European Journal of Medical Research

RESEARCH

Open Access

# Individualized drug therapy and survival prediction in ICU patients with acute kidney injury: construction and validation of a nomogram

Rui Yang[1,2†], Xiaozhe Su[3†], Ziqi Liu[4], Shuai Shao[1,2], Yinhuai Wang[1], Hao Su[1*] and Haiqing He[1*]

## Abstract

**Background** Acute kidney injury (AKI) is defined by a sharp decrease in the estimated glomerular filtration rate (eGFR). However, the impact of medication history on the survival of AKI patients has received little attention. Hence, it is necessary to investigate the potential of medication history as a predictor of survival outcomes among AKI patients in the intensive care unit (ICU).

**Methods** Critically ill AKI patients were sourced from the MIMIC-IV database. To ascertain significant, drug-related, independent predictors of survival, univariate Cox analysis and stepwise Cox regression were performed. Based on the identified predictor, a nomogram was developed to estimate the individualized survival probability for AKI patients. Additionally, to address potential confounders among patients with medications referenced in the nomogram, a propensity score matching procedure was applied. Ultimately, a comparative analysis was performed to elucidate the prognostic disparities among these patient subgroups.

**Results** This study enrolled 1,208 patients and developed a nomogram incorporating oxygen flow rate, respiratory frequency, continuous venovenous hemodiafiltration status, age, and medication use (including ibuprofen, epinephrine, cefazolin, warfarin, and vasopressin). The predictive model demonstrated diagnostic accuracy, with AUC values for 1-year, 3-year, and 5-year survival among AKI patients of 0.827, 0.799, and 0.777 in the training dataset, and 0.760, 0.743, and 0.740 in the internal validation dataset, respectively. Kaplan–Meier survival analyses revealed significant differences in survival outcomes among AKI patients based on their exposure to different medications.

**Conclusions** In summary, the developed prediction model demonstrated accuracy for AKI patients in the ICU and helped clinical decision-making. However, future studies will require external validation to confirm these findings.

**Keywords** Survival, Prognosis, Drug therapy, Acute kidney injury, Intensive care unit, Nomogram

†Rui Yang and Xiaozhe Su have contributed equally to this work.

*Correspondence:
Hao Su
suhao8262@csu.edu.cn
Haiqing He
hqhecs@csu.edu.cn
Full list of author information is available at the end of the article

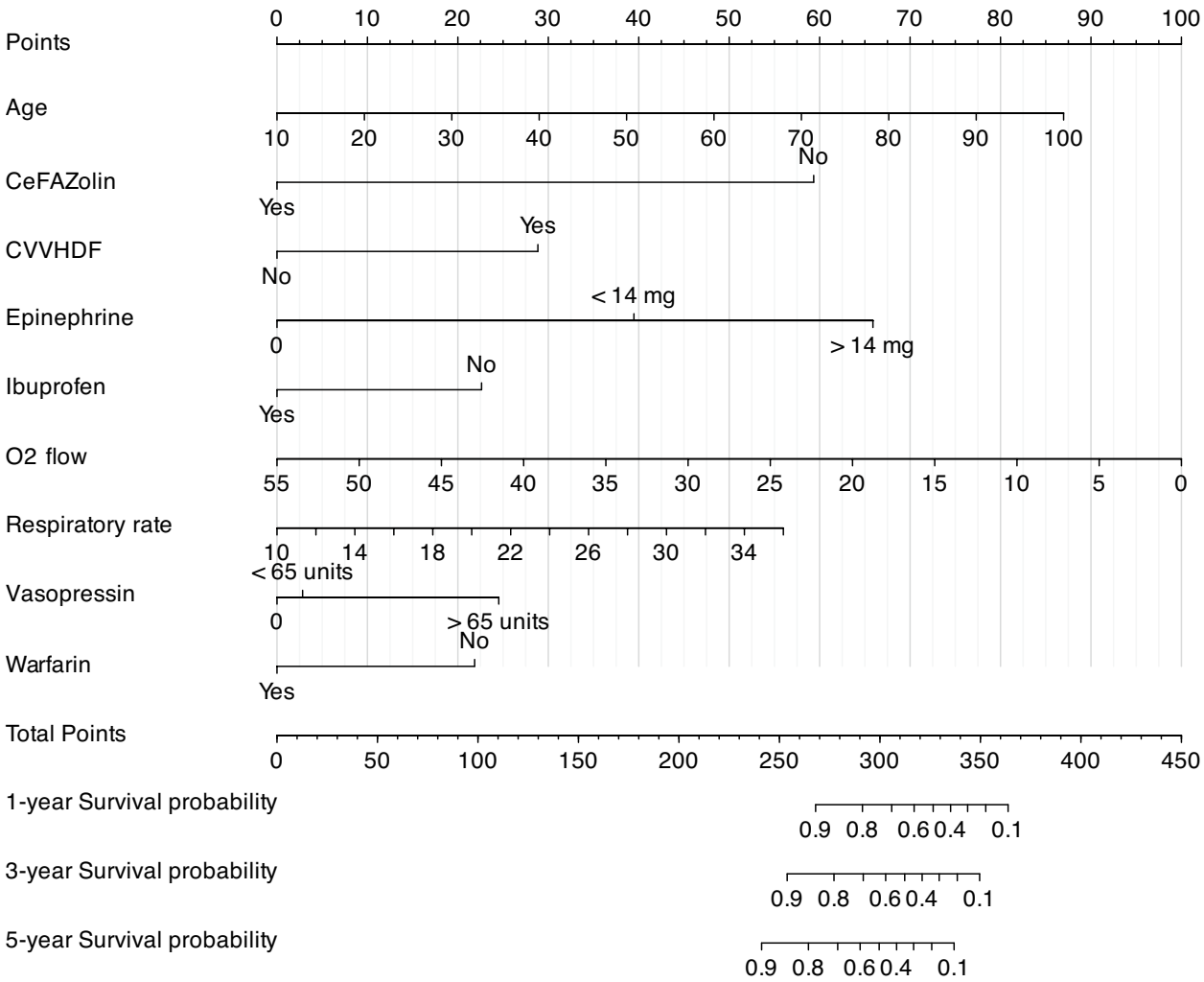


**Fig. 1** Nomogram

## Background

Acute kidney injury (AKI) is characterized by a sharp decrease in estimated glomerular filtration rate (eGFR) and is considered a part of the summarized clinical syndrome known as acute kidney diseases and disorders (AKD) [1]. AKI is typically marked by increased serum creatinine levels with or without oliguria [2]. Persistent complications associated with AKI encompass electrolyte imbalances, systemic volume overload, and uremia, leading to systemic dysfunction of multiple organs [3]. Therefore, AKI can impose a substantial medical and economic burden and represents a significant threat to public health [4].

Patients in the intensive care unit (ICU) have a higher incidence of AKI, up to 25% [5]. Most conventional therapies only delay the progression of AKI [6]. Sohaney et al. [7] reported that the overall incidence of AKI was about 20% of all included hospitalized patients, the crude mortality among hospitalized AKI patients was six times higher than hospitalized patients without an episode of AKI, and the mortality at 1-year follow-up was twice as high as hospitalized patients without AKI. Thus, new tools and indicators are needed to predict patient survival.

Most AKI patients in the ICU are treated with drug therapies [8], including non-steroidal anti-inflammatory drugs (NSAIDs), epinephrine, vasopressin, and warfarin. NSAIDs, such as aspirin and ibuprofen, are often prescribed for AKI patients to relieve the systemic inflammatory response and mitigate the impact of secondary kidney injury [9]. Besides, epinephrine has been shown to increase mean arterial pressure by activating both α-1 and β-1 receptors [10], so that it can maintain basal blood pressure and renal blood

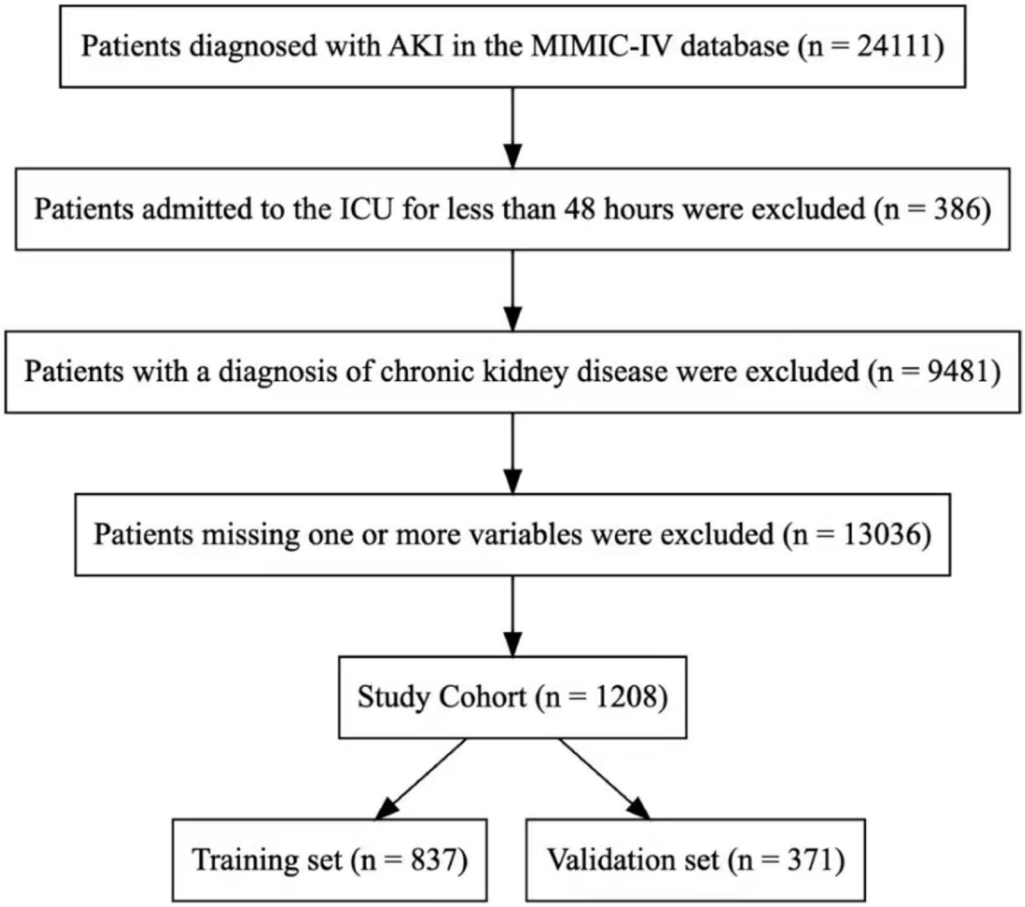


**Fig. 2** Flowchart. Detailed exclusion conditions and final numbers and subgroups included in the study cohort

flow [11]. In addition, vasopressin can activate V2 receptors on the basal surface of the tubular cells to increase the permeability of the epithelial membrane and preferentially constrict glomerular arterial vessels, thereby enhancing glomerular perfusion pressure and urine output[12]. Warfarin is an anticoagulant used for preventing thrombosis in different populations. Long-term warfarin therapy elevates the risk of AKI, associated comorbidities, hemorrhage, renal ischemia, atheroembolism, and allergic acute interstitial nephritis [13]. However, there are currently no effective tools for predicting the impact of these drugs on the survival of AKI patients.

The complex interplay among AKI, patient outcomes, and medication history is crucial for clinical management. Recent advances in machine learning have opened new avenues for predicting AKI outcomes, including the role of medication history in patient prognosis. A pioneering study by Nateghi Haredasht et al. developed machine learning-based prediction models for the progression of chronic kidney disease following AKI stage 3 in ICU patients, and the results underscored the potential of machine learning techniques in supporting clinical decisions [14]. This study, along with a systematic review, highlights the lack of validated models for predicting renal insufficiency post-AKI [14] and the necessity for more precise and clinically applicable predictive tools. Zhou et al. developed machine learning models to predict mortality in patients with sepsis-associated AKI and demonstrated that the XGBoost yielded the best performance in predicting in-hospital mortality [15]. These studies collectively highlight the prediction power of machine learning in AKI outcomes.

Nomograms integrate diverse prognostic and determinant variables to generate individual probabilities of clinical events, which fulfill the requirement for integrated biological and clinical models and promote the development of personalized medicine [16]. Although nomograms have been widely used in clinical decision support, their construction, interpretation, and impact on patients remain incompletely understood [16]. Hence, our research aims to construct a model to predict the survival of AKI patients in the ICU and investigate the connection between their medication history and

**Table 1** Clinical features of patients in the training set and validation set

| Characteristic | Overall, $N=1,208$[1] | Training set, $N=837$[1] | Validation set, $N=371$[1] | *p* value[2] |
|---|---|---|---|---|
| Survival status | 161 (13%) | 115 (14%) | 46 (12%) | 0.5 |
| Sex = Male | 758 (63%) | 517 (62%) | 241 (65%) | 0.3 |
| RTI | 281 (23%) | 192 (23%) | 89 (24%) | 0.7 |
| Age (median [IQR]) | 67 (57, 75) | 67 (57, 75) | 67 (58, 75) | 0.9 |
| Time in ICU (median [IQR]) | 38 (10, 805) | 42 (11, 976) | 31 (9, 567) | 0.029 |
| BMI (median [IQR]) | 29 (25, 34) | 29 (25, 34) | 29 (25, 34) | 0.2 |
| *Other treatment* | | | | |
| PICC | 131 (11%) | 90 (11%) | 41 (11%) | 0.9 |
| CVVHDF | 16 (1.3%) | 10 (1.2%) | 6 (1.6%) | 0.6 |
| Bipap | 10 (0.8%) | 7 (0.8%) | 3 (0.8%) | >0.9 |
| Tracheostomy | 25 (2.1%) | 18 (2.2%) | 7 (1.9%) | 0.8 |
| IHD | 24 (2.0%) | 17 (2.0%) | 7 (1.9%) | 0.9 |
| *Laboratory data* | | | | |
| Creatinine (median [IQR]) | 0.90 (0.80, 1.10) | 0.90 (0.80, 1.10) | 0.90 (0.80, 1.10) | 0.2 |
| Respiratory rate (median [IQR]) | 16 (16, 18) | 16 (16, 18) | 16 (16, 18) | 0.8 |
| ABP (mean) (median [IQR]) | 74 (67, 84) | 74 (67, 84) | 74 (67, 84) | 0.6 |
| Plateau pressure (median [IQR]) | 17.0 (15.0, 20.0) | 16.4 (14.7, 20.0) | 17.0 (15.0, 20.0) | 0.5 |
| FiO2* (median [IQR]) | 100 (50, 100) | 100 (50, 100) | 100 (50, 100) | 0.6 |
| Flow rate* (median [IQR]) | 43 (38, 47) | 43 (38, 48) | 43 (38, 47) | 0.8 |
| O2 flow* (median [IQR]) | 10.0 (4.0, 10.0) | 10.0 (4.0, 10.0) | 10.0 (4.0, 10.0) | 0.4 |
| *Drugs* | | | | |
| 1. Oral tablets | | | | |
| Aspirin | 890 (74%) | 613 (73%) | 277 (75%) | 0.6 |
| Ibuprofen | 130 (11%) | 102 (12%) | 28 (7.5%) | 0.016 |
| Heparin | 928 (77%) | 658 (79%) | 270 (73%) | 0.027 |
| Warfarin | 332 (27%) | 232 (28%) | 100 (27%) | 0.8 |
| Clopidogrel | 181 (15%) | 122 (15%) | 59 (16%) | 0.6 |
| Phenylephrine | 497 (41%) | 338 (40%) | 159 (43%) | 0.4 |
| Tacrolimus | 40 (3.3%) | 26 (3.1%) | 14 (3.8%) | 0.5 |
| Amoxicillin | 8 (0.7%) | 6 (0.7%) | 2 (0.5%) | >0.9 |
| Ampicillin | 10 (0.8%) | 7 (0.8%) | 3 (0.8%) | >0.9 |
| Azithromycin | 25 (2.1%) | 14 (1.7%) | 11 (3.0%) | 0.15 |
| Cefazolin | 245 (20%) | 167 (20%) | 78 (21%) | 0.7 |
| CefePIME | 84 (7.0%) | 58 (6.9%) | 26 (7.0%) | >0.9 |
| Ceftriaxone | 69 (5.7%) | 43 (5.1%) | 26 (7.0%) | 0.2 |
| Cephalexin | 7 (0.6%) | 5 (0.6%) | 2 (0.5%) | >0.9 |
| Ciprofloxacin | 48 (4.0%) | 37 (4.4%) | 11 (3.0%) | 0.2 |
| Gentamicin | 2 (0.2%) | 1 (0.1%) | 1 (0.3%) | 0.5 |
| Levofloxacin | 12 (1.0%) | 10 (1.2%) | 2 (0.5%) | 0.4 |
| Linezolid | 5 (0.4%) | 5 (0.6%) | 0 (0%) | 0.3 |
| Meropenem | 28 (2.3%) | 21 (2.5%) | 7 (1.9%) | 0.5 |
| Metronidazole | 45 (3.7%) | 35 (4.2%) | 10 (2.7%) | 0.2 |
| Mupirocin | 152 (13%) | 105 (13%) | 47 (13%) | >0.9 |
| Piperacillin | 49 (4.1%) | 40 (4.8%) | 9 (2.4%) | 0.056 |
| Sulfameth | 28 (2.3%) | 16 (1.9%) | 12 (3.2%) | 0.2 |
| Trimethoprim | 28 (2.3%) | 16 (1.9%) | 12 (3.2%) | 0.2 |
| Vancocin | 306 (25%) | 211 (25%) | 95 (26%) | 0.9 |
| 2. Intravenous infusion | | | | |
| Dobutamine | | | | 0.4 |

**Table 1** (continued)

| Characteristic | Overall, $N=1,208$[1] | Training set, $N=837$[1] | Validation set, $N=371$[1] | $p$ value[2] |
|---|---|---|---|---|
| 0 | 1,184 (98%) | 817 (98%) | 367 (99%) | |
| < 400 mg | 9 (0.7%) | 8 (1.0%) | 1 (0.3%) | |
| > 400 mg | 15 (1.2%) | 12 (1.4%) | 3 (0.8%) | |
| Epinephrine | | | | 0.2 |
| 0 | 930 (77%) | 640 (76%) | 290 (78%) | |
| < 14 mg | 136 (11%) | 90 (11%) | 46 (12%) | |
| > 14 mg | 142 (12%) | 107 (13%) | 35 (9.4%) | |
| Norepinephrine | | | | 0.2 |
| 0 | 930 (77%) | 640 (76%) | 290 (78%) | |
| < 14 mg | 136 (11%) | 90 (11%) | 46 (12%) | |
| > 14 mg | 142 (12%) | 107 (13%) | 35 (9.4%) | |
| Vasopressin | | | | 0.6 |
| 0 | 1,075 (89%) | 741 (89%) | 334 (90%) | |
| < 65 units | 70 (5.8%) | 49 (5.9%) | 21 (5.7%) | |
| > 65 units | 63 (5.2%) | 47 (5.6%) | 16 (4.3%) | |
| Neuroblock | | | | 0.7 |
| 0 | 1,156 (96%) | 799 (95%) | 357 (96%) | |
| < 250 mg | 18 (1.5%) | 14 (1.7%) | 4 (1.1%) | |
| > 250 mg | 34 (2.8%) | 24 (2.9%) | 10 (2.7%) | |

RTI: respiratory tract infection; ABP, arterial blood pressure; BMI, body mass index; PICC, peripherally inserted central catheter; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; $FiO_2$, fraction of inspiration $O_2$. *: For patients receiving mechanical ventilation

survival. Through machine learning techniques, we aim to provide a deeper understanding of AKI survival and contribute to the clinical application of such models in the ICU.

## Methods

### Data source

The data of patients used in this study were collected from the MIMIC-IV 1.0 database. This extensive open-access database contains a wealth of health-related information from patients in the ICU at Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2008 to 2019 [17]. Because of the open-access nature of the database, informed consent was not required. Data collection was approved by PhysioNet (https://physionet.org/) following ethical training and adherence to relevant ethical guidelines.

### Study population and data extraction

Data extraction was conducted using PgAdmin PostgreSQL 14.5 (Bedford, USA). Patients meeting the following criteria were included:

(i) Adults aged 18 and above;
(ii) Diagnosed with AKI according to the KDIGO guidelines.
(iii) ICU duration over 24 h (los_icu ≥ 1).
(iv) Admitted to the ICU (if the patient had multiple admissions, only the first was analyzed) (Fig. 1).

The extraction process is depicted in Fig. 2. Patients with complete survival data were randomly assigned to a training set ($n=837$) and a validation set ($n=371$) in a 7:3 ratio using the createDataPartition function from the caret R package. The variables collected included age, body mass index (BMI), survival status, medication history, creatinine levels, respiratory rate settings, and additional parameters. Details on the specific indicators are displayed in Table 1.

### Statistical analysis

Data analysis was made in R software 3.6.3. The distribution of continuous variables was assessed

**Table 2** Univariate and stepwise Cox regression analysis on the included variables

| Factors | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** |
| **ABP (mean)** | | **0.98(0.97–1.00)** | **0.0181** | | |
| Age | | 1.02(1.01–1.03) | 0.0025 | 1.03(1.02–1.05) | < 0.0001 |
| Amoxicillin (Yes) | | 2.11(0.67–6.68) | 0.2027 | | |
| Ampicillin (Yes) | | 2.04(0.28–14.66) | 0.4800 | | |
| Aspirin (Yes) | | 0.46(0.31–0.68) | 0.0001 | | |
| Azithromycin (Yes) | | 2.59(1.05–6.36) | 0.0382 | | |
| Bipap (Yes) | | 2.01(0.28–14.51) | 0.4872 | | |
| BMI | | 0.97(0.94–0.99) | 0.0132 | | |
| CeFAZolin (Yes) | | 0.1(0.02–0.39) | 0.0011 | 0.15(0.04–0.6) | 0.0078 |
| CefePIME(Yes) | | 1.81(1.02–3.24) | 0.0441 | | |
| Ceftriaxone (Yes) | | 1.59(0.85–2.96) | 0.1452 | | |
| Cephalexin (Yes) | | 1.53(0.37–6.23) | 0.5548 | | |
| Ciprofloxacin (Yes) | | 0.98(0.45–2.1) | 0.9541 | | |
| Clopidogrel (Yes) | | 0.82(0.52–1.29) | 0.3873 | | |
| Creatinine | | 1.19(0.93–1.54) | 0.1695 | | |
| CVVHDF(Yes) | | 2.94(1.37–6.34) | 0.0059 | 2.53(1.11–5.76) | 0.0266 |
| Dobutamine | 0 | Ref | | | |
| | < 400 mg | 4.77(1.50–15.17) | 0.0081 | | |
| | > 400 mg | 4.79(1.74–13.21) | 0.0025 | | |
| Epinephrine | 0 | Ref | | | |
| | < 14 mg | 3.60(1.63–7.95) | 0.0016 | 3.57(1.58–8.05) | 0.0022 |
| | > 14 mg | 12.1(7.22–20.29) | < 0.0001 | 8.35(4.2–16.59) | < 0.0001 |
| $FiO_2$* | | 1.00(0.99–1.01) | 0.7211 | | |
| Flow rate* | | 1.00 (0.98–1.02) | 0.8444 | | |
| Gender (Male) | | 0.75(0.52–1.08) | 0.1211 | | |
| Gentamicin (Yes) | | 5.10(0.71–36.76) | 0.1059 | | |
| Heparin (Yes) | | 1.68(0.61–4.62) | 0.3124 | | |
| Ibuprofen (Yes) | | 0.46(0.26–0.80) | 0.0056 | 0.48(0.27–0.86) | 0.0142 |
| IHD (Yes) | | 1.36(0.55–3.34) | 0.5018 | | |
| Levofloxacin (Yes) | | 0.48(0.07–3.47) | 0.4705 | | |
| Linezolid (Yes) | | 4.06(1.00–16.52) | 0.0503 | | |
| Meropenem (Yes) | | 1.05(0.43–2.60) | 0.9090 | | |
| Metronidazole (Yes) | | 0.97(0.45–2.08) | 0.9327 | | |
| Minute volume | | 1.06(0.97–1.17) | 0.1948 | | |
| Mupirocin (Yes) | | 0.13(0.02–0.91) | 0.0397 | | |
| Neuroblock | 0 | Ref | | | |
| | < 250 mg | 5.99(2.15–16.69) | 0.0006 | | |
| | > 250 mg | 1.07(0.26–4.40) | 0.9209 | | |
| Norepinephrine | 0 | Ref | | | |
| | < 14 mg | 3.60(1.63–7.95) | 0.0016 | | |
| | > 14 mg | 12.1(7.22–20.29) | < 0.0001 | | |
| $O_2$ flow* | | 0.95(0.91–1.00) | 0.0302 | 0.94(0.9–0.98) | 0.0077 |
| Phenyllphrine (Yes) | | 0.99(0.68–1.45) | 0.9679 | | |
| PICC(Yes) | | 1.54(0.96–2.47) | 0.0754 | | |
| Piperacillin (Yes) | | 1.56(0.79–3.08) | 0.2016 | | |
| Plateau pressure | | 1.05(1.01–1.09) | 0.0089 | | |
| Respiratory rate | | 1.09(1.05–1.14) | < 0.0001 | 1.07(1.03–1.12) | 0.0013 |
| RTI (Yes) | | 1.50(1.03–2.18) | 0.0339 | | |

**Table 2** (continued)

| Factors | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR (95%CI) | P | HR (95%CI) | P |
| **ABP (mean)** | | **0.98(0.97–1.00)** | **0.0181** | | |
| Sulfameth (Yes) | | 1.09(0.34–3.43) | 0.8868 | | |
| Tacrolimus (Yes) | | 0.55(0.22–1.35) | 0.1918 | | |
| Tidal volume set | | 0.995(0.992–0.998) | 0.0002 | | |
| Tracheostomy (Yes) | | 0.51(0.07–3.63) | 0.4972 | | |
| Trimethoprim (Yes) | | 1.09(0.34–3.43) | 0.8868 | | |
| Vancocin (Yes) | | 1.21(0.82–1.79) | 0.3453 | | |
| Vasopressin | 0 | Ref | | | |
| | < 65 units | 5.06(2.54–10.06) | < 0.0001 | 1.1(0.5–2.42) | 0.8213 |
| | > 65 units | 10.71(5.94–19.32) | < 0.0001 | 2.2(1.06–4.59) | 0.0352 |
| Warfarin (Yes) | | 0.61(0.39–0.96) | 0.0316 | 0.49(0.31–0.78) | 0.0025 |

RTI: respiratory tract infection; BMI, body mass index; PICC, peripherally inserted central catheter; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; ABP, arterial blood pressure; $FiO_2$, fraction of inspiration $O_2$. *: For patients receiving mechanical ventilation

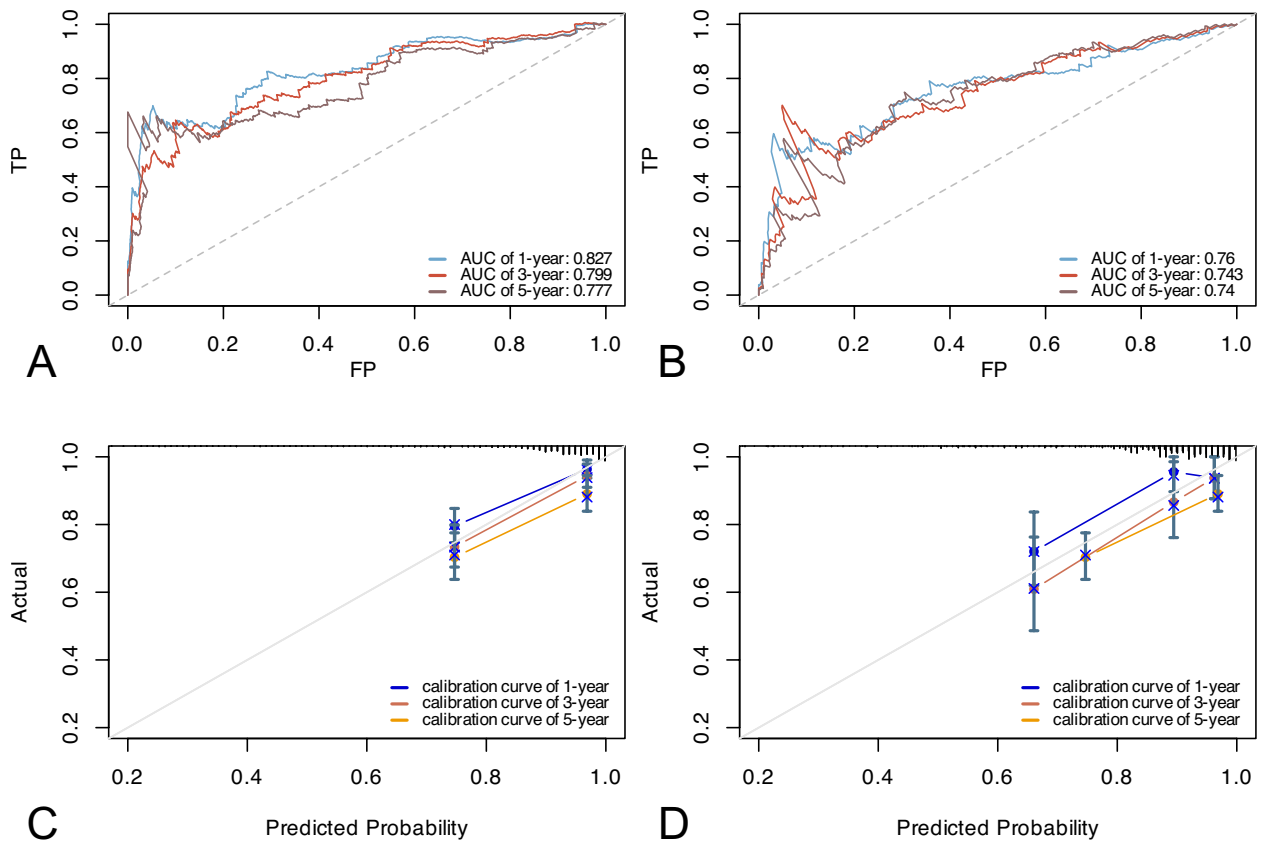


**Fig. 3** Predictive performance evaluation results for the nomogram: **A** the training set's ROC curve indicates Area Under Curve (AUC) values of 0.827, 0.799, and 0.777 for the 1-year, 3-year, and 5-year survival predictions in AKI patients, respectively; **B** the validation set's ROC curve shows AUC values of 0.760, 0.743, and 0.740 for the 1-year, 3-year, and 5-year survival predictions in AKI patients, respectively; **C** calibration curves for the 1-year, 3-year, and 5-year survival predictions in the training set of AKI patients; **D** calibration curves for the 1-year, 3-year, and 5-year survival predictions in the validation set of AKI patients

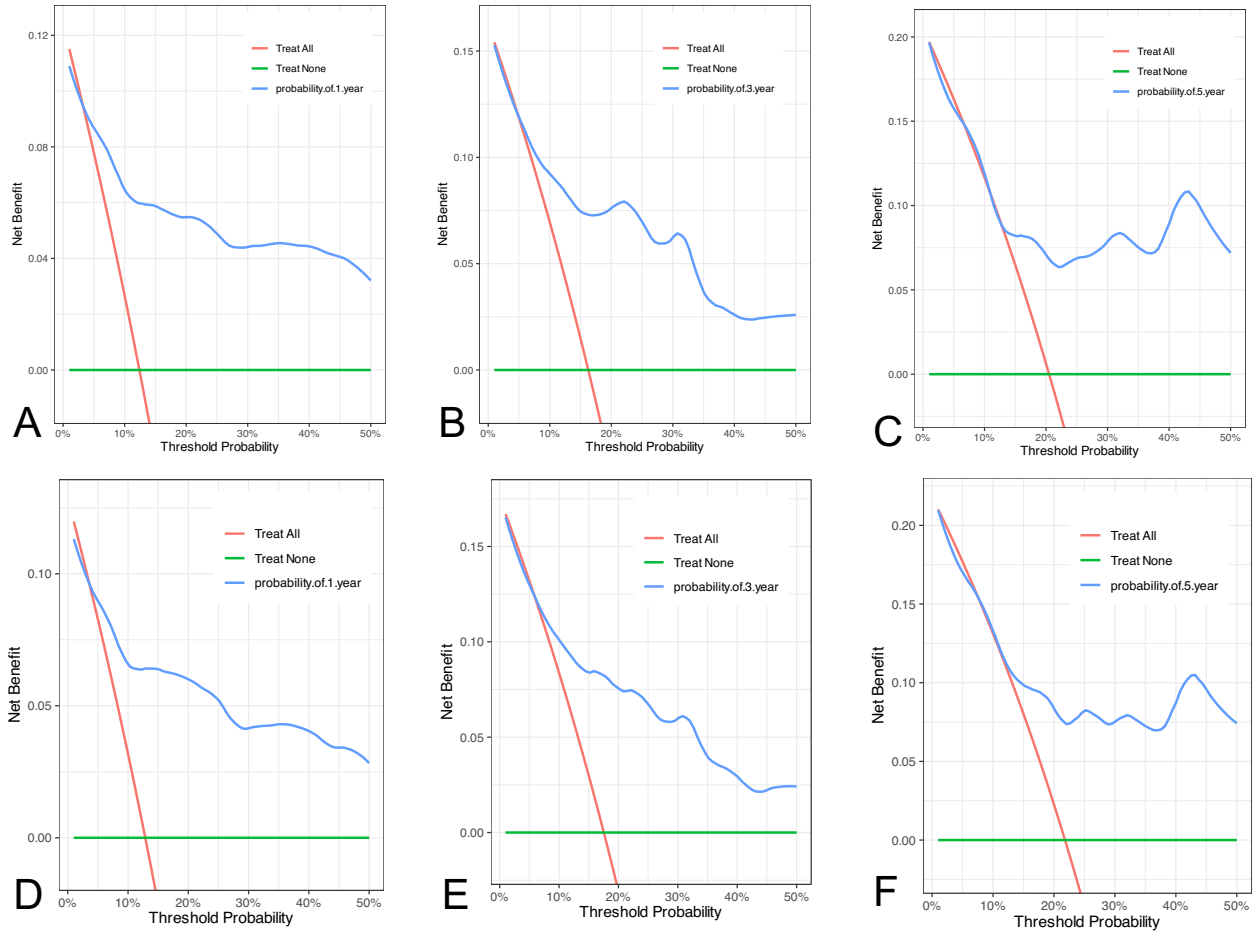


**Fig. 4** The clinical utility of predictive models through decision curves: **A**: the 1-year survival probability decision curve for AKI patients in the training set; **B**: the 3-year survival probability decision curve for AKI patients in the training set; **C**: the 5-year survival probability decision curve for AKI patients in the training set; **D**: the 1-year survival probability decision curve for AKI patients in the validation set; **E**: the 3-year survival probability decision curve for AKI patients in the validation set; **F**: the 5-year survival probability decision curve for AKI patients in the validation set

with the Shapiro–Wilk test. Data that were normally distributed are delineated as mean ± standard deviation, otherwise, as median with interquartile range (IQR). Categorical variables are manifested as percentages. The t tests and Wilcoxon rank-sum tests were leveraged for comparisons of continuous variables and Chi-square tests for categorical data. Key predictors for survival in AKI patients were discerned through univariate and stepwise Cox regression analyses. Propensity score matching (PSM) was utilized to include medications in the nomogram. The prognoses of patient groups were compared using the log-rank test and Kaplan–Meier survival curves were plotted.

## Results

### Patient characteristics

Initially, 24,111 individuals diagnosed with AKI were selected from the MIMIC-IV database. According to exclusion criteria (Fig. 2), 1,208 patients were finally included and further assigned to a training subset (837 patients) and a validation subset (371 patients). Demographic and clinical characteristics for these cohorts are listed in Table 1. The median age of all study populations was 67 years, with an interquartile range of 57–75 years. Similarly, the median arterial blood pressure for all groups was 74, with an interquartile range of 67–84. Sex and the use of oral ibuprofen and heparin tablets differed significantly ($p < 0.05$) among the groups, whereas other baseline characteristics were similar (Table 1).

### Construction and validation of the predictive nomogram

The results of univariate and stepwise Cox regression analyses are detailed in Table 2. Variables that were significant in the univariate analysis ($p < 0.05$) were included in the stepwise model. The predictive

**Table 3** Differences in confounders before and after PSM

| Factors | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | No | Yes | P | Yes | No | P |
| *1. Cefazolin* | | | | | | |
| *n* | 963 | 245 | | 233 | 233 | |
| Sex = Male (%) | 591 (61.4) | 167 (68.2) | 0.059 | 161 (69.1) | 155 (66.5) | 0.62 |
| Age (median [IQR]) | 66.12 [55.82, 74.40] | 68.67 [61.06, 75.56] | 0.002 | 68.36 [61.35, 75.63] | 68.18 [60.67, 74.89] | 0.634 |
| BMI (median [IQR]) | 28.72 [24.87, 33.61] | 29.82 [26.28, 33.95] | 0.029 | 29.42 [26.05, 34.41] | 29.67 [26.01, 33.91] | 0.941 |
| Creatinine (median [IQR]) | 0.90 [0.70, 1.10] | 0.90 [0.80, 1.10] | 0.869 | 0.90 [0.70, 1.10] | 0.90 [0.80, 1.10] | 0.553 |
| *2. Epinephrine* | | | | | | |
| *n* | 930 | 278 | | 235 | 235 | |
| Gender = Male (%) | 589 (63.3) | 169 (60.8) | 0.485 | 150 (63.8) | 145 (61.7) | 0.703 |
| Age (median [IQR]) | 67.15 [58.14, 74.70] | 65.69 [53.73, 73.78] | 0.056 | 66.09 [54.82, 74.11] | 66.44 [55.42, 74.76] | 0.767 |
| BMI (median [IQR]) | 29.04 [25.35, 33.68] | 28.85 [24.58, 33.61] | 0.646 | 28.70 [25.17, 33.55] | 29.31 [24.69, 33.64] | 0.729 |
| Creatinine (median [IQR]) | 0.90 [0.80, 1.10] | 0.90 [0.72, 1.28] | 0.029 | 0.90 [0.80, 1.10] | 0.90 [0.70, 1.10] | 0.797 |
| *3. Ibuprofen* | | | | | | |
| *n* | 1078 | 130 | | 164 | 44 | |
| Gender = Male (%) | 700 (64.9) | 58 (44.6) | < 0.001 | 85 (51.8) | 16 (36.4) | 0.098 |
| Age (median [IQR]) | 67.46 [58.32, 75.07] | 56.69 [44.85, 67.35] | < 0.001 | 61.46 [53.26, 71.08] | 57.73 [49.26, 72.62] | 0.62 |
| BMI (median [IQR]) | 28.95 [25.22, 33.62] | 29.23 [24.91, 34.41] | 0.788 | 28.60 [25.15, 33.65] | 30.30 [25.55, 36.45] | 0.22 |
| Creatinine (median [IQR]) | 0.90 [0.80, 1.10] | 0.90 [0.70, 1.00] | 0.006 | 0.90 [0.70, 1.10] | 0.90 [0.80, 1.40] | 0.024 |
| *4. Vasopressin* | | | | | | |
| *n* | 1075 | 133 | | 125 | 125 | |
| Gender = Male (%) | 680 (63.3) | 78 (58.6) | 0.346 | 83 (66.4) | 75 (60.0) | 0.359 |
| Age (median [IQR]) | 66.70 [57.41, 74.59] | 66.55 [56.53, 75.19] | 0.942 | 63.31 [54.96, 74.04] | 66.64 [56.41, 75.19] | 0.298 |
| BMI (median [IQR]) | 29.07 [25.34, 33.76] | 27.99 [24.06, 32.74] | 0.076 | 29.07 [25.39, 34.69] | 28.07 [24.06, 33.16] | 0.264 |
| Creatinine (median [IQR]) | 0.90 [0.80, 1.10] | 1.00 [0.70, 1.20] | 0.080 | 0.90 [0.80, 1.10] | 1.00 [0.70, 1.20] | 0.982 |
| *5. Warfarin* | | | | | | |
| *n* | 876 | 332 | | 295 | 295 | |
| Gender = Male (%) | 551 (62.9) | 207 (62.3) | 0.912 | 172 (58.3) | 181 (61.4) | 0.502 |
| Age (median [IQR]) | 65.78 [56.10, 73.82] | 69.10 [60.61, 76.66] | < 0.001 | 67.72 [59.03, 75.07] | 68.04 [59.37, 75.62] | 0.633 |
| BMI (median [IQR]) | 28.70 [24.95, 33.59] | 29.59 [25.56, 33.74] | 0.078 | 29.24 [25.47, 34.66] | 29.39 [25.45, 33.64] | 0.837 |
| Creatinine (median [IQR]) | 0.90 [0.70, 1.10] | 0.95 [0.80, 1.10] | 0.008 | 0.90 [0.70, 1.10] | 0.90 [0.80, 1.10] | 0.165 |

nomogram was developed based on variables that were significantly associated with the survival of AKI patients in the training set, including oxygen flow rate, respiratory rate, continuous venovenous hemodiafiltration (CVVHDF), age, and the history of medication use for ibuprofen, epinephrine, cefazolin, warfarin, and vasopressin. Figure 1 displays the nomogram. The AUC values of the nomogram for 1-, 3-, and 5-year survival predictions were 0.827, 0.799, and 0.777 in the training set, and 0.760, 0.743, and 0.740 in the validation set, respectively (Fig. 3). The calibration curves (Fig. 3) for both sets confirmed the predictive accuracy of the nomogram, and the clinical decision curves (Fig. 4) demonstrated the practical value of the nomogram in guiding clinical decisions.

### PSM results

PSM (1:1) was performed using sex, age, BMI, and creatinine as covariates with a caliper of 0.01. Significant differences in age and BMI were noted for those with a medication history of cefazolin ($n = 466$). For ibuprofen, initial differences in sex, age, and creatinine were insignificant after matching ($n = 208$). Those with a medication history of vasopressin showed initial differences in BMI and creatinine, which were insignificant after PSM ($n = 250$). Those with a medication history of Warfarin exhibited initial differences in age,

**Table 4** Prognostic comparisons of drug groups after PSM

| Characteristic | HR | 95% CI | *p* value |
|---|---|---|---|
| *Cefazolin* | | | |
| No | – | – | |
| Yes | 0.159 | 0.057, 0.447 | < 0.001 |
| *Epinephrine* | | | |
| No | – | – | |
| Yes | 11.383 | 4.887, 26.514 | < 0.001 |
| *Ibuprofen* | | | |
| No | – | – | |
| Yes | 0.482 | 0.234, 0.993 | 0.048 |
| *Vasopressin* | | | |
| No | – | – | |
| Yes | 19.898 | 6.547, 60.479 | < 0.001 |
| *Warfarin* | | | |
| No | – | – | |
| Yes | 0.585 | 0.368, 0.930 | 0.024 |

BMI, and creatinine, with no significant differences after PSM ($n = 390$). Demographic and clinical characteristics are listed in Table 3.

### Prognostic differences after PSM

After PSM, the prognostic outcomes of the cohorts were compared. Cefazolin was significantly associated with improved patient prognosis, indicating a protective effect. Similarly, epinephrine also showed a significant link to better patient outcomes. Ibuprofen was a protective factor for prognosis, and this association was statistically significant. Conversely, warfarin and vasopressin were identified as significant risk factors, indicating a negative impact on prognosis. The differences in prognostic outcomes are detailed in Table 4.

K–M survival curves noted that patients taking cefazolin had a notably higher survival probability ($p < 0.0001$) than those not taking cefazolin. Those using ibuprofen also had a higher survival probability ($p = 0.044$). For warfarin, patients not using it had a slightly lower survival probability, but this difference was not statistically significant ($p = 0.05$). Interestingly, patients who did not use vasopressin had a significantly higher survival probability ($p < 0.0001$) than those who did. Similarly, patients not using epinephrine had a higher survival probability significant ($p < 0.0001$). The K–M survival curves after PSM are displayed in Fig. 5.

## Discussion

AKI is a frequent issue in ICUs [5]. Research indicates that prevention and early detection of AKI can improve patient outcomes [3]. However, many patients have AKI upon ICU admission. As a result, ICU physicians

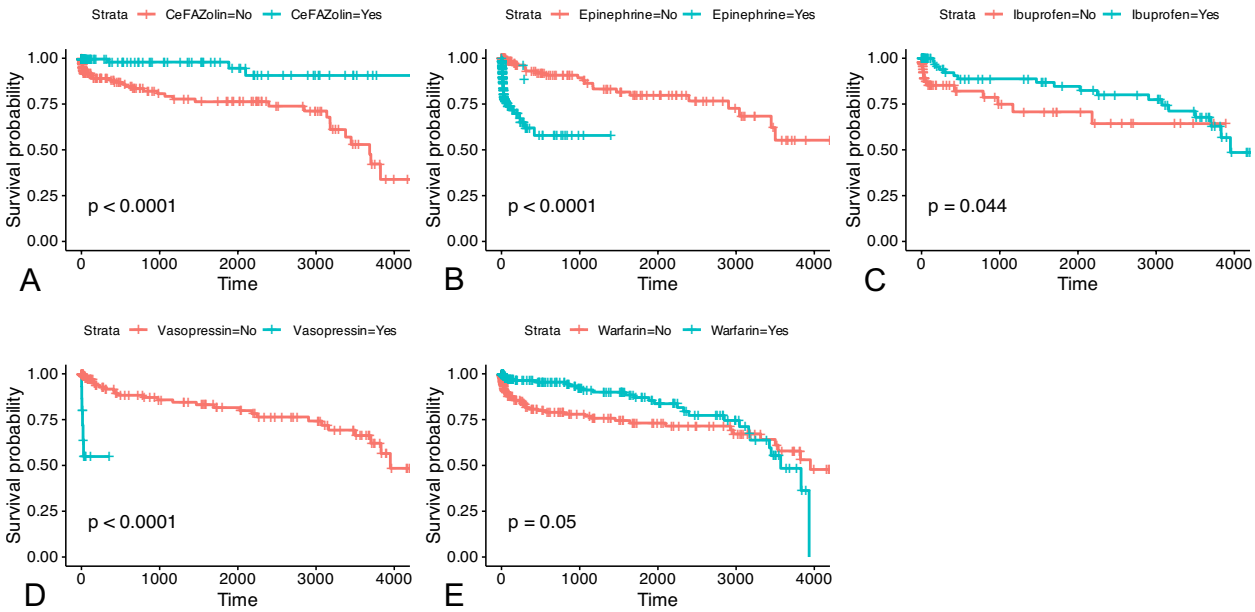


**Fig. 5** Kaplan–Meier survival curves for AKI patients after propensity score matching. **A**: The Kaplan–Meier survival curve indicated that AKI patients who used cefazolin had significantly higher survival probabilities compared to those who did not ($p < 0.0001$). **B**: Those who used ibuprofen showed a higher survival probability than non-users, though this was not statistically significant ($p = 0.044$). **C**: Patients not using warfarin had a lower survival probability than users, but this difference was not statistically significant ($p = 0.05$). **D**: Patients who abstained from vasopressin demonstrated significantly higher survival probabilities than those who used it ($p < 0.0001$). **E**: Those who did not use epinephrine had significantly higher survival probabilities compared to users ($p < 0.0001$)

often focus more on how to treat AKI and predict its progression rather than on preventing or diagnosing it first. As for drug therapy for AKI, the effectiveness can differ across patients. To make well-informed decisions together, families and medical professionals need to make reliable predictions, not just rely on a doctor's intuition and experience.

In our research, clinical indicators were utilized to create a nomogram to predict survival for ICU patients with AKI. Our study population consisted of 1,208 individuals from the MIMIC-IV database. Through univariate and stepwise Cox regression analyses, the medication history of ibuprofen, epinephrine, cefazolin, warfarin, and vasopressin was identified to have a significant correlation with the survival of AKI patients in the training dataset. Then, a nomogram was established for AKI prognosis based on these significant factors, and its reliability was confirmed. The nomogram showed high predictive accuracy, calibration, and clinical applicability, indicating its potential as a useful tool for predicting AKI patient outcomes in the ICU setting. To our knowledge, this is the first nomogram designed to predict the survival of AKI patients in ICUs based on their medication history.

To mitigate the impact of confounders related to the drugs included in the nomogram, PSM was conducted to create two comparable cohorts. This allowed the comparisons of prognostic differences between patients who used these drugs and those who did not. The PSM results demonstrated that, after adjustment, the prognostic changes in patients using these drugs were consistent with the patterns identified in the nomogram. Because of the limited clinical utility of prognostic models based on a single biomarker, we opted for a nomogram, a widely employed prediction model that is effective in forecasting survival for a diverse range of ICU patients [18, 19].

Our research revealed that oxygen flow, respiratory rate, CVVHDF, age, and the use of specific medications (ibuprofen, epinephrine, cefazolin, warfarin, and vasopressin) significantly affected the survival of AKI patients. The predictive analysis suggested that ibuprofen could act as a protective factor for survival in these patients. Research suggested that short-term or low-dose ibuprofen could alleviate kidney inflammation without causing renal damage [20]. Additionally, a real-world analysis of post-marketing surveillance data demonstrated that ibuprofen was relatively less nephrotoxic than acetaminophen in AKI patients [21]. Our results also showed that the prognosis of AKI patients deteriorated with age. This observation is consistent with numerous other studies that have underscored old age as a crucial factor for a higher incidence and poorer outcomes of AKI patients in the ICU [22, 23]. The predictive nomogram also uncovered that the use of cefazolin was a protective factor for AKI prognosis. Studies have indicated that cephalosporin antibiotics could indirectly protect renal function by reducing systemic inflammation and immune overreaction in the treatment of specific bacterial infections [24, 25]. Antibiotic administration is definitely protective for pediatric patients in the ICU [26]. Similarly, our predictive nomogram suggested that the use of warfarin might be a protective factor for AKI patients. Although warfarin may elevate the risk of bleeding, this increase is not pronounced at low doses [27]. A retrospective study from the MIMIC-IV database showed that warfarin administration was associated with improved short-term survival in AKI patients with atrial fibrillation [28].

Moreover, the predictive nomogram suggested that epinephrine use was negatively associated with AKI prognosis. The association between excessive fluid overload and acute kidney injury is well established. Specifically, fluid accumulation and consecutive increases in renal venous and interstitial pressure will result in a reduced trans-renal pressure gradient for renal blood flow [29]. Several studies have assessed the relationship between epinephrine usage and the survival of AKI patients in the ICU following cardiac surgery, and they consistently identify the use of epinephrine as a risk factor for poor survival [30]. Additionally, our predictive nomogram indicated that vasopressin was an adverse factor for AKI prognosis. Vasopressin induces the recruitment of aquaporine-2 and increases the permeability of the epithelial membrane to water [31]. Vasopressin might improve kidney function in patients at risk of kidney failure and reduce the incidence of renal failure and dysfunction [11].

However, our study has limitations. The retrospective and observational nature may introduce selection bias. As a single-site, retrospective study, it cannot disclose the causation. Our model, utilizing data from the MIMIC-IV database, lacked accessible variables like oral drug doses and durations, and some widely reported predictors. More randomized clinical trials and additional predictors are needed to validate our model. Missing data were estimated, which might deviate from actual values. Internal validation was performed, but external

validation across multiple centers is necessary to assess the models' predictive power.

## Conclusion

In conclusion, the survival of AKI patients in the ICU is influenced by various factors, including $O_2$ flow, respiratory rate, CVVHDF, age, and the medication history of ibuprofen, epinephrine, cefazolin, warfarin, and vasopressin. The nomogram based on 9 key factors has remarkable predictive accuracy and clinical applicability. This model may facilitate the early identification of AKI patients at elevated risk of mortality, thereby improving patient outcomes.

### Abbreviations

| | |
|---|---|
| AKI | Acute kidney injury |
| ABP | Arterial blood pressure |
| BMI | Body mass index |
| CVVHDF | Continuous venovenous hemodiafiltration |
| CO | Cardiac output |
| COX | Cyclooxygenase |
| $FiO_2$ | Fraction of inspiration O2 |
| IHD | Intermittent hemodialysis |
| KDIGO | Kidney disease improving global guidelines |
| K–M | Kaplan–Meier |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| PICC | Peripherally inserted central catheter |
| PSM | Propensity score matching |
| RRT | Renal replacement therapy |
| RTI | Respiratory tract infection |

### Acknowledgements

Not applicable.

### Author contributions

All authors contributed to the study conception and design. Conceptualization: Rui Yang; Methodology: Xiaozhe Su; Formal analysis and investigation: Ziqi Liu and Hao Su; Writing—original draft preparation: Rui Yang, Shuai Shao and Xiaozhe Su; Writing—review and editing: Haiqing He; Funding acquisition: Hao Su, Haiqing He; Resources: Yinhuai Wang; Supervision: Haiqing He. All authors commented on previous versions of the manuscript.

### Funding

This work was supported by the Scientific Research Launch Project for new employees of the Second Xiangya Hospital of Central South University.

### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Competing interest

The authors declare no competing interests.

### Author details

[1]Department of Urology, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan, China. [2]Xiangya School of Medicine, Central South University, Changsha 410013, Hunan, China. [3]Department of Urology, Renmin Hospital of Wuhan University, Wuhan 430060, China. [4]Department of Acupuncture and Moxibustion, The First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan, China.

Received: 6 February 2024 Accepted: 15 January 2025
Published online: 03 February 2025

### References

1. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nat Rev Dis Primers. 2021;7(1):52.
2. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394(10212):1949–64.
3. Griffin BR, Liu KD, Teixeira JP. Critical care nephrology: core curriculum 2020. Am J Kidney Dis. 2020;75(3):435–52.
4. Huang J, Xu D, Yang L. Acute kidney injury in Asia: disease burden. Semin Nephrol. 2020;40(5):443–55.
5. Bouchard J, Acharya A, Cerda J, Maccariello ER, Madarasu RC, Tolwani AJ, Liang X, Fu P, Liu ZH, Mehta RL. A prospective international multicenter study of AKI in the intensive care unit. Clin J Am Soc Nephrol. 2015;10(8):1324–31.
6. Dagar N, Kale A, Jadhav HR, Gaikwad AB. Nutraceuticals and network pharmacology approach for acute kidney injury: a review from the drug discovery aspect. Fitoterapia. 2023;168: 105563.
7. Sohaney R, Yin H, Shahinian V, Saran R, Burrows NR, Pavkov ME, Banerjee T, Hsu CY, Powe N, Steffick D, et al. In-hospital and 1-year mortality trends in a national cohort of US veterans with acute kidney injury. Clin J Am Soc Nephrol. 2022;17(2):184–93.
8. Levey AS, James MT. Acute kidney injury. Ann Intern Med. 2017;167(9):ITC66-IT80.
9. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. Eur J Intern Med. 2015;26(4):285–91.
10. Schetz M. Vasopressors and the kidney. Blood Purif. 2002;20(3):243–51.
11. Fage N, Asfar P, Radermacher P, Demiselle J. Norepinephrine and vasopressin in hemorrhagic shock: a focus on renal hemodynamics. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms24044103.
12. Pickkers P, Darmon M, Hoste E, Joannidis M, Legrand M, Ostermann M, Prowle JR, Schneider A, Schetz M. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. Intensive Care Med. 2021;47(8):835–50.
13. Oliver T, Salman LA, Ciaudelli B, Cohen DA. Anticoagulation-related nephropathy: the most common diagnosis you've never heard of. Am J Med. 2019;132(8):e631–3.
14. Nateghi Haredasht F, Viaene L, Pottel H, De Corte W, Vens C. Predicting outcomes of acute kidney injury in critically ill patients using machine learning. Sci Rep. 2023;13(1):9864.
15. Zhou H, Liu L, Zhao Q, Jin X, Peng Z, Wang W, Huang L, Xie Y, Xu H, Tao L, et al. Machine learning for the prediction of all-cause mortality in patients with sepsis-associated acute kidney injury during hospitalization. Front Immunol. 2023;14:1140755.
16. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173-180.
17. Rogers P, Wang D, Lu Z. Medical information mart for intensive care: a foundation for the fusion of artificial intelligence and real-world data. Front Artif Intell. 2021;4: 691626.
18. Guo Q, Wu M, Li H, Ouyang H, Sun R, Wang J, Liu Z, Wang J, Zhang Y. Development and validation of a prognostic nomogram for myocardial infarction patients in intensive care units: a retrospective cohort study. BMJ Open. 2020;10(12): e040291.
19. Yang Y, Dong J, Li Y, Chen R, Tian X, Wang H, Hao C. Development and validation of a nomogram for predicting the prognosis in cancer patients with sepsis. Cancer Med. 2022;11(12):2345–55.

20. Pergolizzi JV Jr, Raffa RB, Nalamachu S, Taylor R Jr. Evolution to low-dose NSAID therapy. Pain Manag. 2016;6(2):175–89.
21. Shao QH, Yin XD, Liu HX, Zhao B, Huang JQ, Li ZL. Kidney injury following ibuprofen and acetaminophen: a real-world analysis of post-marketing surveillance data. Front Pharmacol. 2021;12: 750108.
22. Sengthavisouk N, Lumlertgul N, Keomany C, Banouvong P, Senavong P, Sayyaphet S, Binbundith S, Kulvichit W, Peerapornratana S, Praditpornsilpa K, et al. Epidemiology and short-term outcomes of acute kidney injury among patients in the intensive care unit in Laos: a nationwide multicenter, prospective, and observational study. BMC Med. 2020;18(1):180.
23. Emigh BJ, Sahi SL, Teal LN, Blake JC, Heron CH, Teixeira PG, Coopwood B, Cardenas TC, Trust MD, Brown CV. Incidence and risk factors for acute kidney injury in severely injured patients using current kidney disease: improving global outcomes definitions. J Am Coll Surg. 2020;231(3):326–32.
24. Lewis SJ, Mueller BA. Antibiotic dosing in patients with acute kidney injury: "Enough But Not Too Much." J Intensive Care Med. 2016;31(3):164–76.
25. Launay M, Demartin AL, Ragey SP, Mismetti P, Botelho-Nevers E, Delavenne X. Severe inflammation, acute kidney injury, and drug-drug interaction: triple penalty for prolonged elimination of apixaban in patients with coronavirus disease 2019: a grand round. Ther Drug Monit. 2021;43(4):455–8.
26. Simo Nebot S, Lopez-Ramos MG, Velasco-Arnaiz E, Jordan I, Fortuny C, Noguera-Julian A. Impact and quality of antimicrobial use in a referral pediatric intensive care unit. Enferm Infecc Microbiol Clin (Engl Ed). 2022;40(2):78–81.
27. Sakaan SA, Hudson JQ, Oliphant CS, Tolley EA, Cummings C, Alabdan NA, Self TH. Evaluation of warfarin dose requirements in patients with chronic kidney disease and end-stage renal disease. Pharmacotherapy. 2014;34(7):695–702.
28. Bo D, Wang X, Wang Y. Survival benefits of oral anticoagulation therapy in acute kidney injury patients with atrial fibrillation: a retrospective study from the MIMIC-IV database. BMJ Open. 2023;13(1): e069333.
29. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol. 2014;10(1):37–47.
30. Huette P, Moussa MD, Beyls C, Guinot PG, Guilbart M, Besserve P, Bouhlal M, Mounjid S, Dupont H, Mahjoub Y, et al. Association between acute kidney injury and norepinephrine use following cardiac surgery: a retrospective propensity score-weighted analysis. Ann Intensive Care. 2022;12(1):61.
31. Demiselle J, Fage N, Radermacher P, Asfar P. Vasopressin and its analogues in shock states: a review. Ann Intensive Care. 2020;10(1):9.

## Publisher's Note