. Demographic information included age, gender, and source of admission. All patients underwent a standard set of investigations, including complete blood count, chest radiograph, urinalysis, two blood cultures, tests for liver function, serum creatinine, urea, cardiac enzymes, electrolytes, calcitonin (PCT), C-reactive protein (CRP), oxygenation index, neutrophil gelatinase-associated lipocalin (NGAL), serum lactate levels, serum cystatin-C level, some complications, APACHE II score and SOFA score within 24 hours of admission. In this study, we employed the Kidney Disease Improving Global Outcomes (KDIGO) definition for the diagnosis of AKI, which designated change in serum creatinine as the primary metric for AKI diagnosis[6]. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sepsis-related organ failure assessment (SOFA) scores for all patients were obtained at admission. Furthermore, we tracked the use of antibiotics, duration of ventilation, vasopressor therapy, and the length of Intensive Care Unit (ICU) stay.

Statistical Analysis

We used IBM SPSS Statistics version 26.0, (IBM Corp., Armonk, NY, USA) and MedCalc statistical software version 17.9 (MedCalc Software, Ostend, Belgium). Categorical variables were expressed as numbers or percentages, while continuous variables were expressed as mean±SD. Tables and graphs were used for descriptive statistics. The results of statistics were compared using the Wilcoxon signed rank, the Mann-Whitney U test, and the independent samples *t*-test. Cumulative mortality was calculated using the Kaplan-Meier method and the log-rank test. A COX regression model was used to analyze prognostic factors for AKI patients. Odds ratios (ORs) and relative ratio (RR) were used to describe the relationship between the variables and poor prognosis. Receiver operating characteristic (ROC) curve analysis was conducted to identify potential predictors and cut-off points, and a $p<0.05$ was considered statistically significant.

Results

Demographic Data

Among 151 sepsis patients with pulmonary infection, 74 patients developed AKI. The characteristics of patients in whom AKI occurred (AKI group) and patients in whom AKI did not occur (Non-AKI group) are shown in Table I. BMI, APACHE II score, SOFA score, serum PCT, serum CRP, white blood cell (WBC) count, lactate, Cystatin-C, NGAL level, TnI, Creatine kinase (CK), and Cr level on admission were significantly higher in the AKI group than in the group without AKI. Also, patients in the AKI group had significantly more combined renal disease on admission, longer duration of mechanical ventilation, more frequent use of vasoactive agents, longer ICU stay, and significantly higher mortality. In addition, there were no statistical differences between the two groups in age and gender.

Risk of Death Associated with AKI in Patients with Pulmonary Infections Combined with Sepsis

There was a high incidence of AKI in 74 patients, and the 28-day overall mortality rate for all patients included was 26.5% (40/151). K-M survival curves indicated a significantly higher mortality rate in patients who developed AKI than in those who did not (Figure 1).

Table I. Demographic characteristics of patients with AKI and without AKI.

Variables	AKI (n=74)	Non-AKI (n=77)	*p*-value
Age (years)	73.5±13.8	75.8±12.1	0.27
Gender (M/F)	50/24	47/30	0.19
BMI (kg/m^2)	24.64±5.97	21.95±5.04	**0.009**
APACHE II Score	25.95±7.02	22.31±7.61	**0.03**
SOFA Score	7.68±2.89	5.00±2.64	**<0.001**
Comorbidities, n (%)			
CKD	10 (13.5%)	1 (1.3%)	**<0.001**
CVD	33 (44.6%)	40 (51.9%)	0.81
Hypertension	58 (78.4%)	54 (70.1%)	0.25
Diabetes	27 (36.5%)	23 (29.9)	0.39
ND	26 (35.1%)	39 (50.6%)	0.08
Serum PCT (ng/ml)	21.33±30.83	4.58±13.36	**<0.001**
Serum D-Dimers (ug/ml)	8.56±12.09	5.37±8.21	0.074
Serum IL-6 (ng/ml)	2.67±2.39	2.37±2.56	0.24
Serum CRP (mg/l)	121.18±84.21	48.35±50.77	**0.001**
WBC (10^9/L)	3.57±3.26	1.57±1.30	**0.03**
Oxygenation Index (mmHg)	193.91±94.67	218.22±96.48	0.12
Serum Lactate (mmol/l)	3.57±3.26	1.57±1.30	**<0.001**
Serum Cystatin-C (mg/L)	1.96±0.91	1.17±0.38	**<0.001**
NGAL (ng/ml)	668.81±561.72	233.70±199.11	**<0.001**
ALT (U/L)	56.13±140.75	43.79±53.40	0.78
AST (U/L)	96.29±192.73	45.29±47.55	0.17
Serum albumin (g/l)	30.22±7.29	32.10±4.17	0.49
BNP (pg/ml)	663.22±725.19	512.61±686.58	0.15
TnI (ng/ml)	4.24±9.39	0.78±1.42	**0.042**
CK (U/L)	1,040.76±2,384.91	218.22±96.48	**<0.001**
Admission SCr (umol/l)	172.64±134.74	56.19±18.13	**<0.001**
Mechanical ventilation (h)	13.78±8.89	5.8±4.32	**0.044**
Medication, n (%)			
β-lactam antibiotics	36 (48.6%)	50 (64.9%)	0.064
Vancomycin	13 (17.6%)	5 (6.5%)	0.071
Vasoactive drugs	40 (54.1%)	21 (27.3%)	**0.001**
Length of stay in ICU (d)	13.37±10.53	9.10±6.01	**0.037**
28-day mortality	31 (41.89%)	9 (11.69%)	**<0.001**

Variables are expressed as median (interquartile range) or number (percentage); BMI=Body Mass Index, CKD=Chronic kidney disease, CVD=cerebrovascular disease, ND=Nervous system diseases, CRP=C-reactive protein, WBC=White blood cell count, NGAL=neutrophil gelatinase-associated lipocalin, BNP=B-type natriuretic peptide, CK=Creatine kinase, ICU=Intensive care unit.

Univariate Analysis of Factors Affecting 28-day Survival in Patients with AKI

In patients with AKI, the APACHE II score, SOFA score, probability of combined renal disease, oxygenation index, serum lactate levels, and Cystatin-C levels were significantly higher in the non-survivors compared to the survivors (Table II, $p<0.05$). Meanwhile, non-survivors were on vancomycin and vasoactive drugs for a longer period of time than the survivors (Table II, $p<0.05$). There was no statistical difference in gender, age, BMI, WBC, duration of mechanical ventilation, and serum CRP level (Table II, $p>0.05$).

Risk Factors for Poor Prognosis in AKI Patients Analyzed by Cox Regression Analysis

APACHE II score, serum lactate level, and serum Cystatin-C level were independent variables in the Cox Regression Analysis for 28-day survival in AKI patients. We concluded that APACHE II score, serum lactate level, and serum Cystatin-C

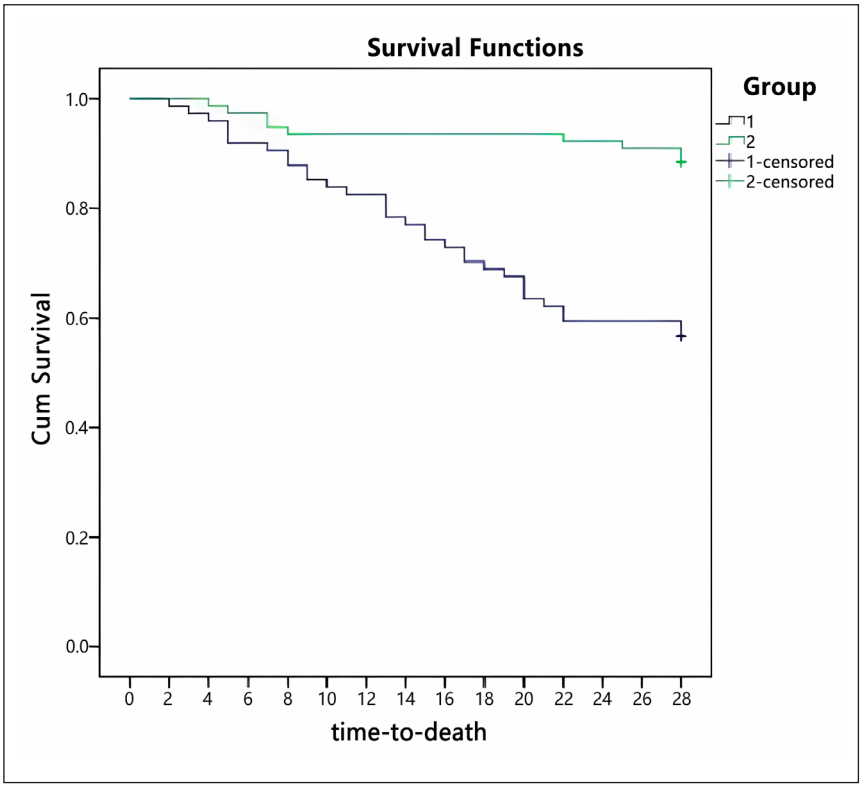

Figure 1. 28d survival curve for sepsis patients with pulmonary infection. Group 1: AKI group; Group 2: Non-AKI group; *p<0.05 by Log-rank (Mantel-Cox) test.

level were risk factors for death within 28 days in patients with AKI combined with sepsis of pulmonary infection (Table III, p>0.05).

The area under the ROC curve for serum cystatin-C level, serum lactate level, APACHE II score, and a combination of three for prediction of 28-day survival predictions were 0.74, 0.67, 0.71, and 0.86, respectively. The sensitivity and specificity of the combination of the three indicators (serum cystatin-C, lactate levels, APACHE II scores) in predicting death within 28 d was 87.50% and 66.67%, respectively, and the combination was superior to any of these tests individually (Figure 2, Table IV).

Discussion

The timely and effective treatment of pulmonary infections combined with sepsis depends on the early diagnosis; thus, it is essential to identify risk factors or biomarkers related to organ dysfunction caused by sepsis (e.g., AKI)[7]. Supportive care and identification of the cause are essential to the treatment of AKI. Therefore, early prediction or detection of AKI and monitoring renal function could improve the outcome in patients with AKI[8]. Therefore, this study investigated the onset of AKI in patients with pulmonary infections combined with sepsis and the effects of the associated risk factors on 28-day survival predictions and the outcome, interrogating a clinical database relating to critically ill patients.

The present study revealed that BMI, APACHE II score, SOFA score, serum PCT, serum CRP, WBC count, lactate, Cystatin-C, NGAL, TnI, CK, and Cr level on admission were significantly higher in the AKI group than in the group without AKI. Also, patients in the AKI group had significantly more combined renal disease on admission, longer duration of mechanical ventilation, more frequent use of vasoactive agents, longer ICU stay, and significantly higher mortality. Therefore, the early detection of AKI and timely intervention are of paramount importance. Sepsis-related AKI with complications was associated with an over 70% mortality rate, which is significantly higher than that of sepsis-related AKI without complications[9]. Moreover, the presence of comorbidities, overload in fluid, medications, and age factors can also increase the risk of AKI[10,11]. Hence, there are many factors associated with the development of AKI.

Table II. Results of univariate analysis of baseline risk factors for 28-day mortality with AKI.

Variables	Survivors (n=29)	Non-survivors (n=45)	*p*-value
Age (years)	76.26±11.69	71.49±15.01	0.13
Gender (M/F)	20/9	33/12	0.05
BMI (kg/m^2)	23.45±6.69	25.49±5.33	0.06
APACHE II Score	28.42±7.42	24.16±6.20	**0.02**
SOFA Score	8.97±3.14	6.74±2.32	**0.001**
Comorbidities, n (%)			
CKD	7 (24.1%)	4 (8.9%)	**<0.001**
CVD	18 (62.1%)	15 (33.3%)	0.067
Hypertension	21 (72.4%)	37 (82.2%)	0.46
Diabetes	11 (37.9%)	16 (35.5)	0.74
ND	12 (41.4%)	14 (31.1%)	0.68
Serum PCT (ng/ml)			
SerumD-Dimer (ug/ml)	25.56±33.7	18.30±28.66	0.59
Serum IL-6 (ng/ml)	9.17±12.42	8.11±11.98	0.64
Serum CRP (mg/l)	2.22±1.64	3.04±2.84	0.46
WBC (10^9/L)	138.50±89.57	96.17±89.57	0.29
Oxygenation Index (mmHg)	14.24±8.68	14.32±7.02	0.96
Serum Lactate (mmol/l)	171.20±93.18	210.68±93.32	**0.049**
Serum Cystatin-C (mg/L)	4.53±3.82	2.88±2.62	**0.04**
NGAL (ng/ml)	2.22±1.01	1.74±0.77	**0.04**
ALT (U/L)	631.91±533.73	696.92±593.63	0.87
AST (U/L)	37.54±30.32	68.84±181.90	0.79
BNP (pg/ml)	88.14±63.04	102.00±248.42	0.84
TnI (ng/ml)	743.53±797.29	582.91±659.76	0.41
Admission SCr (umol/l)	3.12±3.46	4.86±11.49	0.48
Medication, n (%)	176.01±136.32	170.21±135.15	0.57
β-lactam antibiotics (n)	13 (44.8%)	23 (51.1%)	0.81
Vancomycin (n)	8 (27.6%)	5 (11.1%)	**0.03**
Vasoactive drugs (n)	21 (72.4%)	19 (42.2%)	**0.01**
Length of stay in ICU (d)	13.89±9.34	12.94±11.53	0.42

Variables are expressed as median (interquartile range) or number (percentage). BMI=Body Mass Index, CKD=Chronic kidney disease, CVD=Cerebrovascular disease, ND=Nervous system diseases, CRP=C-reactive protein, WBC=White blood cell count, NGAL=neutrophil gelatinase-associated lipocalin, BNP=B-type natriuretic peptide, CK=Creatine kinase, ICU=Intensive care unit.

The prognosis and risk factors of acute kidney injury (AKI) in patients with sepsis due to pulmonary infection have been discussed. We found that the APACHE II score, SOFA score, probability of combined renal disease, oxygenation index, serum lactate levels and Cystatin-C levels were significantly higher in the non-survivors compared to the survivors in patients with AKI, which was consistent with the literature. These included changes in some metabolic levels, such as the increasing of serum lactate levels. Furthermore, these metabolic changes have been report-

Table III. Cox regression analysis of prognostic factors in patients with patients in AKI.

Variables	RR	*p*-value	95% CI
APACHE II Score	3.60	0.01	1.13-22.89
Serum lactate	1.91	0.03	1.14-3.38
Serum Cystatin-C	1.27	0.04	1.08-1.95

RR: relative risk; CI: confidence interval.

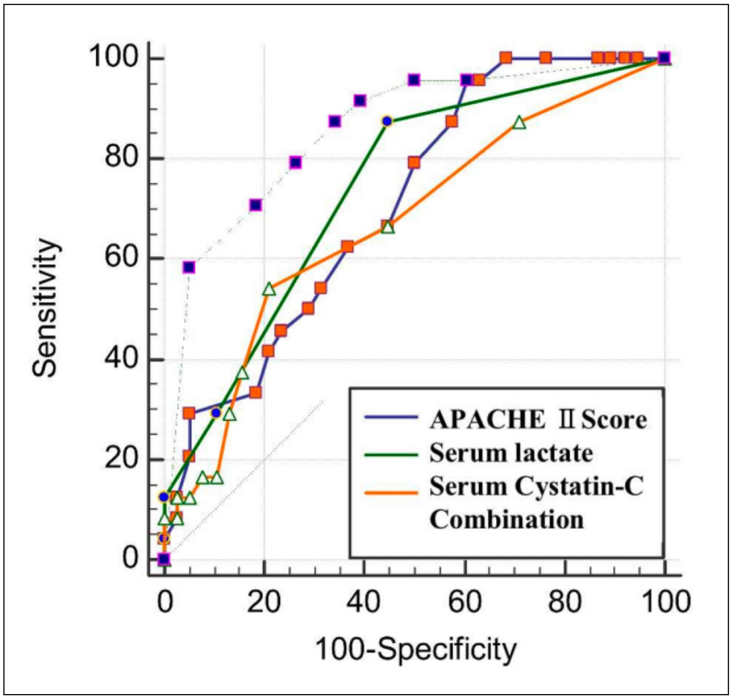

Figure 2. Serum cystatin-C, Serum lactate, APACHE II score, and a combination of three for prediction of 28-day survival predictions.

Table IV. Serum Cystatin-C, Serum lactate, APACHE II score and a combination of three for prediction of 28-day survival predictions.

Variables	AUC	Sensitivity	Specificity
APACHE II Score	0.71	96.55	40.00
Serum Cystatin-C	0.74	89.66	52.27
Serum lactate	0.67	52.72	77.78
Combination	0.86	87.50	66.67

AUC=area under the receiver operating characteristic curve.

ed as markers of cell death and tissue damage in animal models of sepsis, suggesting the danger of organ damage in AKI[12]. Among patients with AKI, serum Cystatin-C level was associated with death within 28 days. Cystatin-C, also known as CysC, is a protein, which is low in molecular weight and belongs to the class of cysteine proteinase inhibitors[13]. As cystatin-C is not secreted into the urine by the tubules, its presence in the urine indicates tubular damage, and its concentration depends on glomerular filtration rate (GFR) and is more sensitive than serum creatinine in the detection of GFR (60-90 ml/min)[14]. In contrast to serum creatinine, Cystatin C is more accurate at predicting PBD-induced AKI in the early stages[15]. Therefore, Cystatin C may be a new predictor of pejorative outcomes in patients with AKI. This study revealed for the first time that the area under the ROC curve for serum cystatin-C, lactate levels, APACHE II scores, and a combination of three for prediction of 28-day survival predictions were 0.74, 0.67, 0.71, and 0.86, respectively. The results showed that serum Cystatin-C level, lactate level, and APACHE II score had a certain predictive value for prognosis in AKI among sepsis patients with pulmonary infection and that the sensitivity and specificity of the combined prediction were higher. As a single factor may not be sufficient to determine the prognosis of a patient with AKI, various factors should be evaluated, in order to better understand the disease and to apply for the proper and timely treatment. Although the combined analyses had lower sensitivity and specificity than the single analyses, it is still optimal, which could be explained by the small sample size of the single-center study.

The specific mechanism by which serum Cystatin-C levels, lactate levels, and APACHE II

scores can improve the prognosis of AKI patients with pulmonary infections combined with sepsis needs to be further investigated. Meanwhile, the sample size of this study is small, which makes it challenging to draw firm conclusions.

Limitations

This study has several important limitations. Firstly, we collected data from the independent intensive care unit (ICU). Therefore, non-ICU patients were not included. Secondly, this study only focused on the occurrence of AKI but did not conduct the AKI stage. Thirdly, our study was limited by its retrospective design, which may have introduced biases in both participant selection and recall of events. Finally, our sample size was relatively small. Hence, enough data were not available to draw objective conclusions for some parameters. It is crucial to perform a study with a larger sample population to validate our results.

Conclusions

In summary, sepsis patients with pulmonary infection have a high risk of AKI, and multiple risk factors contribute to this risk. AKI patients may also be adversely affected by a variety of factors, including APACHE II scores, serum cystatin-C levels, and serum lactate levels, all of which are commonly used to assess outcomes.

Ethics Approval

The clinical study protocol was approved by the Ethics Committee of Nanjing First Hospital (Approval number: KY20201102-03).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

HD. Q designed the study. WN wrote the initial draft of the manuscript and produced the figures. WN contributed to the analysis and interpretation of data. HD. Q revised the work critically for important intellectual content. HD. Q supervised the whole study. All authors approved the final version of the manuscript and agreed to be 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.

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Data Availability

All data generated or analyzed during this study are included in this published article.

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