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# Development of a risk stratification-based model for prediction of acute kidney injury in critically ill patients

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**Abstract**

Acute kidney injury (AKI) is a complex syndrome with a variety of possible etiologies and symptoms. It is characterized by high mortality and poor recovery of renal function. The incidence and mortality rates of patients with AKI in intensive care units are extremely high. It is generally accepted that early identification and prompt treatment of AKI are essential to improve outcomes. This study aimed to develop a model based on risk stratification to identify and diagnose early stage AKI for improved prognosis in critically ill patients.

This was a single-center, retrospective, observational study. Based on relevant literature, we selected 13 risk factors (age, sex, hypertension, diabetes, coronary heart disease, chronic kidney disease, total bilirubin, emergency surgery, mechanical ventilation, sepsis, heart failure, cancer, and hypoalbuminemia) for AKI assessment using the Kidney Disease Improving Global Outcomes (KDIGO) diagnostic criteria. Univariate and multivariate analyses were used to determine risk factors for eventual entry into the predictive model. The AKI predictive model was established using binary logistic regression, and the area under the receiver operating characteristic curve (AUROC or AUC) was used to evaluate the predictive ability of the model and to determine critical values.

The AKI predictive model was established using binary logistic regression. The AUROC of the predictive model was 0.81, with a sensitivity of 69.8%, specificity of 83.4%, and positive likelihood ratio of 4.2.

A predictive model for AKI in critically ill patients was established using 5 related risk factors: heart failure, chronic kidney disease, emergency surgery, sepsis, and total bilirubin; however, the predictive ability requires validation.

**Abbreviations:** AKI = Sepsis induced acute kidney injury, IGFBP-7 = insulin-like growth factor binding protein-7, ICU = intensive care unit, IL-17 = interleukin, KDIGO = kidney disease improving global outcomes, PLR = the platelet-to-lymphocyte ratio, qSOFA = quick Sequential Organ Failure Assessment, RIFLE = Risk Injury Failure Loss End-stage renal disease, SCr = serum creatinine, SOFA = Sequential Organ Failure Assessment, TIMP-2 = tissue inhibitor of metalloproteinases-2.

**Keywords:** acute kidney injury, critically ill patients, predictive model

## 1. Introduction

Acute kidney injury (AKI) is a complex syndrome with multiple etiologies and clinical manifestations. It is characterized by a high mortality rate and high cost of treatment, with a poor prognosis. The incidence of AKI in the intensive care unit (ICU) is 5.7% to 67%.[1] Due to the significant increase in complications and mortality in recent years, the length of hospital stay and the cost of treatment have also increased, and the prognosis has been poor.[2,3] The diagnosis of AKI is based on changes in functional indexes, such as serum creatinine (Scr) and urine output.[1] However, studies have shown that Scr is not sensitive to acute changes in renal function and can vary widely with age, sex, muscle mass, diet, drugs, and hydration. In addition, Scr does not directly indicate renal tubular injury but reflects the glomerular filtration rate (GFR). Even in the presence of structural renal integrity, increased Scr levels can be observed when renal hypoperfusion is present, which leads to prerenal azotemia. Therefore, Scr is considered to be an "imperfect gold standard" for diagnosing AKI.[4] In most clinical situations, the true baseline value of Scr is unknown, making it difficult to be evaluated. In view of the phenotypic variability of AKI, with its different underlying pathophysiologies, it is unclear whether different methods for monitoring and diagnosing AKI are needed. Moreover, urine output is affected by varying factors such as GFR, volume status, diuresis, and urinary obstruction. As a result, Scr and urine output both lack sensitivity and specificity and are not reliable diagnostic indicators for AKI. Similarly, they cannot accurately reflect early stage changes in renal function, thus leading to a delay in diagnosis and treatment.[5] Several urine and serum biomarkers of renal injury have been found to show sensitivity and specificity for the initial stages of AKI.[6–8] These new markers include insulin-like growth factor-binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinases-2 (TIMP-2),

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kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin–18 (IL-18), protein C, and cysteine protease inhibitor C, none of which have been routinely used in clinical practice.[9–12]

## 2. Design

This single-center, retrospective, observational study was approved by the medical ethics committee of Lanzhou University Second Hospital, Number: 2017A-062. This research was part of the Epidemiology of Acute kidney injury in Critically ill patients in Gansu Province (EACG) study and was registered in the Chinese clinical trial center as number ChiCTR1800016945.

## 3. Enrollment

Data from patients who were diagnosed with AKI and admitted between September 2016 and December 2017 were collected from the surgical intensive care unit (SICU) in Lanzhou University Second Hospital. The inclusion criteria were the following:

1. an increase in Scr levels by more than 26.5 μmol/L (0.3 mg/dl) within 48 hours or Scr levels exceeding the base value by 1.5 times within 7 days, and
2. a urine output of <0.5 ml/(kg·h) for more than 6 hours.

The exclusion criteria were:

age <18 years,
on maintenance hemodialysis,
history of renal transplantation,
lacking complete admission records or a hospital stay of <24 hours, and
AKI onset before admission to the ICU.

## 4. AKI assessment

We diagnosed patients who met the Kidney Disease Improving Global Outcomes (KDIGO) inclusion criteria as having AKI. If the basal Scr level was unknown, we used the average Scr level during the first 3 ICU days of the patient.

## 5. Data collection

Data gathered and logged into Excel before further analysis included essential information (age, sex), preexisting diseases (hypertension, coronary heart disease, heart failure, chronic kidney disease [CKD], and cancer), laboratory values (sepsis, hypoalbuminemia), and whether the patient was on mechanical ventilation or had undergone emergency surgery.

## 6. Statistics

The AKI predictive model was established using binary logistic regression; statistical significance was assumed when $P < .05$. The Hosmer–Lemeshow goodness of fit test was applied to determine whether the predictive model was feasible. We established the prognostic ability of the model to discriminate between patients with AKI and those without AKI by using the area under the receiver operating characteristic curve (AUROC).

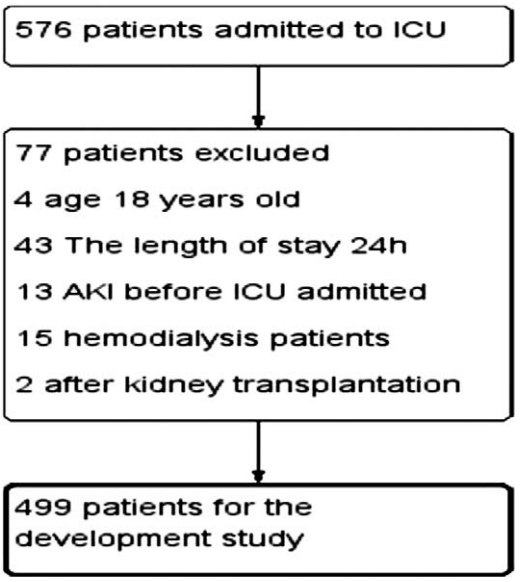



**Figure 1.** Flow chart of development study.

## 7. Sample size

The predictive model was based on 13 factors, indicating the need for at least 5 to 10 patients with AKI. With an anticipated AKI incidence of 20% to 40% and an attrition rate of 10%, we aimed to enroll at least 481 patients [(13 × 10/0.3)/0.9].

## 8. Results

Of the 576 cases collected, 77 did not meet the inclusion criteria: age < 18 years (4 cases), on maintenance hemodialysis (15 cases), hospital admission less than 24 hours (43 cases), prior renal transplantation (2 cases), and AKI onset before ICU admission (13 cases) (Fig. 1). The average age of the 499 remaining patients was 55 ± 18 years. Of these, 149 developed AKI, and 104 of the 149 were male (Table 1). The AKI incidence rate was 29.86%. Among these patients, 154 had hypertension, 88 had diabetes, 20 had coronary heart disease, 58 had chronic kidney disease, 178

**Table 1**

**Patients' characteristics in study. Values are numbers (percentages).**

| Variable | Values |
|---|---|
| Male sex | 327 (65.5) |
| Age | 55 ± 18 |
| Hypertension | 154 (30.9) |
| Type 2 diabetes mellitus | 88 (17.6) |
| Coronary heart disease | 20 (4.0) |
| Chronic kidney disease | 58 (11.6) |
| Emergency surgery | 178 (35.7) |
| Mechanical ventilation | 317 (63.5) |
| Sepsis | 125 (25.1) |
| Heart failure | 39 (7.8) |
| Tumor | 24 (4.8) |
| Hypoalbuminemia | 365 (73.1) |
| Total bilirubin (μmol/l) | 32.75 ± 49.44 |

**Table 2**

**Univariate analysis.**

| Variable | $\chi^2$ | *P* values |
|---|---|---|
| Male sex | 1.71 | .19 |
| Hypertension | 0.72 | .40 |
| Type 2 diabetes mellitus | 2.98 | .10 |
| Chronic kidney disease | 7.14 | .00 |
| Emergency surgery | 4.91 | .03 |
| Mechanical ventilation | 0.78 | .42 |
| Sepsis | 2.18 | .00 |
| Heart failure | 7.18 | .01 |
| Tumor | 2.10 | .18 |
| Hypoalbuminemia | 9.56 | .00 |
| Coronary heart disease | 0.24 | .80 |

had undergone emergency surgery, 317 received mechanical ventilation, 125 had sepsis, 39 had heart failure, 24 had cancer, and 365 had hypoalbuminemia. Correlation analysis was performed based on the risk factors. Univariate analysis indicated that heart failure, CKD, emergency surgery, sepsis, hypoalbuminemia, and total bilirubin were risk factors for AKI ($P < .05$) (Tables 2 and 3). Multivariate analysis showed that hypoalbuminemia was not a risk factor for AKI ($P = .065$). Ultimately, risk factors for AKI were heart failure, CKD, emergency surgery, sepsis, and total bilirubin (Table 4). The odds ratio for heart failure was 3.201, 4.272 for CKD, 2.085 for emergency surgery, 3.185 for sepsis, and 1.040 for total bilirubin. The AKI predictive model was established using binary logistic regression, with the equation as follows: risk of AKI = 1/[1 + exp - (−3.368 + heart failure × 1.163 + sepsis × 1.158 + chronic kidney disease × 1.452 + total bilirubin × 0.039 + emergency surgery × 0.735)]. Since the Hosmer–Lemeshow test showed a *P* value of .588, the model fit the observation data well. The AUROC was 0.81 (Fig. 2), with a sensitivity of 69.8%, specificity of 83.4%, and positive likelihood ratio of 4.2, indicating that the model was a good predictor of AKI.

## 9. Discussion

AKI is a life-threatening clinical syndrome that is frequently observed in the ICU. With an incidence of up to 25% to 50%, AKI always leads to a poor prognosis, high mortality, and overuse of medical resources.[13] One study[14] revealed a 3% to 10% prevalence of AKI in general inpatients, compared to 30% to 60% in critically ill patients, with a mortality rate as high as 30% to 80%. In severe cases that progressed to chronic kidney disease, renal replacement therapy was generally required. The incidence of AKI was 29.86% in the current research, and the results in other studies also confirm a high incidence of AKI in ICU patients. Most patients in the present research developed AKI within 48 hours of admission. Patients with AKI have a high risk of death and incur a longer ICU stay; however, the incidence in clinical practice is often underestimated. A multicenter retrospective study by Ying et al[15] showed that in China, the incidence of critically ill patients with AKI was 30.04%, with a mortality rate of 16.7%. Only 5.4% of patients discharged from the hospital were diagnosed according to the KDIGO criteria, indicating that clinicians do not pay sufficient attention to AKI. In the current study, the accuracy of diagnosis was <48.6%, while 51.4% remained undiagnosed for AKI. Standardized diagnostic and staging criteria for AKI have provided a deeper understanding of morbidity and pathogenesis in ICU patients, although timely identification, treatment, and prognosis can vary widely. Several urine and serum biomarkers of renal injury are sensitive and specific for early detection of AKI. These new markers, including KIM-1, IGFBP7, TIMP-2, NGAL, IL-18, protein C, and cysteine protease inhibitor C, have not been routinely used in clinical practice for AKI diagnosis, although they demonstrate a potential for prediction of AKI in adult (AUROC > 0.8) and pediatric (AUROC > 0.95) patients. Kashani et al[16] reported that the combined use of IGFBP7 (AUC of 0.76) and TIMP-2 (AUC of 0.79) exhibited an AUC of 0.80. Urine [TIMP-2] [IGFBP7] was significantly superior to all previously described markers of AKI ($P < .002$), none of which achieved an AUC > 0.72. Unfortunately, strategies based on these biomarkers are costly and the general use of these biomarkers is hindered by clinical individual heterogeneity.[17] The current study established an AKI predictive model based on patient population statistics and confirmed that it was a reliable predictor of AKI in critically ill

**Table 3**

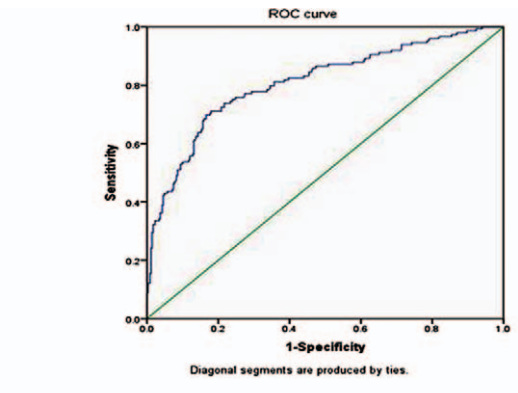
**Univariate analysis.**

| Variable | Z value | *P* values |
|---|---|---|
| Age | −3.35 | .06 |
| Total bilirubin | −35.93 | .00 |

**Table 4**

**Variables of AKI prediction model and regression coefficients.**

| Variable | Regression coefficient | Odds ratio (95% CI) | *P* value |
|---|---|---|---|
| Heart failure | 1.16 | 3.2 (1.52–6.74) | .002 |
| Sepsis | 1.16 | 3.19 (1.94–5.21) | .000 |
| Chronic kidney disease | 1.45 | 4.27 (2.27–8.05) | .000 |
| Total bilirubin | 0.04 | 1.04 (1.03–1.05) | .000 |
| Emergency surgery | 0.74 | 2.09 (1.3–3.34) | .002 |
| Intercept | −3.37 | | .000 |




| AUROC(95%CI 0.78 to 0.85) | Sensitivity (%) | Specificity (%) | Positive likelihood ratio | Cutoff value |
|---|---|---|---|---|
| 0.81 | 69.8 | 83.4 | 4.2 | 0.314 |

**Figure 2.** Area under the receiver operating characteristic curve (AUROC).

ICU patients (AUROC of 0.81). The risk factors used in our AKI predictive model included sex, age, hypertension, diabetes, coronary heart disease, heart failure, sepsis, mechanical ventilation, total bilirubin, hypoalbuminemia, emergency surgery, cancer, chronic kidney disease, and nephrotoxin exposure, which were all consistent with previous AKI literature.[18] AKI in an ICU setting is associated with high mortality. Supportive therapy for high-risk patients who can benefit from monitoring can be helpful, along with primary prevention strategies to reduce the incidence of AKI. Although AKI risk factors have been identified and used in other studies,[13,19,20] risk prediction tools for AKI in adult ICU patients are limited. Malhotra et al[21] developed a good risk prediction model with an AUROC of 0.79 (95% confidence interval [CI] 0.70–0.89) in their test cohort. In the external validation cohort, the AUROC value was 0.81 (95% CI 0.78–0.83). Flechet et al[22] developed the AKI-123 and AKI-23 models, with an AUC of 0.82 (95% CI 0.82–0.82) and 0.84 (95% CI 0.83–0.84) after 24 hours, respectively. NGAL was less discriminating, with an AUC of 0.74 (95% CI 0.74–0.74) for AKI-123 and 0.79 (95% CI 0.79–0.79) for AKI-23. Based on our research, heart failure, sepsis, CKD, total bilirubin, and emergency surgery were independent risk factors for AKI in more severe cases, with CKD being the most significant risk factor. Patients with CKD develop more severe renal dysfunction, making AKI very likely. The risk of AKI in patients with CKD is 4.272 times greater than in those without CKD. Accordingly, effective fluid management and the avoidance of nephrotoxic drugs and contrast medium are necessary in patients with a history of CKD. In addition, studies[23,24] have reported that age, sex, hypertension, diabetes, coronary heart disease, mechanical ventilation, cancer, and hypoalbuminemia are also independent risk factors for AKI.

### 9.1. Limitations

Unfortunately, our study has several limitations as follows. Firstly, we did not explore these factors, which require further research and further model validation tests to be carried out as the next step. Secondly, Since internal and external validation tests have not been performed, it is not possible to compare them with existing prediction models or scores.

When an established model can be verified, it will undergo a comparison in subsequent studies.

In conclusion, a predictive model for AKI in critically ill patients was established using 5 related risk factors: heart failure, chronic kidney disease, emergency surgery, sepsis, and total bilirubin; however, the predictive ability requires validation.

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## Author contributions

**Conceptualization:** Yu Chen.
**Data curation:** Fang Feng, Min Li, Xue-ni Chang, Baohua Wei, Chen-ming Dong.
**Writing – original draft:** Yu Chen.

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