Original Paper

Risk Factor Analysis for AKI Including Laboratory Indicators: a Nationwide Multicenter Study of Hospitalized Patients

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Key Words

Acute kidney injury • Epidemiology • Mortality • Risk factors • Serum uric acid

Abstract

Background/Aims: Risk factor studies for acute kidney injury (AKI) in China are lacking, especially those regarding non-traditional risk factors, such as laboratory indicators. **Methods:** All adult patients admitted to 38 tertiary and 22 secondary hospitals in China in any one month between July and December 2014 were surveyed. AKI patients were screened according to the Kidney Disease: Improving Global Outcomes' definition of AKI. Logistic regression was used to analyze the risk factors for AKI, and Cox regression was used to analyze the risk of in-hospital mortality for AKI patients; additionally, a propensity score analysis was used to reconfirm the risk factors among laboratory indicators for mortality. **Results:** The morbidity of AKI was 0.97%. Independent risk factors for AKI were advancing age, male gender, hypertension, and chronic kidney disease. All-cause mortality was 16.5%. The predictors of mortality in AKI patients were advancing age, tumor, higher uric acid level and increases in Acute Physiologic Assessment and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores. The hazard ratio (HR) for mortality with uric acid levels > 9.1 mg/dl compared with ≤ 5.2 mg/dl was 1.78 (95% CI: 1.23 to 2.58) for the AKI patients as a group, and was 1.73 (95% CI: 1.24 to 2.42) for a propensity score-matched set. **Conclusion:** In addition to traditional risk factors, uric acid level is an independent predictor of all-cause mortality after AKI.

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Introduction

Acute kidney injury (AKI) is a common critical disorder in hospitalized patients that carries a high risk of mortality. A meta-analysis in 2015 involving more than 700 studies revealed an AKI morbidity rate for hospitalized patients of 21%, and a 21% mortality rate among AKI patients; furthermore, it indicated that the prognosis of AKI had not significantly improved [1]. The risk of developing chronic kidney disease (CKD) among AKI patients was 8.8 times higher than the risk among non-AKI patients; similarly, the risk of progression to end-stage renal disease (ESRD) was 3.1 times higher, and the risk of mortality was 2 times higher [2]. The pathogenic mechanism of AKI remains unclear at present. Because the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not recommend any drug for the prevention and treatment of AKI [3], therapy still relies on long-standing symptomatic and supportive treatment. However, AKI is to some extent preventable, controllable, and even reversible with timely intervention. Therefore, it is particularly important to identify risk factors that predispose individuals to develop AKI and that predict mortality in those with AKI. However, existing risk factors mainly focus on specific susceptibilities and certain demographic characteristics, comorbidities, and treatments, and they ignore non-traditional risk factors, especially laboratory indicators.

In this study, we combined data from 38 tertiary hospitals and 22 secondary hospitals in China to conduct a large-scale, multidisciplinary, cooperative AKI study of adult hospitalized patients. This study covered 21 of 31 provinces, autonomous regions, and direct-controlled

municipalities in China and 79% of the Chinese population. The purpose was to explore risk factors that affect the development of AKI and mortality in AKI patients.

Materials and Methods

Study Design and Population

We selected 38 representative tertiary hospitals and 22 secondary hospitals in 21 provinces, autonomous regions, and direct-controlled municipalities in mainland China to conduct a nationwide, multicenter, cross-sectional study based on the sampling method. All patients ≥ 18 years old who were hospitalized in any one month between July 1st and December 31st of 2014 were included. Through case analysis, AKI patients who were hospitalized for > 24 h and diagnosed and treated for the first time were screened according to the AKI clinical practice guidelines released by KDIGO in 2012. Patients undergoing maintenance hemodialysis (including peritoneal dialysis) and those with CKD stage 5 without dialysis, kidney organ transplantation, and nephrectomy were excluded. This study was approved by the Ethics Committee of People's Liberation Army (PLA) General Hospital and other participating institutions in China.

Data Sources

Information for the hospitalized patients, including gender, age, underlying disease, survival status at discharge, and length of hospital stay, was collected. Demographic data, underlying and concomitant disease, laboratory indicators within 24 h of AKI diagnosis, injury factors for AKI development, use of suspected nephrotoxic drugs, AKI etiology and renal replacement therapy (RRT) parameters were retrieved from the AKI on-line electronic medical record registration system (<http://pd.cnrd.net:6780/aki/user.do?action=firstpage>). AKI was defined as an increase in creatinine of more than $26.5 \mu\text{mol/l}$ (0.3 mg/dl) within 48 h or a confirmed/speculated increase in creatinine of 1.5-fold over baseline within 7 d. The AKI stage was determined by the highest creatinine level after AKI development [3]. Underlying and concomitant diseases were determined by the ICD-10 codes assigned at discharge. CKD was determined based on the diagnostic coding, history of renal injury more than 3 months prior to admission, or an estimated glomerular filtration rate (eGFR) $< 60 \text{ mL/min/1.73 m}^2$ (calculated based on the Modification of Diet in Renal Disease (MDRD) formula) for more than 3 months [4]. Injury factors and causes were confirmed by two trained senior physicians in the Department of Nephrology and were based on patient records. An AKI case was considered drug-related if it met one of the following criteria: the diagnosis obtained from renal biopsy was drug-related AKI or the patient received nephrotoxic drugs more than 3 days before the creatinine change and no other apparent causes were discovered [5]. For patients who had received more than one type of RRT, as long as continuous RRT (CRRT) was included, then CRRT was considered as the predominant mode in the study [6]. Sustained low-efficiency dialysis (SLED) was determined by the use of extended duration RRT (6-18 h), in which conventional hemodialysis machines with reduced dialysate and blood flow rates were used [7]. The dialysate and blood flow rates were all 100-300 mL/min.

Statistical Analysis

SPSS 22.0 software was used for the statistical analysis (SPSS, Inc., Chicago, IL, USA). Variables are expressed as the mean $\pm$ SD, median (Qu, Q₁), or n (%), as appropriate. Comparisons between two groups were performed using the t test, Mann-Whitney U test, or Pearson χ^2 test, as appropriate. Univariate logistic regression analysis was performed for all factors that could cause AKI, including demographic data, and underlying disease. Additionally, a collinearity diagnosis was performed. The variables that satisfied statistical significance ($P < 0.05$) in univariate logistic regression analysis and showed no collinearity with others were used for the multivariate logistic regression analysis. Univariate Cox regression analysis was performed on all factors that could affect the mortality of AKI patients, including demographic data, AKI stage, underlying disease, concomitant disease, injury factors, heart rate, mean arterial pressure (MAP), laboratory indicators, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and RRT. The same method was used to perform multivariate Cox regression analysis. To reconfirm the laboratory indicators that constituted risk factors, a propensity score was performed between the survivors and non-survivors among AKI patients using 1:1

Table 1. Comparison of characteristics between AKI and non-AKI groups

Variables	AKI (n=1845)	Non-AKI (n=189 190)	All (n=191 035) (n=189,190)patients(n=191,035)	P value
Age (years)	60.5 ± 17.4 1254 (68.0%)	53.1 ± 17.0	53.1 ± 17.0	< 0.001*
Men		94 346 (49.9%)	95 600 (50.0%)	< 0.001*
Regional distribution				< 0.001*
South Central	124 (6.7%)	25 026 (13.2%)	25 150 (13.2%)	
Northeast	246 (13.3%)	39 031 (20.6%)	39 277 (20.6%)	
Northwest	397 (21.5%)	38 060 (20.1%)	38 457 (20.1%)	
East	233 (12.6%)	20 116 (10.6%)	20 349 (10.7%)	
North	354 (19.2%)	29 558 (15.6%)	29 912 (15.7%)	
Southwest	491 (26.6%)	37 399 (19.8%)	37 890 (19.8%)	
Underlying diseases				
Hypertension	772 (41.8%)	38 900 (20.6%)	39 672 (20.8%)	< 0.001*
Diabetes	329 (17.8%)	21 277 (11.2%)	21 606 (11.3%)	< 0.001*
Cardiovascular disease	457 (24.8%)	31 642 (16.7%)	32 099 (16.8%)	< 0.001*
Chronic liver disease	89 (4.8%)	10 105 (5.3%)	10 194 (5.3%)	0.33
COPD	121 (6.6%)	6579 (3.5%)	6700 (3.5%)	< 0.001*
CKD	187 (10.1%)	10 533 (5.6%)	10720 (5.6%)	< 0.001*

Variables were expressed with mean ± SD, median (Qu, Q_L) or n (%).

AKI, acute kidney injury; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease

*P < 0.05.

matching. The matched variables included other data, in addition to laboratory indicators. A multivariate Cox regression analysis was then used to evaluate independent risk factors in matched patients. All p values were two-sided. P < 0.05 was defined as statistically significant.

Results

The 191, 035 hospitalized patients had a mean age of 53.1 ± 17.0 years. The male-to-female ratio was 1.0: 1.0. Among these patients, 1845 were diagnosed with AKI, and the morbidity rate was 0.97%. The mean age of the AKI patients was higher than that of the non-AKI patients (60.5 ± 17.4 vs. 53.1 ± 17.0, P < 0.001), and the AKI patients included a higher percentage of males (68% vs. 49.9%, P < 0.001).

Risk Factors for AKI Development

Table 1 shows the risk factors related to AKI development. The univariate regression analysis revealed that advancing age, male gender, and the presence of hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and CKD were risk factors for AKI development. The independent risk factors associated with AKI

Table 2. Factors associated with AKI development according to multivariate logistic regression analysis

Variables	OR (95% CI)	P value
Sex (male* vs female)	0.52 (0.47, 0.57)	< 0.001†
Age (per 10 years increase)	1.18 (1.15, 1.22)	< 0.001†
Underlying diseases (yes vs no*)		
Hypertension	2.16 (1.94, 2.40)	< 0.001†
Diabetes	1.09 (0.96, 1.24)	0.18
Cardiovascular disease	0.99 (0.88, 1.11)	0.86
COPD	1.18 (0.97, 1.43)	0.10
CKD	1.42 (1.21, 1.66)	< 0.001†

All variables listed in the table were included in the logistic regression model and adjusted for regional distribution.
AKI, acute kidney injury; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease
*Reference value; †P < 0.05.

development are presented in Table 2. The multivariate logistic regression analysis revealed advancing age, male gender, hypertension and CKD as risk factors for AKI development.

Epidemiological Characteristics of AKI Patients (Table 3)

Among the 1845 AKI patients, the male-to-female ratio was 2.12: 1.00. Of these AKI patients, 1148 (62.2%), 372 (20.2%), 325 (17.6%) were Stage I, stage II, and stage III, respectively. The top three diseases underlying AKI were hypertension (41.8%), coronary heart disease (19.6%), and diabetes (17.8%). Infection (46.6%) was the most common risk factor, followed by drug use (35.9%). The mean hemoglobin level of the patients who were diagnosed with AKI within 24 h was 11.5 ± 2.9 g/dl, which was lower than that of healthy individuals. The albumin (3.3 ± 0.8 g/dl) level was also slightly lower. In terms of disease severity, the APACHE II score was 11 (7, 16), and the SOFA score was 5 (2, 9). Of the AKI patients, 73 (4.0%) had multiple organ dysfunction syndrome (MODS), and 82 (4.4%) had sepsis. Most of the cases were due to pre-renal etiology, followed by renal etiology; post-renal etiology accounted for less than 10% of the cases. There were 257 cases of drug-related AKI (Table 4), comprising 13.9% of the AKI patients. Antibiotics-induced AKI accounted for almost half of the cases (48.2%, 124 cases). One hundred forty-nine (8.1%)

Table 3. Epidemiological and clinical characteristics of survivors and non-survivors among AKI patients
Variables were expressed with mean $\pm$ SD, median (Q_1 , Q_3) or n (%). Conversion factor for total bilirubin, direct bilirubin, serum creatinine, and serum uric acid in mg/dL to μ mol/L, $\times 17.1$, $\times 17.1$, $\times 88.40$, $\times 59.48$, respectively; Conversion factor for urea nitrogen, serum glucose, serum calcium, and serum phosphate in mg/dL to mmol/L, $\times 0.357$, $\times 0.05551$, $\times 0.2495$, $\times 0.3229$, respectively. AKI, acute kidney injury; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; MODS, Multiple Organ Dysfunction Syndrome; CPR, cardiopulmonary resuscitation; BMI, Body Mass Index; MAP, mean arterial pressure; DIC, Disseminated Intravascular Coagulation; Hb, hemoglobin; WBC, white blood cell; PLT, platelet count; TP, total protein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct Bilirubin; SCr, serum creatinine; BUN, blood urea nitrogen; SUA, Serum uric acid; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; RRT, renal replacement therapy. Hypovolemia: according to the judgment of the clinical physicians, a reduced effective blood volume induced by a variety of causes that cannot maintain the normal blood supply and oxygen supply for tissues in the body and a systolic blood pressure ≤ 90 mmHg for more than 1 h [37]. Low cardiac output: insufficient cardiac systolic function with various causes, a reduction of systemic blood pressure (≤ 90 mmHg), and concomitant tissue hypoxia syndrome [37]. Massive blood transfusion: transfusion of more than 10 units of red blood cells within a short time frame (within 72 h) [37]. Post - CPR: patients lose autonomic circulation and pulse due to cardiopulmonary respiratory and circulatory system collapse; therefore, the patients require CPR, defibrillation, or adrenaline to save their lives and survive for more than 24 h [37]. Rhabdomyolysis: serum creatine kinase > 5000 U/L or plasma myoglobin > 5000 μ g/L [37]. *P < 0.05

Variables	Survivors (n = 1540)	Non-survivors (n = 305)	All (n = 1845)	P value
Age (years)	59.8 ± 17.3	64.5 ± 17.7	60.5 ± 17.4	< 0.001*
Men	1046 (67.9%)	208 (68.2%)	1254 (68.0%)	0.93
Regional distribution				< 0.001*
Central and southern	110 (7.2%)	14 (4.6%)	124 (6.8%)	
North	302 (19.6%)	52 (17.0%)	354 (19.2%)	
East	202 (13.1%)	31 (10.2%)	233 (12.6%)	
Northwest	347 (22.5%)	50 (16.4%)	397 (21.5%)	
Southwest	394 (25.6%)	97 (31.8%)	491 (26.6%)	
Northeast	185 (12.0%)	61 (20.0%)	246 (13.3%)	
AKI stage				< 0.001*
1	988 (64.2%)	160 (52.5%)	1148 (62.2%)	
2	304 (19.7%)	68 (22.3%)	372 (20.2%)	
3	248 (16.1%)	77 (25.2%)	325 (17.6%)	
Underlying diseases				
Hypertension	639 (41.5%)	133 (43.6%)	772 (41.8%)	0.49
Coronary heart disease	293 (19.0%)	68 (22.3%)	361 (19.6%)	0.19
Diabetes	272 (17.7%)	57 (18.7%)	329 (17.8%)	0.67
Tumor	223 (14.5%)	59 (19.3%)	282 (15.3%)	0.03*
Heart failure	158 (10.3%)	40 (13.1%)	198 (10.7%)	0.14
CKD	160 (10.4%)	27 (8.9%)	187 (10.1%)	0.42
Respiratory failure	92 (6.0%)	55 (18.0%)	147 (8.0%)	< 0.001*
COPD	93 (6.0%)	28 (9.2%)	121 (6.6%)	0.04*
Hepatic cirrhosis	74 (4.8%)	17 (5.6%)	91 (4.9%)	0.57
Concomitant diseases				
Sepsis	53 (3.4%)	20 (6.6%)	73 (4.0%)	< 0.001*
MODS	48 (3.1%)	34 (11.1%)	82 (4.4%)	0.01*
Injury factors				
infection	687 (44.6%)	172 (56.4%)	859 (46.6%)	< 0.001*
medicine	565 (36.7%)	98 (32.1%)	663 (35.9%)	0.13
Hypovolemia	307 (19.9%)	73 (23.9%)	380 (20.6%)	0.12
Low cardiac output	232 (15.1%)	77 (25.2%)	309 (16.7%)	< 0.001*
Massive blood transfusion	77 (5.0%)	14 (4.6%)	91 (4.9%)	0.76
Post-CPR	41 (2.7%)	20 (6.6%)	61 (3.3%)	0.001*
DIC	23 (1.5%)	13 (4.3%)	36 (2.0%)	0.001*
Rhabdomyolysis	22 (1.4%)	2 (0.7%)	24 (1.3%)	0.42
Heart rate (bpm)	82 (76, 98)	87 (80, 105)	84 (76, 99)	< 0.001*
BMI (kg/m ²)	23.6 ± 3.7	23.0 ± 3.4	23.5 ± 3.6	0.01*
MAP (mmHg)	94.3 ± 18.0	92.0 ± 21.5	93.9 ± 18.6	0.10
Baseline SCr (mg/dl)	1.04 (0.85, 1.42)	1.06 (0.79, 1.45)	1.04 (0.83, 1.42)	0.63
Laboratory index				
Hb (g/dl)	11.5 ± 2.9	11.2 ± 3.0	11.5 ± 2.9	0.11
WBC (10 ⁹ /L)	9.2 (6.4, 13.6)	11.5 (7.9, 17.9)	9.6 (6.6, 14.2)	< 0.001*
PLT (10 ⁹ /L)	172 (109, 234)	148 (80, 217)	167 (104, 232)	< 0.001*
TP (g/dl)	6.2 ± 1.2	5.9 ± 1.2	6.2 ± 1.2	0.001*
ALB (g/dl)	3.4 ± 0.8	3.2 ± 0.8	3.3 ± 0.8	< 0.001*
ALT (U/L)	22.0 (13.2, 45.0)	31.5 (17.0, 77.5)	23.6 (14.0, 50.9)	< 0.001*
AST (U/L)	28.0 (18.0, 61.0)	51.0 (27.2, 139.0)	31.0 (19.1, 71.2)	< 0.001*
TBiL (mg/dl)	0.8 (0.5, 1.4)	1.0 (0.6, 2.1)	0.8 (0.5, 1.5)	< 0.001*
DBiL (mg/dl)	0.3 (0.2, 0.6)	0.4 (0.2, 1.0)	0.3 (0.2, 0.6)	< 0.001*
SCr (mg/dl)	1.7 (1.3, 2.6)	1.8 (1.4, 3.1)	1.8 (1.3, 2.7)	0.01*
BUN (mg/dl)	32.0 (20.9, 49.9)	41.5 (25.5, 67.1)	33.1 (21.6, 53.2)	< 0.001*
SUA (mg/dl)	6.8 (5.2, 8.9)	7.4 (5.6, 10)	6.8 (5.2, 9.1)	0.001*
Serum glucose (mg/dl)	108.4 (90.1, 150.6)	123.8 (100.5, 171.5)	111.2 (91.0, 153.1)	< 0.001*
Serum potassium (mmol/L)	4.1 (3.7, 4.5)	4.2 (3.7, 4.9)	4.1 (3.7, 4.6)	0.04*
Serum calcium (mg/dl)	8.6 (8.0, 9.2)	8.3 (7.6, 8.9)	8.6 (7.9, 9.1)	< 0.001*
Serum phosphate (mg/dl)	3.8 (3.0, 4.7)	3.9 (2.9, 5.6)	3.8 (3.0, 4.8)	0.17
Serum sodium (mmol/L)	138.9 (135, 142)	138.4 (134.0, 143.0)	138.8 (135, 142)	0.64
APACHE II score	10 (7, 15)	15 (10, 21)	11 (7, 16)	< 0.001*
SOFA score	5 (2, 8)	8 (4, 11)	5 (2, 9)	< 0.001*
AKI classification				0.004*
Pre-renal	721 (46.8%)	161 (52.8%)	882 (47.8%)	
Intrinsic-renal	659 (42.8%)	131 (43.0%)	790 (42.8%)	
Post-renal	160 (10.4%)	13 (4.3%)	173 (9.4%)	
RRT	115 (7.5%)	34 (11.1%)	149 (8.1%)	0.031*
Hospital stay (days)	13 (8, 21)	10 (4, 22)	13 (7, 21)	< 0.001*

Table 4. Percentage of drug-related AKI among the AKI patients

	Survivors (n = 1540)	Non-Survivors (n = 305)	Total (n = 1845)	P value
Drug related AKI	220 (14.3%)	37 (12.1%)	257 (13.9%)	0.32
Antibiotics	103 (6.7%)	21 (6.9%)	124 (6.7%)	0.90
ACEI/ARB	40 (2.6%)	6 (2.0%)	46 (2.5%)	0.52
anticancer drugs	27 (1.8%)	5 (1.6%)	32 (1.7%)	0.89
contrast medium	29 (1.9%)	2 (0.7%)	31 (1.7%)	0.13
Other drugs	21 (1.4%)	3 (1.0%)	24 (1.3%)	0.78

Variables were expressed with n (%).

AKI, acute kidney injury; ACEI/ARB, Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blocker

Table 5. Risk factors associated with all-cause in-hospital mortality in AKI patients according to multivariate Cox regression analysis

variables	HR (95% CI)	P value
Age (per 10 years increase)	1.17 (1.08, 1.27)	< 0.001*
Tumor (yes vs no†)	1.45 (1.05, 2.00)	0.025*
SUA (mg/dl)	1.06 (1.02, 1.10)	0.002*
APACHE II score	1.03 (1.01, 1.04)	0.005*
SOFA score	1.05 (1.02, 1.09)	0.003*

The variables with a P < 0.05 in univariate Cox regression analysis were analyzed by multivariate Cox regression analysis. All variables with a P < 0.05 in multivariate Cox regression analysis were listed in the table and adjusted for regional distribution.

AKI, acute kidney injury; SUA, Serum uric acid; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment. †Reference value; *P < 0.05.

patients underwent RRT, with intermittent hemodialysis (IHD), CRRT, SLED and others (i.e., hemoperfusion, and hemodiafiltration) accounting for 31.5% (47 cases), 43.6% (65 cases), 10.1% (15 cases) and 14.8% (22 cases), respectively.

Mortality and Risk Factors in AKI Patients

Regarding mortality, 305 AKI patients died during hospitalization; the total mortality rate was 16.5%, which was higher than that of non-AKI patients (0.6%, P < 0.001). The AKI patients had a longer hospitalization time (13 (7, 21) days vs. 8 (5, 13) days, P < 0.001) than the non-AKI hospitalized patients. Table 3 shows the epidemiological and clinical characteristics of the survivors and non-survivors among the AKI patients. The surviving patients were younger than those who died (59.8 ± 17.3 vs. 64.5 ± 17.7 years, P < 0.001). Of the non-survivors with AKI, 25.2% were at stage III, which was a higher proportion than that of the survivors (16.1%). Except for hemoglobin, serum phosphorus, and serum sodium, all laboratory indicators differed significantly between these two groups. Serum uric acid (SUA) was used as a continuous variable in the Cox regression analysis. The APACHE II and SOFA scores of the non-survivors were higher than those of the survivors. The mortality rate of the patients who received RRT due to critical illness was significantly higher than that of the patients who did not. Among the AKI patients who received RRT, those who underwent CRRT had a higher mortality rate than those who underwent IHD, SLED, and other modalities. The mortality rates were 30.8%, 12.8%, 13.3% and 27.3%, respectively. According to the univariate Cox regression analysis, the risk factors affecting the mortality of AKI patients included tumor, respiratory failure, COPD, MODS, sepsis, low cardiac output, disseminated intravascular coagulation (DIC), and post-resuscitation status. The multivariate Cox regression analysis showed that the independent factors affecting AKI patient mortality (Table 5) included age (increased by 10 years) (HR 1.17, 95% CI 1.08-1.27), tumor (HR 1.45, 95% CI 1.05-2.00), SUA (HR 1.06, 95% CI 1.02-1.10), APACHE II score (HR 1.03, 95% CI 1.01-1.04), and SOFA score (HR 1.05, 95% CI 1.02-1.09).

Risk Factor for Mortality among Laboratory Indicators: Serum Uric Acid

Among the laboratory indicators, SUA was the only independent predictor of mortality in the AKI patients. Figure 1 shows the different percentages of SUA among the survivors and non-survivors. The non-survivor group of AKI patients had a greater proportion of patients with a higher SUA level.

Furthermore, we transformed the SUA level into a categorical variable according to percentile, as follows: ≤ 25 th percentile ($SUA \leq 5.2$ mg/dl), 26th-50th percentile ($5.2 < SUA \leq 6.8$ mg/dl), 50th - 75th percentile ($6.8 < SUA \leq 9.1$ mg/dl), > 75 th percentile ($SUA > 9.1$ mg/dl). Table 6 shows the mortality for the different SUA groups. A Cox regression analysis was also conducted (Figure 2, Table 7); using $SUA \leq 5.2$ mg/dl as the reference group, the HR for $SUA > 9.1$ mg/dl was 1.78 (95%CI 1.23-2.58), that of $6.8 < SUA \leq 9.1$ mg/dl was 1.40 (95% CI 0.96-2.03) and that of $5.2 < SUA \leq 6.8$ mg/dl was 1.11 (95% CI 0.76-1.61).

Fig. 1. Distribution of the proportions of serum uric acid concentrations in survivors and non-survivors.

Table 6. Mortality of different SUA groups

	Group 1	Group 2	Group 3	Group 4	Total
SUA (mg/dl)	≤ 5.2	5.2 - 6.8	6.8 - 9.1	> 9.1	
Cases	455	452	472	466	1845
Mortality (%)	14.2	14.5	15.2	22.1	16.5
SUA, Serum uric acid

Fig. 2. Adjusted hazard ratio for mortality in all AKI patients with different serum uric acid levels. Adjusted for age, AKI stage, underlying disease, concomitant disease, damage factors, heart rate, BMI, region, laboratory indicators, APACHE II score, SOFA score, and RRT.

After the propensity score analysis, a total of 294 pairs of AKI patients with different survival conditions were included in the matched group set. There were no differences in demographic data, medical history, baseline renal function, and disease severity in the set. $SUA > 9.1$ mg/dl (HR1.73, 95%CI 1.24-2.42) was still an independent risk factor for mortality in the multivariate Cox analysis for the matched sample set.

Discussion

AKI itself is not a single disease, rather, it is a clinical syndrome with complex

Table 7. Risk factors associated with all-cause in-hospital mortality in AKI patients according to multivariate Cox regression analysis

variables	HR (95% CI)	P value
Age (per 10 years increase)	1.17 (1.08, 1.27)	< 0.001*
Tumor (yes vs no [†])	1.46 (1.05, 2.02)	0.02*
SUA (mg/dl)		
≤ 5.2	1 [#]	
5.2 - 6.8	1.11 (0.76, 1.61)	0.60
6.8 - 9.1	1.40 (0.96, 2.03)	0.08
> 9.1	1.78 (1.23, 2.58)	0.002*
APACHE II score	1.03 (1.01, 1.05)	0.003*
SOFA score	1.05 (1.02, 1.09)	0.003*

The variables with a P < 0.05 in univariate Cox regression analysis were analyzed by multivariate Cox regression analysis. All variables with a P < 0.05 in multivariate Cox regression analysis were listed in the table and adjusted for regional distribution.
AKI, acute kidney injury; SUA, Serum uric acid; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment. †Reference value; *P < 0.05.

etiologies and high mortality [8]. Even a slight increase in creatinine will increase the possibility of a poor prognosis, by increasing the risk of mortality, progression to CKD or ESRD, or a cardiovascular event [9, 10]. However, AKI is preventable and can even be reversed in early stages [1]. Indeed, if AKI is discovered and treated early and risk factors are removed as soon as possible, the progression of the disorder can be reduced, and patients' prognosis can be improved [1]. Therefore, it is very important to fully understand the risk factors and clinical characteristics of AKI's development and progression. However, non-traditional risk factors, especially laboratory indicators, tend to be neglected [11]. Accordingly, we designed a nationwide, multicenter study of AKI and selected representative hospitals, including some secondary hospitals in mainland China. Cases were collected according to the definition and diagnostic standards of the AKI clinical practice guidelines released in March 2012 to explore the risk factors, particularly laboratory indicators, that contribute to the development of AKI and a poor prognosis.

The AKI morbidity rate in this study was 0.97%, which was consistent with previous reports in China [12] but significantly lower than the reported 21% for developed countries [1]. The main reason for this difference may be that AKI lacks specific symptoms, and its diagnosis is primarily based on changes in creatinine level. The lack of awareness of AKI in China result in a low frequency of serum creatinine measurements. The repeated creatinine assay rate in China ranges from 24.76% to 30% [12], which is much lower than the reported rate of 63.2% in developed countries [13]. Therefore, the prevalence of AKI in China is undoubtedly underestimated. Mehta et al [1]. reported a worldwide pooled incidence of AKI of 21% in a systematic review; however, this result was strongly dependent on the sampled population. Specialized populations, such as patients in intensive-care units (ICU), were included in the systematic review. Although some reports from several regions of Africa and Asia were included, the majority were from high-income countries, where populations were heavily weighted with ICU patients with high incidence and severity levels. Because of the incomplete Medical Grading System, a fair number of hospitalized patients in China are general patients with less severe disease, compared with those in developed countries, which will also result in a lower occurrence of AKI.

Many risk factors have been reported to be associated with the incidence of AKI, including age, female gender, CKD, diabetes, heart diseases, and lung diseases [3, 12, 14]. In accordance with previous studies, we found that advancing age, hypertension, and CKD were risk factors for AKI development. A large-scale prospective cohort study by Jiang et al [15]. indicated that male gender was an independent risk factor for cardiac surgery-related AKI, and a nationwide retrospective cohort study performed by Xue et al [16]. obtained the same conclusion. However, some large-scale observational studies on cardiac surgery [17], contrast agents [18], and aminoglycoside-related AKI [19] confirmed that female gender

was an independent risk factor for hospital-acquired AKI. Our study revealed that men had a greater risk of developing AKI than women, which was the same result as the former study. This issue remains controversial and requires further investigation.

The mortality rate of the AKI patients in our study was 16.5%, consistent with other studies in China [20]. Most studies have consistently reported that the risk factors associated with a poor AKI prognosis include advancing age, cardiovascular disease, AKI stage, and so on [21]. In addition to examining these basic risk factors, we also systemically and comprehensively collected the laboratory indicators of patients with AKI, and examined the APACHE II and SOFA scores of these patients to better predict the mortality risk of AKI patients. The results showed that advancing age, tumor, high APACHE II and SOFA scores and high uric acid levels increased the mortality risk of hospitalized AKI patients. The APACHE II score is mainly used in ICUs to evaluate disease severity [22], whereas the SOFA score is used to evaluate the severity of functional failure of all organs [23]. Considering that AKI patients have high mortality, we used these two scores to evaluate all AKI patients, not only those in ICUs. The results showed that the mortality risks increased with the increase of the APACHE II or SOFA score. Similarly, two international multicenter prospective studies separated by 10 years confirmed a similar effect of the APACHE II score for predicting mortality risk [24, 25]. These results indicate that APACHE II and SOFA scores can accurately predict critical illness and mortality risk in AKI patients. The clinical value of these scores should be further examined and validated in studies with larger sample sizes.

Furthermore, we analyzed laboratory indicators and found that uric acid level was related to all-cause mortality. When analyzed as a dichotomous variable, the uric acid level and mortality risk of AKI patients displayed a J-shaped pattern. A propensity score came to the same conclusion. Considerable clinical evidence has suggested that elevated uric acid levels play an independent role in increased mortality, cardiovascular disease (CVD), and renal disease [26, 27]. The relationship between serum uric acid and mortality risk in different populations, such as CKD patients [28], hemodialysis patients [29], peritoneal dialysis patients [30, 31], and the general population [32], has been confirmed. High SUA has also been reported to be an independent predictor for AKI [33, 34]. In this study, we found that AKI patients with elevated serum uric acid concentrations had a higher in-hospital mortality risk. The underlying mechanisms are discussed below, but must be explored further. Hyperuricemia results in endothelial dysfunction by inhibiting nitric oxide production [35]. Elevated SUA levels increase insulin resistance, dyslipidemia, hypertension and atherosclerosis. High SUA concentrations are significantly correlated with a decline in residual kidney function after adjusting for confounding factors [36]. Uric acid could have pro-inflammatory effects, increase oxidative stress, and damage the microcirculation [21], thereby increasing mortality risk and explaining why a high SUA level can serve as a marker of poor prognosis. Nevertheless, as high SUA might be a symptom of AKI, it is unclear whether the poor prognosis is due to uric acid itself or to AKI. Additionally, it remains unclear whether a reduction in uric acid could improve prognosis.

Although this study involved a nationwide epidemiological survey of AKI patients and collected many risk factors for AKI and prognostic factors for mortality, there are limitations. First, we did not perform long-term follow-up on AKI patients to evaluate the risk factors that affected their long-term prognosis. We have been conducting research in this area with AKI patients. Second, accurate measurement of urine output is so difficult for ordinary patients that most studies diagnose AKI only based on creatinine standards, as we did for this study. Furthermore, this multicenter study included AKI patients in general; therefore, the risk factors for some specific causes of AKI, such as contrast-induced AKI and AKI after cardiac surgery require further exploration.

Conclusion

In summary, our study showed that the morbidity of hospitalized AKI patients in China was relatively lower than that in developed countries, though the mortality was the same. APACHE II and SOFA scores can be used to evaluate the in-hospital mortality risk of AKI patients. In addition to traditional risk factors, uric acid levels should be considered an independent predictor of all-cause mortality in AKI patients.

Disclosure Statement

The authors declare that they have no competing interests.

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