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Prospective Validation for Severe Acute Kidney Injury Predicting Model based on transcontinental databases

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054092
Article Type:	Original research
Date Submitted by the Author:	16-Jun-2021
Complete List of Authors:	Liang, Qiqiang; Zhejiang University School of Medicine Second Affiliated Hospital Xu, Yongfeng; HealSci Technology Co Zhou, Yu; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Xinyi; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Juan; Zhejiang University School of Medicine Second Affiliated Hospital Huang, Man; Zhejiang University School of Medicine Second Affiliated Hospital,
Keywords:	Acute renal failure < NEPHROLOGY, INTENSIVE & CRITICAL CARE, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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4 **1 Prospective Validation for Severe Acute Kidney Injury Predicting Model based**
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6 **2 on transcontinental databases**
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4 **23 Abstract:**

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6 **24 Objectives:** There are many studies of acute kidney injury (AKI) diagnosis models lack of external
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9 **25 validation and prospective validation.** We constructed the models using three databases to predict severe
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11 **26 AKI within 48 hours in intensive care unit (ICU) patients.**

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14 **27 Design:** A retrospective and prospective cohort study.

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17 **28 Setting:** We studied critically ill patients in our database (SHZJU-ICU) and two other public databases,
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19 **29 the Medical Information Mart for Intensive Care (MIMIC) and AmsterdamUMC databases, including**
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21 **30 basic demographics, vital signs, and laboratory results. We predicted the diagnosis of severe AKI in**
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23 **31 patients in the next 48 hours using machine-learning algorithms with the three databases. Then, we**
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25 **32 carried out real-time severe AKI prediction in the prospective validation study at our centre for one year.**

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28 **33 Participants:** All patients included in three databases with uniform exclusion criteria.

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31 **34 Primary and secondary outcome measures:** Effect evaluation index of prediction models.

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34 **35 Results:** We included 58492 patients, and a total of 5257 (9.0%) patients met the definition of severe
35
36 **36 AKI. In the internal validation of the SHZJU-ICU and MIMIC databases, the best area under the receiver**
37
38 **37 operating characteristic curve (AUROC) of the model was 0.86. The external validation results by**
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40 **38 AmsterdamUMC database were also satisfactory, with the best AUROC of 0.86. A total of 2532 patients**
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42 **39 were admitted to the center for prospective validation; 358 positive results were predicted, and 344**
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44 **40 patients were diagnosed with severe AKI, with an accuracy of 83.5% and an AUROC of 0.84.**

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46
47 **41 Conclusion:** The prediction model of severe AKI exhibits promises as a clinical application based on
48
49 **42 dynamic vital signs and laboratory results of multi-center databases with prospective and external**
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51 **43 validation.**

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54 **44 Keywords:** Machine learning; Acute kidney injury; Real-time prospective validation; External
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4 45 validation.

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6 46 **Strengths and limitations of this study:**

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9 47 An important verification step from artificial intelligence research to clinical use;

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11 48 Three large database containing different national populations and regions;

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14 49 The prediction model with excellent performance in complete data validation;

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17 50 Differences in the samples proportion of three databases;

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20 51 The dimensions of variables are not rich enough.

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24 53 **Introduction:**

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27 54 Acute kidney injury (AKI), as a common clinical complication in the intensive care unit (ICU),
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30 55 significantly increases the duration of hospitalization and mortality[1]. AKI is divided into three types
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33 56 according to the various aetiologies: prerenal (renal hypoperfusion), intrarenal (vascular, glomerular, or
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35
36 57 tubulointerstitial lesions), and postrenal (urinary tract obstruction)[2]. Although nearly all diseases
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39 58 associated with ICU admission may cause AKI, acute tubular necrosis (ATN) and prerenal azotaemia
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42 59 are the most common causes[3].

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45 60 All AKI diagnostic criteria including the latest Kidney Disease: Improving Global Outcomes (KDIGO)
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48 61 standard are currently based on the creatinine level and urine volume[4]. However, the increase in the
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51 62 creatinine level or decrease in the urine volume lags the onset of AKI[2]. Many studies have suggested
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54 63 that early diagnosis and treatment of reversible AKI can reduce mortality[5]. Therefore, the creatinine
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57 64 level and urine volume are not satisfactory to meet clinical diagnostic demands. Consequently, many
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60 65 researchers have tried to develop an early warning model by analysing the risk factors for AKI[6].

66 Patient complications, such as diabetes, hypertension, cardiovascular disease, chronic liver disease,

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4 67 sepsis, and trauma, are identified as important risk factors for AKI[7]. The AKI prediction model and
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6 68 scoring system developed based on high-risk factors has gradually become the focus of research
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9 69 considering the lower clinical application threshold compared with that of new biomarkers[6]. Although
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11 70 most previous prediction models use the multiple logistic regression model, a variety of AKI prediction
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14 71 models based on machine learning have resulted in satisfactory outcomes[6]. Since the first AKI
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17 72 prediction model study based on artificial intelligence was published in 2016, researchers have built more
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19 73 than 20 published AKI prediction models successively by using local or multi-centre databases[6,8-14].
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22 74 The results indicate that these models can predict the occurrence of AKI and the need for renal
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24 75 replacement therapy (RRT) within 24 or 48 hours, with accuracies ranging from 81% to 97%[6,15]. In
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27 76 addition, many studies have focused on subspecialized conditions, including cardiac surgery, trauma,
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30 77 and burns[14-16]. However, the common defect in these studies is the lack of external validation and
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33 78 prospective validation, which causes the prediction model to deviate from the clinical scenarios and limits
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36 79 extrapolation beyond the scope of the data.

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38 80 In this study, we built models to predict AKI within 48 hours in critically ill patients by using
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41 81 transcontinental three databases. Then, we evaluated the clinical effect of the model through a one-year
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44 82 prospective validation at our centre.

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47 48 84 **Materials and Methods:**

49 50 85 **Study Population**

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53 86 We collected patients using three ICU databases and prospectively validated the models in our centre.
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56 87 The first database was our centre general ICU database (SHZJU-ICU) of the Second Affiliated Hospital
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59 88 of Zhejiang University School of Medicine, an academic teaching hospital. Since its establishment in
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4 89 2017, it has included 12000 ICU patients' data and is updated daily. The Medical Information Mart for
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6 90 Intensive Care (MIMIC) III database, the second one, is an open ICU database provided by the
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9 91 Massachusetts Institute of Technology and includes nearly 60000 ICU patients from North America[17].
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11 92 Lastly, the AmsterdamUMC database is an available European ICU database with health data related to
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14 93 23000 patients admitted to ICUs in parts of Europe[18]. The research flow chart is shown in Figure 1.
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16
17 94 The study was evaluated and approved by the Ethics Committee of the Second Affiliated Hospital of
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19
20 95 Zhejiang University School of Medicine as study number 2019-078.

21 22 96 **Study definition**

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24
25 97 In this study, the diagnosis of AKI was confirmed based on three stages according to the KDIGO
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27 98 criteria[4]. We defined the patients who met the KDIGO AKI II and III criteria as severe AKI groups
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30 99 and the others as negative groups. We excluded patients with lack of creatinine measurements during
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33 100 admission, patients with creatinine baseline more than 3.0 mg/dL at admission, patients who met severe
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36 101 AKI diagnosis within 24 hours, and patients who used RRT within 48 hours after admission[19]. In
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38 102 addition, we excluded pregnant women, patients younger than 14 years old, and patients hospitalized in
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41 103 the ICU for fewer than 3 days. After the patient was admitted to ICU, we performed a prediction every
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43 104 24 hours and recorded a prediction time. If the patient was diagnosed with severe AKI within 48 hours,
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46 105 the predictive time was defined as a positive predictive point, and the others were defined as a negative
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48 106 point.

49 50 51 107 **Data Collection**

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53 108 The variables included demographic data, vital signs, basic and primary diseases, laboratory results,
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56 109 important operation records, and drug records. Comorbidity included hypertension, diabetes, cardiopathy,
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59 110 liver disease, and malignant tumors. The primary disease was the main cause of admission to the ICU
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4 111 following the ICD-10 codes. The vital signs and clinical laboratory results were transformed into
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6 112 different variables according to the average, variance, maximum, minimum, and final value before
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9 113 diagnosis. We used the Pearson correlation coefficient to analyze the characteristics of the variables,
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11 114 selected the variables with high correlation. We transformed the MIMIC and AmsterdamUMC databases
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14 115 according to our centre database structure, unifying the unit and diagnostic codes. We deleted more than
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16
17 116 50% of the missing values and replaced the remaining missing values with multiple interpolations. All
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20 117 Missing data between three databases and values included in the model shown in supplementation file
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22 118 Table S1.

23 24 25 119 **Model construction and external validation**

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27 120 The ratio of the training and internal validation sets was 4:1. The two database training sets were
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29
30 121 mixed into a new training set. There were more negative data than positive data, so we randomly sampled
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32 122 the negative datasets and constructed a new data subset with a sampling ratio of positive and negative
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34
35 123 data of 1:5. We used multiple logistic regression, random forest, XGBoost, AdaBoost, LightGBost,
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37 124 gradient boosting decision tree (GBDT), and debug to assess the variables and model-related parameters
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39
40 125 by the fivefold cross-validation method. After the models were built, we used the SHZJU-ICU and
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43 126 MIMIC test sets for internal validation of the model and the AmsterdamUMC database for external
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46 127 validation. The most appropriate cut-off value was determined according to the K-S curve. The prediction
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48 128 model represents the results of each prediction with a probability between 0 to 1.0. We define results
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51 129 more than 0.6 as high-risk, that is, positive results, and the rest as negative results. Through internal
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54 130 validation and external validation, we calibrated the model by adjusting the super-parameters and using
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56 131 the Platt calibration algorithm and compared the calibration effect by drawing a reliability diagram. The
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59 132 model was visualized and analyzed by a visual programming scheme. All model building and validation
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4 133 processes were performed in Python 3.6.
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6 134 **Prospective validation**
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9 135 The prospective research period was 2020.01.01 to 2020.12.31. We collected real-time data when
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11 136 patients were admitted to the ICU, transformed the data according to the requirements, and formed a
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13 137 complete sample for the prediction model after passing the integrity test. We had established a
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15 138 visualization scheme and allowed researchers to review the predictions daily. The daily prediction results
16
17 139 were not publicly accessible during the study to avoid affecting clinicians' decisions, but the diagnosis
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19 140 results were available to the researchers as visual graphics. We sampled the 20% predicted data every
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21 141 month and deleted samples with more than 50% missing values to ensure data correctness. The criteria
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23 142 to terminate prediction were A. a positive diagnosis; B. Transfer out of ICU or death with negative
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25 143 diagnosis. All diagnosis of severe AKI needs to be reviewed by two ICU attending physicians
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27 144 independently, and if the they have different opinion, the third one will be appealed.
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30 145 **Statistical analysis:**
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32 146 The population characteristics were reported as the medians and inter-quartile ranges (IQRs) for
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34 147 skewed data and the means and standard deviations for normally distributed data. The independent
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36 148 sample T-test was used for normally distributed data, and the rank-sum test was used for the rest.
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38 149 Dichotomous variables were assessed by the chi-square test, and a P value less than 0.05 was considered
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40 150 statistically significant. The non-normally distributed data were analyzed by exponential transformation
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42 151 and logarithmic transformation, and the variables that did not reach a normal distribution were deleted.
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44 152 The effect of the model was evaluated by parameters such as the AUROC, accuracy, specificity, and F1-
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46 153 score.
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4 **155 Results:**

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6 **156** According to the inclusion criteria and exclusion criteria, we selected 58492 patients from three
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9 **157** databases who met the requirements of the study, including 6461 patients from the SHZJU-ICU database,
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11 **158** 36690 patients from the MIMIC database, and 15341 patients from the AmsterdamUMC database. A
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14 **159** total of 5257 (9.0%) patients met the definition of severe AKI (11.8% in SHZJU-ICU, 7.6% in MIMIC,
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16
17 **160** and 10.9% in AmsterdamUMC). The distributions of age and sex in the three centers were similar, but
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19 **161** the differences in race were large. Asian patients accounted for more than 99% in the SHZJU-ICU
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21 **162** database, and only approximately 2.5% in the MIMIC database. White people accounted for more than
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24 **163** 70% of the MIMIC database. In addition, patients from the MIMIC database had a higher incidence of
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27 **164** the tumor, liver cirrhosis, diabetes, and hypertension. Patients in the AmsterdamUMC and SHZJU-ICU
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29
30 **165** databases had a higher proportion of mechanical ventilation and overall survival rate. Severe AKI
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33 **166** patients had longer ICU hospital stays and higher mortality. More details are presented in Table 1.
34
35 **167** Table 1: Clinical Demographics and Outcomes in patients with or without severe acute
36 **168** kidney injury.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P- valu e	MIMIC Negative (N=33879)	MIMIC Severe AKI (N=2811)	P- value	AmsterdamUMC Negative (N=13661)	AmsterdamUMC severe AKI (N=1680)	P- value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.00 4	62.0 [45.0-76.0]	64.0 [52.0-76.0]	<0.001	64.5 [54.5,74.5]	64.3 [52.5,78.5]	0.04
Gender, male (%)	3561 (64.9)	438 (59.8)	0.00 7	18976 (56.0)	1524 (54.2)	0.06	8920 (65.3)	1054 (63.9)	0.03
Race							/	/	/
White	3 (0.05)	1 (0.1)	1	23796 (70.2)	2005 (71.3)	0.23	/	/	/
Black	1 (0.02)	0	1	2455 (7.2)	199 (7.1)	0.45	/	/	/
Asian	5691(99.9)	764 (99.7)	1	918 (2.7)	70 (2.5)	0.54	/	/	/
Other	0	1 (0.1)	1	6710 (19.8)	537 (19.1)	0.34	/	/	/
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.0 01	1.1 (0.41)	1.1 (0.50)	0.04	1.2 (0.35)	1.1 (0.38)	<0.00 1

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Admission BUN	18 (11)	21 (9)	<0.0	17 (12)	23 (12)	<0.001	18 (13)	23 (10)	<0.00
(mg/dL), mean			01						1
(sd)									
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.0	6652 (19.6)	752 (26.8)	<0.001	/	/	/
			01						
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	1180 (3.5)	426 (15.2)	<0.001	/	/	/
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	4840 (14.3)	336 (12.0)	0.001	/	/	/
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.00	7250 (21.4)	789 (28.1)	<0.001	/	/	/
			2						
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	16328 (48.2)	1513 (53.8)	<0.001	/	/	/
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.0	13009 (38.4)	1503(53.5)	<0.001	7718(56.5)	1248(74.3)	<0.00
			01						1
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.0	12455 (36.7)	1430 (50.8)	<0.001	/	/	/
			01						
ICU Hours,	50.8	164.4	<0.0	51.0	103.4	<0.001	24.0	142.0	<0.00
median [IQR]	[23.0-139.5]	[70.3-328.6]	01	[28.5-110.3]	[50.1-261.3]		[19.8,63.5]	[45.4,394.2]	1
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.0	25648 (75.7)	1356 (48.2)	<0.001	10942(80.1)	1033 (61.5)	<0.00
			01						1

169 SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university
 170 school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile
 171 Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood
 172 urea nitrogen.

173 There were significant differences in the important parameters of the variables among the different
 174 models (see Figure S1). However, the trend of the creatinine level in the past week was still an important
 175 variable, followed by urine volume, blood urea nitrogen level, temperature, and length of ICU stay. The
 176 cut-off value used to distinguish between a negative and positive prediction was determined by the K-S
 177 curve, with value of 0.423 (see Figure S2). The GBDT model had the best prediction effect in the test
 178 set, followed by XGBoost and LightGBoost. In the two central internal validation sets, the two best-
 179 performing machine learning algorithms with great AUROC are LightGBoost (SHZJU-ICU of 83.2%,
 180 MIMIC of 86.0%) and XGBoost (SHZJU-ICU 85.9%, MIMIC 85.6%), as detailed in Figure 2. Overall,
 181 the sensitivity (SHZJU-ICU 0.84, MIMIC 0.83) and the negative predictive value (SHZJU-ICU 0.90,
 182 MIMIC 0.90) of the predictive model were high, but the specificity was general (SHZJU-ICU 0.79,

183 MIMIC 0.75), as shown in Table 2. In the external validation based on AmsterdamUMC database, the
 184 overall model validation effect results were satisfactory, and XGBoost had the best performance, with
 185 an AUROC of 0.84, as shown in Figure 2 and Table 2. We built a visual prediction interface based on
 186 the prediction model (supplementation file Figure S3).

187

188 Table 2: Model validation results by three databases with machine learning algorithm

<i>Model</i>	<i>AUROC</i>	<i>Accuracy</i>	<i>Sensitivity</i>	<i>Sepecificity</i>	<i>PPV</i>	<i>NPV</i>	<i>F1</i>
Internal validation with SHZJU-ICU database							
<i>Logistic regression</i>	0.748	0.662	0.834	0.576	0.496	0.874	0.622
<i>LightGBoost</i>	0.832	0.741	0.839	0.692	0.576	0.896	0.683
<i>GBDT</i>	0.845	0.765	0.843	0.725	0.606	0.902	0.705
<i>AdaBoost</i>	0.806	0.721	0.824	0.67	0.555	0.884	0.663
<i>Random Forest</i>	0.821	0.763	0.71	0.789	0.627	0.845	0.666
<i>XGBoost</i>	0.859	0.779	0.81	0.763	0.631	0.889	0.709
Internal validation with MIMIC database							
<i>Logistic regression</i>	0.733	0.695	0.643	0.72	0.535	0.801	0.584
<i>LightGBoost</i>	0.86	0.768	0.822	0.741	0.613	0.893	0.702
<i>GBDT</i>	0.846	0.765	0.786	0.755	0.616	0.876	0.691
<i>AdaBoost</i>	0.837	0.732	0.831	0.683	0.567	0.89	0.674
<i>Random Forest</i>	0.832	0.738	0.791	0.712	0.578	0.872	0.668
<i>XGBoost</i>	0.856	0.758	0.833	0.721	0.598	0.895	0.695
External validation with AmsterdamUMC database							
<i>Logistic regression</i>	0.704	0.767	0.516	0.893	0.706	0.787	0.596
<i>LightGBoost</i>	0.859	0.763	0.827	0.731	0.606	0.894	0.7
<i>GBDT</i>	0.861	0.764	0.84	0.727	0.606	0.901	0.704
<i>AdaBoost</i>	0.85	0.755	0.813	0.726	0.597	0.886	0.689
<i>Random Forest</i>	0.82	0.743	0.77	0.729	0.587	0.864	0.666
<i>XGBoost</i>	0.865	0.75	0.873	0.688	0.584	0.916	0.7
Prospective validation with SHZJU-ICU							
<i>Logistic regression</i>	0.758	0.772	0.648	0.834	0.662	0.826	0.655
<i>LightGBoost</i>	0.819	0.796	0.596	0.895	0.74	0.816	0.66
<i>GBDT</i>	0.827	0.781	0.706	0.818	0.66	0.848	0.683
<i>AdaBoost</i>	0.808	0.766	0.686	0.805	0.638	0.837	0.661
<i>Random Forest</i>	0.804	0.755	0.715	0.775	0.613	0.845	0.66
<i>XGBoost</i>	0.841	0.779	0.724	0.807	0.652	0.854	0.686

189 AUROC: Area Under Receiver Operating Characteristic; PPV: Positive Predictive Value; NPV:
 190 Negative Predictive Value; SHZJU-ICU: The general ICU database of the second affiliated

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3 191 hospital of Zhejiang university school of medicine; *MIMIC*: Medical Information Mart for
4 192 Intensive Care; *GBDT*: Gradient Boosted Decision Tree.

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9 194 According to the inclusion and exclusion criteria, we delete 267 patients among 94 patients with
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11 195 creatinine baseline more than 3.0 mg/dL at admission, 39 patients met severe AKI diagnosis within 24
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13 196 hours, and 26 patients who used RRT within 48 hours after admission, 108 patients hospitalized in the
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15 197 ICU for fewer than 3 days. A total of 2532 patients were admitted to our centre for prospective validation,
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17 198 and the prediction model made 16858 times predictions. In the prospective cohort, there was no
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19 199 significant difference in age, gender, baseline creatinine and urea nitrogen, and complications. The
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21 200 proportion of mechanical ventilation and the ICU stay time in AKI patients were longer with higher
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23 201 mortality. Above all, there was no significant difference between the prospective and the retrospective
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25 202 cohort. More detail sees in supplementation file Table S2. In the end, 358 positive results were predicted,
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27 203 and the rest were negative results. There are 344 patients with severe AKI were diagnosed and the
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29 204 prediction accuracy was 83.5%. The model with the highest area under the curve was XGBoost, 0.84.
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31 205 The results of the prospective study are similar to those of the external validation of the model, and are
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33 206 relatively stable. More detail is presented in Figure 3 and Table 2.

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43 207 **Discussion:**

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45 208 In this study, we built predictive models by machine learning to predict the incidence of severe AKI
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47 209 with three databases in different regions and in the next 48 hours. After internal and external validation,
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49 210 prospective validation over one year was carried out to verify the model effects. The three databases
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51 211 come from three countries that are in Asia, Europe, and North America, which proves that the model is
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53 212 universal to some extent.

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58 213 Despite the huge amount of data, many databases are still not suitable for prospective research
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4 214 because they are not updated promptly. Tomasev, N and colleagues have provided research on AKI
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6 215 prediction models with a large amount of data[10]. The study covered 703782 adult patients with 6 billion
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9 216 individual items, including 620000 elements. In this study, a depth neural network model was used for
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12 217 real-time prediction. A total of 55.8% of severe AKI patients were predicted within the first 48 hours,
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14 218 although each accurate prediction was accompanied by two mispredictions[10]. This study provided a
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17 219 new scheme for real-time prediction and indicated that we should prospectively evaluate and
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20 220 independently validate models to explore their effectiveness. In a prospective study, Marine, F compared
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22 221 an AKI prediction model with clinicians in 252 patients and found that the clinical effect of the random
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24 222 forest model for predicting AKI-II/III was equivalent to that of clinicians. Our prediction model graphical
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27 223 visualization of the model was installed in the centre's database for better usage. In addition, our database
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30 224 is updated daily to achieve daily predictions and present the results to researchers. In the prospective
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33 225 validation of our study, the stability of the prediction model confirmed its promise, which provides a
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35 226 basis for future research.

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38 227 There are many studies of artificial intelligence for predicting the occurrence of AKI, but most of them
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40 228 are single-centre studies, and the extrapolation effect has been controversial. In 2016, Koyner, J, and his
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43 229 colleague published the first study of an AKI prediction model based on multi-centre data. In all 202961
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45 230 patients, 17541 (8.6%) had AKI, 4251 (3.5%) had AKI-II, and 1242 (0.6%) had AKI-III. A multivariate
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47
48 231 logistic regression model was used to predict AKI in this study with an AUROC of 0.74 (95% CI=0.74).
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50
51 232 With the classification of AKI, the AUROC of the prediction model gradually increased to 0.84[8].
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54 233 Subsequently, the study team used a new machine learning algorithm, to build a more accurate model to
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56 234 predict the occurrence of AKI-II, with an AUROC of 0.9 within 24 hours and 0.87 within 48 hours[19].
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59 235 Recently, the research team included data from two other centres, namely, LUMC (N=200613) and NUS
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4 236 (N=246895), to externally validate the AKI-II prediction model with AUROCs reaching 0.85 to 0.86,
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6 237 suggesting that the artificial intelligence model has stable predictive ability[12]. This series of studies
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9 238 included many data points, suggesting the feasibility of artificial intelligence in the diagnosis of AKI,
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11 239 but the proportion of positive patients (3.5%) and ICU patients (30%) was too low to properly predict
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13 240 AKI. Our research is similar to the above. The SAHZJU-ICU database is a single-centre database
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15 241 representing south-eastern China, and the MIMIC database is a well-known open ICU database in the
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17 242 United States. The AmsterdamUMC database is a public database located in Europe. The population
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19 243 structure and diseases in the three databases are complete but different in the distribution of complications
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21 244 and race. Therefore, it provides a prediction model with unparalleled stability compared with other
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23 245 studies.

24 246 Limitations:

25 247 This retrospective multi-centre study was unable to carry out more clinical feature mining and
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27 248 comparison because of different data structures. The differences between the three databases partly
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29 249 reflect some demographic differences between Europe, the United States and China, resulting in a decline
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31 250 in the accuracy of the prediction model. There are some differences in the number of patients included
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33 251 in the three databases, which may affect the choice of variables. Second, in the prospective data study in
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35 252 2020, there may be deviations in the inclusion of patients in the centre, thus affecting the interpretation
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37 253 of the follow-up forward-looking results. Finally, given the low incidence of severe AKI and the great
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39 254 difference in the proportion of positive and negative samples, the data may be accidental.

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41 256 **Conclusion:**

42 257 Based on databases of patients of different races from different countries, we constructed stable

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4 258 machine learning models to predict the occurrence of AKI in the next 48 hours. Prospective validation
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6 259 through the implementation of an updated local database is an effective exploration of further research.
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11 261 Data Availability Statement:

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14 262 The model code can be obtained by email if readers need it, but we cannot guarantee that all the
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17 263 code will be provided. Two public databases can be applied from the official website of their respective
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19 264 databases.

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22 265 Ethics approval:

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25 266 Our research was approved by the ethics committee of the Second Affiliated Hospital of Zhejiang
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27 267 University School of Medicine.

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32 269 **Reference:**

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25 332 **Footnotes**

26
27 333 Contributions: Conceptualization, QL and MH; Methodology, YX; Software, YX; Validation, YZ, and
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29 334 YX.; Formal Analysis, JC and XC; Resources, MH; Data Curation, QL; Writing – Original Draft
30
31 335 Preparation, QL; Writing – Review & Editing, MH; Visualization, YX; Supervision, YZ and QL; Project
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33 336 Administration, QL;

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36
37 337 **Funding:** This research received no specific grant from any funding agency in the public, commercial
38
39 338 or not-for-profit sectors.

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42 339 Conflicts of Interest: Not Applicable.

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45 340 Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or
46
47 341 reporting, or dissemination plans of this research.

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49 342 Provenance and peer review Not commissioned; externally peer reviewed.

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51
52 343 Acknowledgements: Thank my colleagues in general ICU for cooperating with us in our prospective
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54 344 study. Thanks to two public databases namely MIMIC and AmsterdamUMC for providing important
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56 345 data.
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6 347 **Supplemental Figure:**

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9 348 File name: **Figure S1.tif**

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11 349 Title and Description of data: The variable importance parameter histogram of early diagnosis prediction
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14 350 models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.

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17 351 File name: **Figure S2.tif**

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19 352 Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative
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22 353 diagnosis of early diagnosis prediction models of severe AKI.

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25 354 File name: **Figure S3.tif**

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27 355 Title of data: The visual interface for prospective studies of the AKI early diagnosis prediction models.

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30 356 Description of data: Different patients have independent card display information, in which the last line
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33 357 of the card is the AKI diagnosis. The visual interface was not available to doctors during the prospective
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36 358 study and was used only by the researchers to verify the diagnosis and for sampling verification.

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38 359 File name: **Table S1.docx**

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40 360 Title and of Description data: Missing data between three databases in the study and values included in
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43 361 the model.

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46 362 File name: **Table S2.docx**

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48 363 Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model
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51 364 building set and prospective validation.

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56 366 Title of data: TRIPOD Checklist of Prediction Model Development and Validation

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59 367 Description of data: Writing norms of this type of research.
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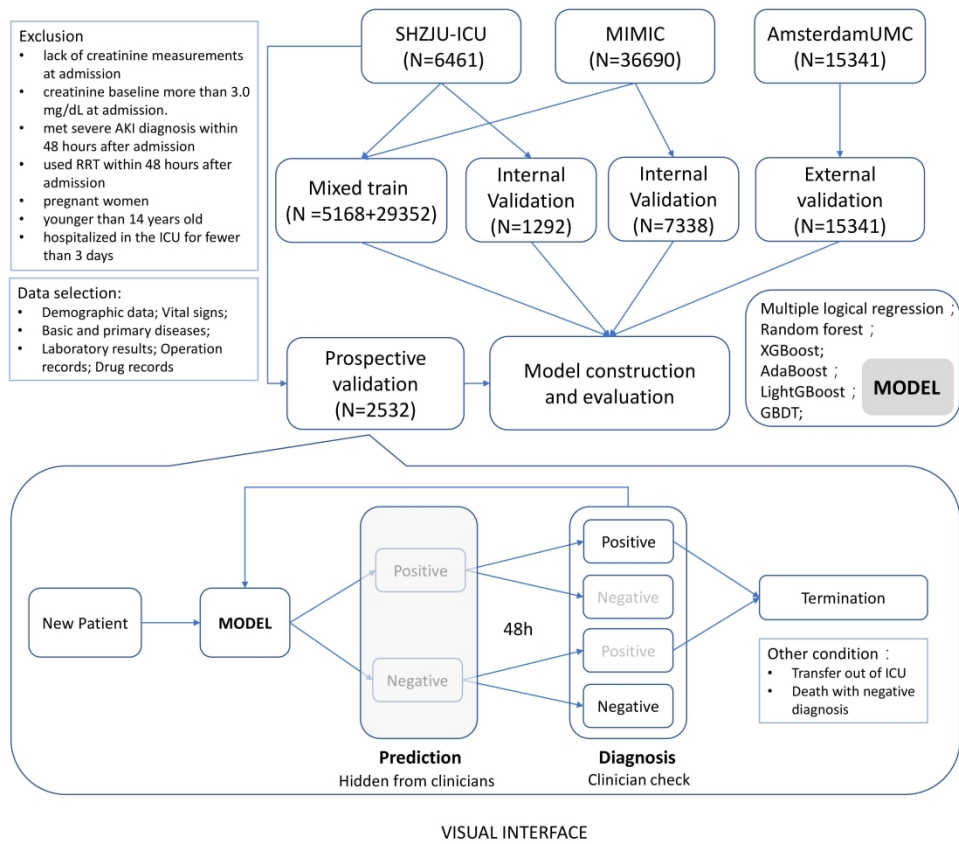
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6 369 **Figure Legend:**

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9 370 Figure 1: The research flow chart. The data collection time interval of the study was 7 days before
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11 371 diagnosis and the prediction interval was 48 hours. The early prediction model of AKI diagnosis was
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13 372 constructed and verified by our database and the MIMIC database and incorporated into the
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15 373 AmsterdamUMC database for external validation. We carried out a one-year prospective validation
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17 374 through the database of the centre.

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19 375 Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC
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21 376 database.

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23 377 Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and
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25 378 the prospective validation in our center for 3B.
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Internal validation set ROC curves

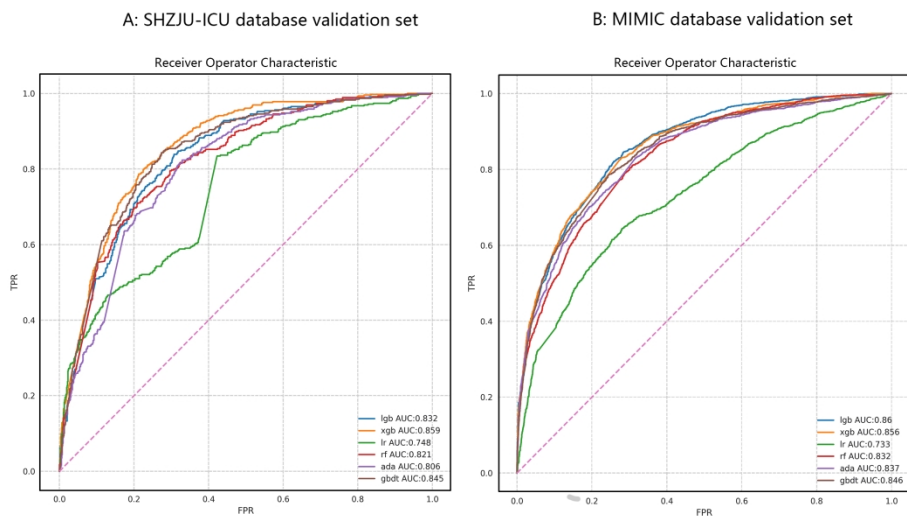


Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC database.

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External and prospective validation set ROC curves

A: AmsterdamUMC database external validation set B: SHZJU-ICU database prospective validation set

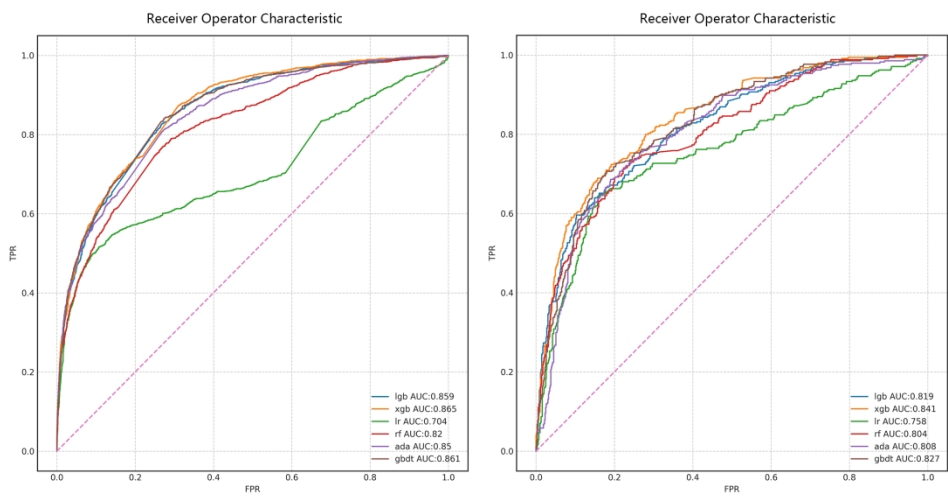
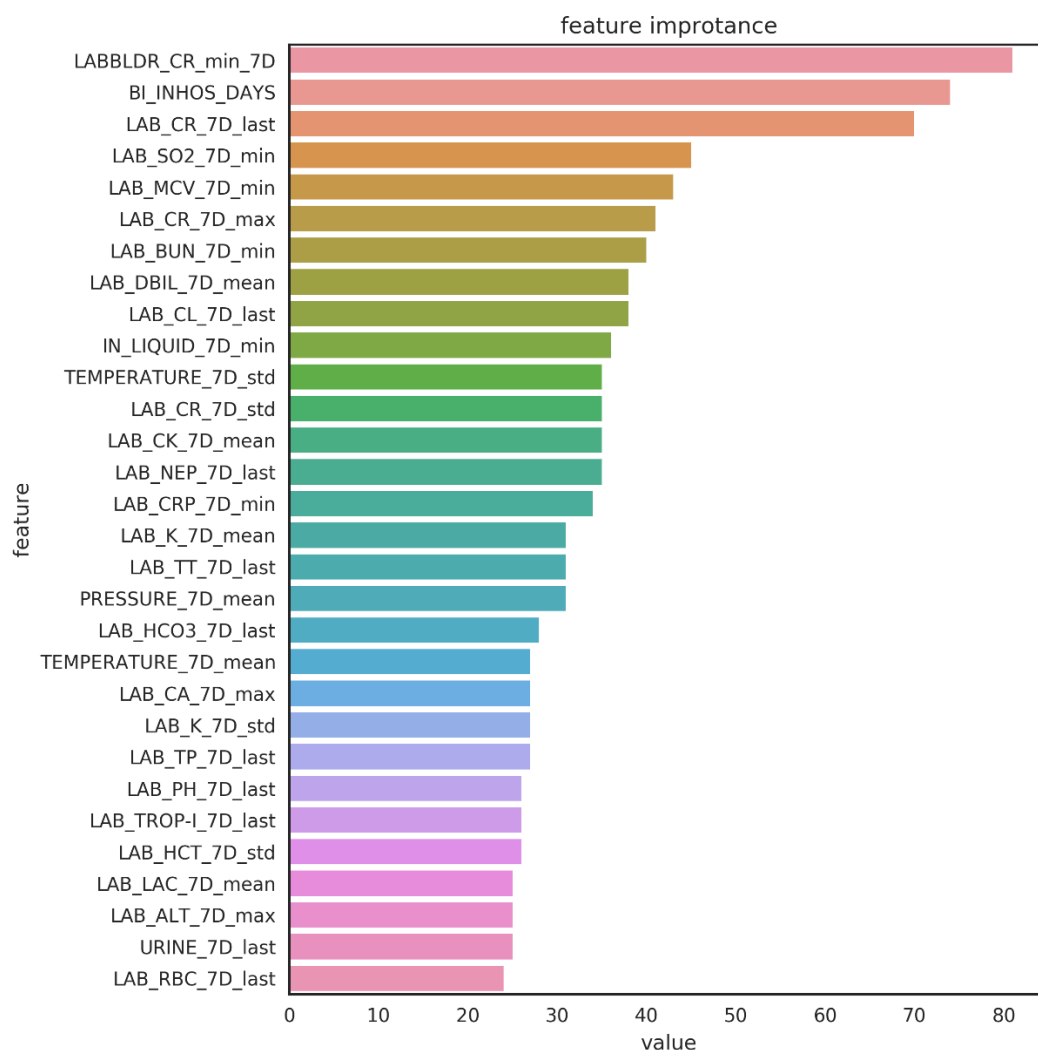


Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and the prospective validation in our center for 3B.

Supplemental Figure:

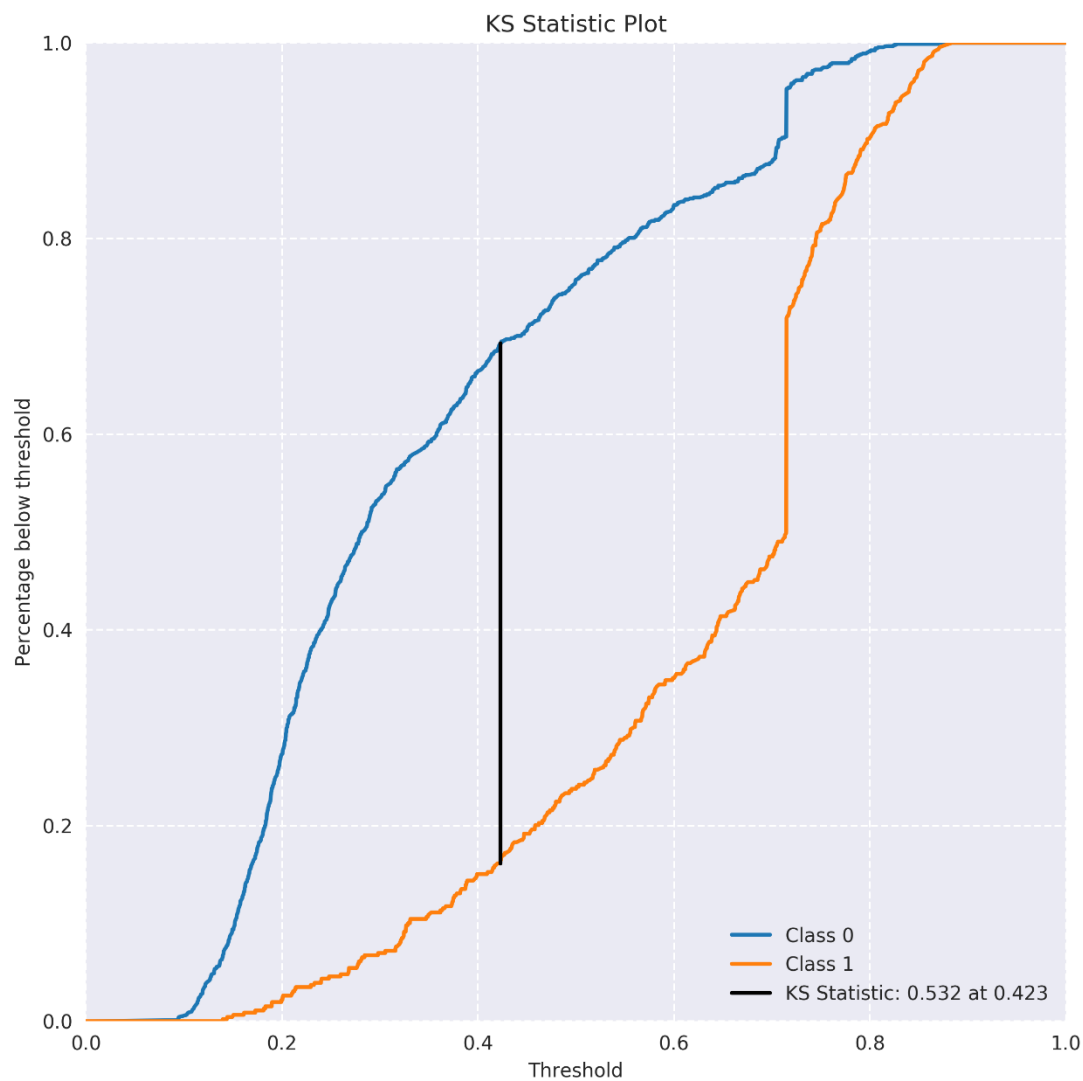
File name: **Figure S1.tif**

Title and Description of data: The variable importance parameter histogram of early diagnosis prediction models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.



File name: **Figure S2.tif**

Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative diagnosis of early diagnosis prediction models of severe AKI.



39 File name: **Figure S3. tif**

40 Title of data: The visual interface for prospective studies of the AKI early diagnosis prediction models.

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43 Description of data: Different patients have independent card display information, in which the last line
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47 of the card is the AKI diagnosis. The visual interface was not available to doctors during the prospective
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50 study and was used only by the researchers to verify the diagnosis and for sampling verification.



File name: **Table S1.docx**

Title and of Description data: Missing data between three databases in the study and values included in the model.

	SHZJU-ICU	MIMIC	AmsterdamUMC	Including in Model
Age	√	√	√	√
Gender	√	√	√	√
Race	√	√	×	×
Primary disease	√	√	×	×
Comorbidity	√	√	×	×
Ventilation	√	√	√	√
Operation	√	√	×	×
ICU hours	√	√	√	√
Survived	√	√	√	√
Vital sign				
Temperature	√	√	√	√
Systolic pressure	√	√	√	√
Diastolic pressure	√	√	√	√
Respiratory rate	√	√	√	√
Heart rate	√	√	√	√
Oxygen saturation	√	√	√	√
Urine	√	√	√	√
GCS score	√	×	×	×
Laboratory results				

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2				
3	Scr	√	√	√
4	BUN	√	√	√
5	RBC	√	√	√
6	MCV	√	√	√
7	Hb	√	√	√
8	WBC	√	√	√
9	NEUT	√	√	√
10	PLT	√	√	√
11	HCV	√	√	×
12	TBLB	√	√	√
13	DBLB	√	√	√
14	IBLB	√	√	√
15	CRP	√	√	√
16	PCT	√	×	×
17	Serum kalium	√	√	√
18	Serum natrium	√	√	√
19	Serum chlorine	√	√	√
20	PT	√	√	√
21	APTT	√	√	√
22	INR	√	√	√
23	CK	√	√	√
24	LDH	√	√	√
25	Troponin	√	√	√
26	Blood glucose	√	√	√
27	PH	√	√	√
28	Lactic acid	√	√	√
29	Anion gap	√	√	√
30	ABC	√	√	√
31	SBC	√	√	√
32	PaCO₂	√	√	√
33	PaO₂	√	√	√
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SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; APTT: Activated partial thromboplastin time; INR: International normalized ratio; LDH: Lactate dehydrogenase; PaCO₂: Partial pressure of carbon dioxide; PaO₂ Partial pressure of oxygen; MCV: Mean corpuscular volume; PH: Potential of hydrogen; WBC: White blood cell count; NEUT: Proportion of neutrophils; CK: Creatine kinase; Scr: Serum Creatinine; BUN: Blood urea nitrogen; RBC: Red blood cell count; Hb: Hemoglobin; PT: Prothrombin time; TBLB: Total bilirubin; DBLB: Direct bilirubin; IBLB: Indirect bilirubin; CRP: C-reactive protein; HCV: Hematocrit value; PCT: Procalcitonin; ABC: Actual Bicarbonate Radical; SBC: Standard Bicarbonate Radical; PLT: Platelet count

File name: **Table S2.docx**

Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model building set and prospective validation.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P-value	SHZJU-ICU Prospective Negative (N=2188)	SHZJU-ICU Prospective Positive (N=344)	P-value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.004	61.3 [47.5-73.4]	62.1 [51.2-70.5]	0.03
Gender, male (%)	3561 (64.9)	438 (59.8)	0.007	1365 (62.4)	207 (60.2)	0.438
Race						
White	3 (0.05)	1 (0.1)	1	2 (0.001)	0	1
Black	1 (0.02)	0	1	0	0	1
Asian	5691(99.9)	764 (99.7)	1	2185 (99.9)	344(100)	1
Other	0	1 (0.1)	1	1 (0.001)	0	1
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.001	0.8 (0.32)	0.9 (0.35)	<0.001
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.001	17 (11)	20 (10)	0.007
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.001	230 (10.5)	26 (7.6)	0.102
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	15 (0.7)	3 (0.8)	0.726
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	98 (4.5)	19 (5.7)	0.403
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.002	142 (6.5)	29 (8.6)	0.203
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	324(14.8)	56 (16.4)	0.466
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.001	1102 (50.4)	239 (69.5)	<0.001
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	1234(56.4)	160 (46.7)	0.001
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	58.7 [34.2-160.4]	145.6 [68.5-314.8]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	1868 (85.4)	178 (51.9)	<0.001

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood urea nitrogen.

File name: **Table S3.docx**

Title of data: TRIPOD Checklist of Prediction Model Development and Validation

Description of data: Writing norms of this type of research.

1Section/Topic		Checklist Item		Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Yes; P1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Yes; P2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Yes; P3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Yes; P4, L76-79
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Yes; P4, L80
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Yes; P4, L84-86
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Yes
	5b	D;V	Describe eligibility criteria for participants.	Yes; P5, L104
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Yes; P6, L111
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Yes; P6, L116
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Yes; P6, L127
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Yes; P6, L116
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Yes; P6, L119
	10c	V	For validation, describe how the predictions were calculated.	Yes; P6, L126
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Yes; P6, L159
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Yes; P6, L111

Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results				
Participants	3a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	3b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, Table2
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Yes
Model specification	5a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	5b	D	Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L236
Interpretation	9a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L217
	9b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L198
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Yes, P9, L193
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	NA

BMJ Open

Prospective Validation for Severe Acute Kidney Injury Predicting Model based on transcontinental databases

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054092.R1
Article Type:	Original research
Date Submitted by the Author:	23-Sep-2021
Complete List of Authors:	Liang, Qiqiang; Zhejiang University School of Medicine Second Affiliated Hospital Xu, Yongfeng; HealSci Technology Co Zhou, Yu; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Xinyi; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Juan; Zhejiang University School of Medicine Second Affiliated Hospital Huang, Man; Zhejiang University School of Medicine Second Affiliated Hospital,
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics
Keywords:	Acute renal failure < NEPHROLOGY, INTENSIVE & CRITICAL CARE, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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4 **1 Prospective Validation for Severe Acute Kidney Injury Predicting Model based**
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6 **2 on transcontinental databases**
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4 **23 Abstract:**

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6 **24 Objectives:** There are many studies of acute kidney injury (AKI) diagnosis models lack of external
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9 **25 validation and prospective validation.** We constructed the models using three databases to predict severe
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11 **26 AKI within 48 hours in intensive care unit (ICU) patients.**

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14 **27 Design:** A retrospective and prospective cohort study.

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17 **28 Setting:** We studied critically ill patients in our database (SHZJU-ICU) and two other public databases,
18
19 **29 the Medical Information Mart for Intensive Care (MIMIC) and AmsterdamUMC databases, including**
20
21 **30 basic demographics, vital signs, and laboratory results.** We predicted the diagnosis of severe AKI in
22
23 **31 patients in the next 48 hours using machine-learning algorithms with the three databases.** Then, we
24
25 **32 carried out real-time severe AKI prediction in the prospective validation study at our centre for one year.**

26
27
28 **33 Participants:** All patients included in three databases with uniform exclusion criteria.

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30
31 **34 Primary and secondary outcome measures:** Effect evaluation index of prediction models.

32
33
34 **35 Results:** We included 58492 patients, and a total of 5257 (9.0%) patients met the definition of severe
35
36 **36 AKI.** In the internal validation of the SHZJU-ICU and MIMIC databases, the best area under the receiver
37
38 **37 operating characteristic curve (AUROC) of the model was 0.86.** The external validation results by
39
40 **38 AmsterdamUMC database were also satisfactory, with the best AUROC of 0.86.** A total of 2532 patients
41
42 **39 were admitted to the center for prospective validation; 358 positive results were predicted, and 344**
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44 **40 patients were diagnosed with severe AKI, with the best sensitivity of 0.72, the specificity of 0.80, and**
45
46 **41 the AUROC of 0.84.**

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49 **42 Conclusion:** The prediction model of severe AKI exhibits promises as a clinical application based on
50
51 **43 dynamic vital signs and laboratory results of multi-center databases with prospective and external**
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53 **44 validation.**

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4 45 **Keywords:** Machine learning; Acute kidney injury; Real-time prospective validation; External
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6 46 validation.

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9 47 **Strengths and limitations of this study:**

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11 48 An important verification step from artificial intelligence research to clinical use;

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13 49 Three large database containing different national populations and regions;

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15 50 The prediction model with excellent performance in complete data validation;

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17 51 Differences in the samples proportion of three databases;

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19 52 The dimensions of variables are not rich enough.

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21 53

22
23 54 **Introduction:**

24
25 55 Acute kidney injury (AKI), as a common clinical complication in the intensive care unit (ICU),

26
27 56 significantly increases the duration of hospitalization and mortality[1]. AKI is divided into three types

28
29 57 according to the various aetiologies: prerenal (renal hypoperfusion), intrarenal (vascular, glomerular, or

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31 58 tubulointerstitial lesions), and postrenal (urinary tract obstruction)[2]. Although nearly all diseases

32
33 59 associated with ICU admission may cause AKI, acute tubular necrosis (ATN) and prerenal azotaemia

34
35 60 are the most common causes[3].

36
37 61 All AKI diagnostic criteria including the latest Kidney Disease: Improving Global Outcomes (KDIGO)

38
39 62 standard are currently based on the creatinine level and urine volume[4]. However, the increase in the

40
41 63 creatinine level or decrease in the urine volume lags the onset of AKI[2]. Many studies have suggested

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43 64 that early diagnosis and treatment of reversible AKI can reduce mortality[5]. Therefore, the creatinine

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45 65 level and urine volume are not satisfactory to meet clinical diagnostic demands. Consequently, many

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47 66 researchers have tried to develop an early warning model by analysing the risk factors for AKI[6].

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4 67 Patient complications, such as diabetes, hypertension, cardiovascular disease, chronic liver disease,
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6 68 sepsis, and trauma, are identified as important risk factors for AKI[7]. The AKI prediction model and
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9 69 scoring system developed based on high-risk factors has gradually become the focus of research
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11
12 70 considering the lower clinical application threshold compared with that of new biomarkers[6]. Although
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14 71 most previous prediction models use the multiple logistic regression model, a variety of AKI prediction
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16
17 72 models based on machine learning have resulted in satisfactory outcomes[6]. Since the first AKI
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19 73 prediction model study based on artificial intelligence was published in 2016, researchers have built more
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21
22 74 than 20 published AKI prediction models successively by using local or multi-centre databases[6,8-14].
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25 75 The results indicate that these models can predict the occurrence of AKI and the need for renal
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27 76 replacement therapy (RRT) within 24 or 48 hours, with accuracies ranging from 81% to 97%[6,15]. In
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30 77 addition, many studies have focused on subspecialized conditions, including cardiac surgery, trauma,
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33 78 and burns[14-16]. However, the common defect in these studies is the lack of external validation and
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36 79 prospective validation, which causes the prediction model to deviate from the clinical scenarios and limits
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38 80 extrapolation beyond the scope of the data.

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40 81 In this study, we built models to predict AKI within 48 hours in critically ill patients by using
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43 82 transcontinental three databases. Then, we evaluated the clinical effect of the model through a one-year
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46 83 prospective validation at our centre.

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49 50 85 **Methods :**

51 52 86 **Study design and setting**

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56 87 We collected patients using three ICU databases and prospectively validated the models in our centre.

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58 88 The first database was our centre general ICU database (SHZJU-ICU) of the Second Affiliated Hospital
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4 89 of Zhejiang University School of Medicine, an academic teaching hospital. Since its establishment in
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6 90 2017, it has included 12000 ICU patients' data and is updated daily. The Medical Information Mart for
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9 91 Intensive Care (MIMIC) III database, the second one, is an open ICU database provided by the
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11 92 Massachusetts Institute of Technology and includes nearly 60000 ICU patients from North America[17].
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14 93 Lastly, the AmsterdamUMC database is an available European ICU database with health data related to
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16
17 94 23000 patients admitted to ICUs in parts of Europe[18]. The research flow chart is shown in Figure 1.
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21 22 96 **Study definition**

23
24 97 In this study, the diagnosis of AKI was confirmed based on three stages according to the KDIGO
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26
27 98 criteria[4]. We defined the patients who met the KDIGO AKI II and III criteria as severe AKI groups
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29
30 99 and the others as negative groups. We excluded patients with lack of creatinine measurements during
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32
33 100 admission, patients with creatinine baseline more than 3.0 mg/dL at admission, patients who met severe
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35
36 101 AKI diagnosis within 24 hours, and patients who used RRT within 48 hours after admission[19]. In
37
38 102 addition, we excluded pregnant women, patients younger than 14 years old, and patients hospitalized in
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40
41 103 the ICU for fewer than 48 hours. After the patient was admitted to ICU, we performed a prediction every
42
43
44 104 24 hours and recorded a prediction time. If the patient was diagnosed with severe AKI within 48 hours,
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46
47 105 the predictive time was defined as a positive predictive point, and the others were defined as a negative
48
49
50 106 point.

51 107 **Data Collection**

52
53 108 The variables included demographic data, vital signs, basic and primary diseases, laboratory results,
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56 109 important operation records, and drug records. Comorbidity included hypertension, diabetes, cardiopathy,
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59 110 liver disease, and malignant tumors. The primary disease was the main cause of admission to the ICU
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4 111 following the ICD-10 codes. The vital signs and clinical laboratory results were transformed into
5
6 112 different variables according to the average, variance, maximum, minimum, and final value before
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9 113 diagnosis. We use a method similar to the forward incremental method in the multivariate logic
10
11 114 regression model, that is, the combination of embedded feature selection and forward addition for feature
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14 115 selection. First of all, all variables are trained in the model, then list by variables importance. variables
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16
17 116 are added to the model one by one according to the variable importance. a variable is retained if it causes
18
19 117 the AUC growth to be greater than 0.01, otherwise delete it. We transformed the MIMIC and
20
21
22 118 AmsterdamUMC databases according to our centre database structure, unifying the unit and diagnostic
23
24
25 119 codes. We deleted variables missing more than 50%. Variables missing more than 30% but less than 50%
26
27 120 are listed to clinicians who determine the potential correlation between these variables and AKI. We
28
29
30 121 carry out multiple interpolation for these variables which clinicians require to be retained, and the others
31
32 122 deleted. Variables missing less than 30% are fill in multiple interpolation. All Missing data between three
33
34
35 123 databases and values included in the model shown in supplementation file Table S1.

37 124 **Model construction and external validation**

39
40 125 The ratio of the training and internal validation sets was 4:1. The SHZJU and MIMIC databases
41
42 126 training sets were mixed into a new training set. There were more negative data than positive data, so we
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45 127 randomly sampled the negative datasets and constructed a new data subset with a sampling ratio of
46
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48 128 positive and negative data of 1:5. We used multiple logistic regression, random forest, XGBoost,
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51 129 AdaBoost, LightGBoost, gradient boosting decision tree (GBDT), and debug to assess the variables and
52
53 130 model-related parameters by the fivefold cross-validation method. After the models were built, we used
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56 131 the SHZJU-ICU and MIMIC test sets for internal validation of the model and the AmsterdamUMC
57
58 132 database for external validation. The most appropriate cut-off value was determined according to the K-S
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4 133 curve. The prediction model represents the results of each prediction with a probability between 0 to 1.0.
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6 134 We define results more than 0.4 as high-risk, that is, positive results, and the rest as negative results.
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9 135 Through internal validation and external validation, we calibrated the model by adjusting the super-
10
11 136 parameters and using the Platt calibration algorithm and compared the calibration effect by drawing a
12
13 137 reliability diagram. The model was visualized and analyzed by a visual programming scheme. All model
14
15 138 building and validation processes were performed in Python 3.6.

19 139 **Prospective validation**

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21
22 140 The prospective research period was 2020.01.01 to 2020.12.31. We collected real-time data when
23
24 141 patients were admitted to the ICU, transformed the data according to the requirements, and formed a
25
26 142 complete sample for the prediction model after passing the integrity test. We had established a
27
28 143 visualization scheme and allowed researchers to review the predictions daily. The daily prediction results
29
30 144 were not publicly accessible during the study to avoid affecting clinicians' decisions, but the diagnosis
31
32 145 results were available to the researchers as visual graphics. We sampled the 20% predicted data every
33
34 146 month and deleted samples with more than 50% missing values to ensure data correctness. When a patient
35
36 147 has the following conditions, AKI prediction system will end the patient's prospective prediction: A. a
37
38 148 positive diagnosis; B. Transfer out of ICU or death with negative diagnosis. All diagnosis of severe AKI
39
40 149 needs to be reviewed by two ICU attending physicians independently, and if the they have different
41
42 150 opinion, the third one will be appealed.

50 151 **Patient and Public Involvement:**

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53 152 The information of cases in three databases was in a state of complete desensitization in the process
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55 153 of building the model. During the prospective study, all the patients signed an informed consent form at
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57 154 the beginning of admission to ICU. The real-time data discussed and used by the study members only,
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4 155 and were not made public during the study period. The study was evaluated and approved by the Ethics
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6 156 Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine as study number
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9 157 2019-078. All data were anonymized before the authors accessed them for the purpose of this study.
10
11 158 According to the inclusion criteria and exclusion criteria, we selected 58492 patients from three databases
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14 159 who met the requirements of the study, including 6461 patients from the SHZJU-ICU database, 36690
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16
17 160 patients from the MIMIC database, and 15341 patients from the AmsterdamUMC database.

161 **Statistical analysis:**

162 The population characteristics were reported as the medians and inter-quartile ranges (IQRs) for
163 skewed data and the means and standard deviations for normally distributed data. The independent
164 sample T-test was used for normally distributed data, and the rank-sum test was used for the rest.
165 Dichotomous variables were assessed by the chi-square test, and a P value less than 0.05 was considered
166 statistically significant. The non-normally distributed data were analyzed by exponential transformation
167 and logarithmic transformation. The effect of the model was evaluated by parameters such as the
168 AUROC, accuracy, specificity, and F1-score.

170 **Results:**

171 A total of 5257 (9.0%) patients met the definition of severe AKI (11.8% in SHZJU-ICU, 7.6% in
172 MIMIC, and 10.9% in AmsterdamUMC). The distributions of age and sex in the three centers were
173 similar, but the differences in race were large. Asian patients accounted for more than 99% in the SHZJU-
174 ICU database, and only approximately 2.5% in the MIMIC database. White people accounted for more
175 than 70% of the MIMIC database. In addition, patients from the MIMIC database had a higher incidence
176 of the tumor, liver cirrhosis, diabetes, and hypertension. Patients in the AmsterdamUMC and SHZJU-

177 ICU databases had a higher proportion of mechanical ventilation and overall survival rate. Severe AKI
 178 patients had longer ICU hospital stays and higher mortality. More details are presented in Table 1.
 179 Table 1: Clinical Demographics and Outcomes in patients with or without severe acute
 180 kidney injury.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P- valu e	MIMIC Negative (N=33879)	MIMIC Severe AKI (N=2811)	P- value	AmsterdamUMC Negative (N=13661)	AmsterdamUMC severe AKI (N=1680)	P- value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.00 4	62.0 [45.0-76.0]	64.0 [52.0-76.0]	<0.001	64.5 [54.5,74.5]	64.3 [52.5,78.5]	0.04
Gender, male (%)	3561 (64.9)	438 (59.8)	0.00 7	18976 (56.0)	1524 (54.2)	0.06	8920 (65.3)	1054 (63.9)	0.03
Race							/	/	/
White	3 (0.05)	1 (0.1)	1	23796 (70.2)	2005 (71.3)	0.23	/	/	/
Black	1 (0.02)	0	1	2455 (7.2)	199 (7.1)	0.45	/	/	/
Asian	5691(99.9)	764 (99.7)	1	918 (2.7)	70 (2.5)	0.54	/	/	/
Other	0	1 (0.1)	1	6710 (19.8)	537 (19.1)	0.34	/	/	/
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.0 01	1.1 (0.41)	1.1 (0.50)	0.04	1.2 (0.35)	1.1 (0.38)	<0.00 1
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.0 01	17 (12)	23 (12)	<0.001	18 (13)	23 (10)	<0.00 1
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.0 01	6652 (19.6)	752 (26.8)	<0.001	/	/	/
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	1180 (3.5)	426 (15.2)	<0.001	/	/	/
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	4840 (14.3)	336 (12.0)	0.001	/	/	/
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.00 2	7250 (21.4)	789 (28.1)	<0.001	/	/	/
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	16328 (48.2)	1513 (53.8)	<0.001	/	/	/
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.0 01	13009 (38.4)	1503(53.5)	<0.001	7718(56.5)	1248(74.3)	<0.00 1
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.0 01	12455 (36.7)	1430 (50.8)	<0.001	/	/	/
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.0 01	51.0 [28.5-110.3]	103.4 [50.1-261.3]	<0.001	24.0 [19.8,63.5]	142.0 [45.4,394.2]	<0.00 1
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.0 01	25648 (75.7)	1356 (48.2)	<0.001	10942(80.1)	1033 (61.5)	<0.00 1

181 SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university
 182 school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile

183 Range; *ICU*: Intensive Care Unit; *AKI*: Acute Kidney Injury. *Scr*: serum creatinine; *BUN*: blood
 184 urea nitrogen.

185 There were significant differences in the important parameters of the variables among the different
 186 models (see Figure S1). However, the trend of the creatinine level in the past week was still an important
 187 variable, followed by urine volume, blood urea nitrogen level, temperature, and length of ICU stay. The
 188 cut-off value used to distinguish between a negative and positive prediction was determined by the K-S
 189 curve, with value of 0.423 (see Figure S2). The GBDT model had the best prediction effect in the test
 190 set, followed by XGBoost and LightGBoost. In the two central internal validation sets, the two best-
 191 performing machine learning algorithms with great AUROC are LightGBoost (SHZJU-ICU of 83.2%,
 192 MIMIC of 86.0%) and XGBoost (SHZJU-ICU 85.9%, MIMIC 85.6%), as detailed in Figure 2. Overall,
 193 the sensitivity (SHZJU-ICU 0.84, MIMIC 0.83) and the negative predictive value (SHZJU-ICU 0.90,
 194 MIMIC 0.90) of the predictive model were high, but the specificity was general (SHZJU-ICU 0.79,
 195 MIMIC 0.75), as shown in Table 2. In the external validation based on AmsterdamUMC database, the
 196 overall model validation effect results were satisfactory, and XGBoost had the best performance, with
 197 an AUROC of 0.84, as shown in Figure 2 and Table 2. We built a visual prediction interface based on
 198 the prediction model (supplementation file Figure S3).

200 Table 2: Model validation results by three databases with machine learning algorithm

Model	AUROC	Accuracy	Sensitivity	Specificity Specificity	PPV	NPV	F1
Internal validation with SHZJU-ICU database							
Logistic regression	0.748	0.662	0.834	0.576	0.496	0.874	0.622
LightGBoost	0.832	0.741	0.839	0.692	0.576	0.896	0.683
GBDT	0.845	0.765	0.843	0.725	0.606	0.902	0.705
AdaBoost	0.806	0.721	0.824	0.67	0.555	0.884	0.663
Random Forest	0.821	0.763	0.71	0.789	0.627	0.845	0.666
XGBoost	0.859	0.779	0.81	0.763	0.631	0.889	0.709
Internal validation with MIMIC database							

Logistic regression	0.733	0.695	0.643	0.72	0.535	0.801	0.584
LightGBost	0.86	0.768	0.822	0.741	0.613	0.893	0.702
GBDT	0.846	0.765	0.786	0.755	0.616	0.876	0.691
AdaBoost	0.837	0.732	0.831	0.683	0.567	0.89	0.674
Random Forest	0.832	0.738	0.791	0.712	0.578	0.872	0.668
XGBoost	0.856	0.758	0.833	0.721	0.598	0.895	0.695
External validation with AmsterdamUMC database							
Logistic regression	0.704	0.767	0.516	0.893	0.706	0.787	0.596
LightGBost	0.859	0.763	0.827	0.731	0.606	0.894	0.7
GBDT	0.861	0.764	0.84	0.727	0.606	0.901	0.704
AdaBoost	0.85	0.755	0.813	0.726	0.597	0.886	0.689
Random Forest	0.82	0.743	0.77	0.729	0.587	0.864	0.666
XGBoost	0.865	0.75	0.873	0.688	0.584	0.916	0.7
Prospective validation with SHZJU-ICU							
Logistic regression	0.758	0.772	0.648	0.834	0.662	0.826	0.655
LightGBost	0.819	0.796	0.596	0.895	0.74	0.816	0.66
GBDT	0.827	0.781	0.706	0.818	0.66	0.848	0.683
AdaBoost	0.808	0.766	0.686	0.805	0.638	0.837	0.661
Random Forest	0.804	0.755	0.715	0.775	0.613	0.845	0.66
XGBoost	0.841	0.779	0.724	0.807	0.652	0.854	0.686

201 AUROC: Area Under Receiver Operating Characteristic; PPV: Positive Predictive Value; NPV:
 202 Negative Predictive Value; SHZJU-ICU: The general ICU database of the second affiliated
 203 hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for
 204 Intensive Care; GBDT: Gradient Boosted Decision Tree.

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206 According to the inclusion and exclusion criteria, we delete 267 patients among 94 patients with
 207 creatinine baseline more than 3.0 mg/dL at admission, 39 patients met severe AKI diagnosis within 24
 208 hours, and 26 patients who used RRT within 48 hours after admission, 108 patients hospitalized in the
 209 ICU for fewer than 48 hours. A total of 2532 patients were admitted to our centre for prospective
 210 validation, and the prediction model made 16858 times predictions. In the prospective cohort, there was
 211 no significant difference in age, gender, baseline creatinine and urea nitrogen, and complications. The
 212 proportion of mechanical ventilation and the ICU stay time in AKI patients were longer with higher
 213 mortality. Above all, there was no significant difference between the prospective and the retrospective
 214 cohort. More detail sees in supplementation file Table S2. In the end, 358 positive results were predicted,

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4 215 and the rest were negative results. There are 344 patients with severe AKI were diagnosed and the
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6 216 prediction accuracy was 83.5%. The model with the highest area under the curve was XGBoost, 0.84
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9 217 with the best sensitivity of 0.72, the specificity of 0.80. The results of the prospective study are similar
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11 218 to those of the external validation of the model, and are relatively stable. More detail is presented in
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14 219 Figure 3 and Table 2.
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221 **Discussion:**

222 In this study, we built predictive models by machine learning to predict the incidence of severe AKI
223 with three databases in different regions and in the next 48 hours. After internal and external validation,
224 prospective validation over one year was carried out to verify the model effects. The three databases
225 come from three countries that are in Asia, Europe, and North America, which proves that the model is
226 universal to some extent.

227 Despite the huge amount of data, many databases are still not suitable for prospective research
228 because they are not updated promptly. Tomasev, N and colleagues have provided research on AKI
229 prediction models with a large amount of data[10]. The study covered 703782 adult patients with 6 billion
230 individual items, including 620000 elements. In this study, a depth neural network model was used for
231 real-time prediction. A total of 55.8% of severe AKI patients were predicted within the first 48 hours,
232 although each accurate prediction was accompanied by two mispredictions[10]. This study provided a
233 new scheme for real-time prediction and indicated that we should prospectively evaluate and
234 independently validate models to explore their effectiveness. In a prospective study, Flechet, M et al
235 compared an AKI prediction model with clinicians in 252 patients and found that the clinical effect of
236 the random forest model for predicting AKI-II/III was equivalent to that of clinicians. Our prediction

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4 237 model graphical visualization of the model was installed in the centre's database for better usage. In
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6 238 addition, our database is updated daily to achieve daily predictions and present the results to researchers.
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9 239 In the prospective validation of our study, the stability of the prediction model confirmed its promise,
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11 240 which provides a basis for future research.

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14 241 There are many studies of artificial intelligence for predicting the occurrence of AKI, but most of them
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16 242 are single-centre studies, and the extrapolation effect has been controversial. In 2016, Koyner, J, and his
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18 243 colleague published the first study of an AKI prediction model based on multi-centre data. In all 202961
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20 244 patients, 17541 (8.6%) had AKI, 4251 (3.5%) had AKI-II, and 1242 (0.6%) had AKI-III. A multivariate
21
22 245 logistic regression model was used to predict AKI in this study with an AUROC of 0.74 (95% CI=0.74).
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24 246 With the classification of AKI, the AUROC of the prediction model gradually increased to 0.84[8].
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26 247 Subsequently, the study team used a new machine learning algorithm, to build a more accurate model to
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28 248 predict the occurrence of AKI-II, with an AUROC of 0.9 within 24 hours and 0.87 within 48 hours[19].
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30 249 Recently, the research team included data from two other centres, namely, LUMC (N=200613) and NUS
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32 250 (N=246895), to externally validate the AKI-II prediction model with AUROCs reaching 0.85 to 0.86,
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34 251 suggesting that the artificial intelligence model has stable predictive ability[12]. This series of studies
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36 252 included many data points, suggesting the feasibility of artificial intelligence in the diagnosis of AKI,
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38 253 but the proportion of positive patients (3.5%) and ICU patients (30%) was too low to properly predict
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40 254 AKI. Our research is similar to the above. The SAHZJU-ICU database is a single-centre database
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42 255 representing south-eastern China, and the MIMIC database is a well-known open ICU database in the
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44 256 United States. The AmsterdamUMC database is a public database located in Europe. The population
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46 257 structure and diseases in the three databases are complete but different in the distribution of complications
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48 258 and race. Therefore, it provides a prediction model with unparalleled stability compared with other
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9 261 Limitations:

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11 262 This retrospective multi-centre study was unable to carry out more clinical feature mining and

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14 263 comparison because of different data structures. The differences between the three databases partly

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17 264 reflect some demographic differences between Europe, the United States and China, resulting in a decline

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20 265 in the accuracy of the prediction model. There are some differences in the number of patients included

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22 266 in the three databases, which may affect the choice of variables. As a result of the study design, we

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25 267 deleted patients with ICU hospitalization of less than 48 hours, which may result in the exclusion of most

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27 268 relatively mild patients and may reduce false positives. Second, in the prospective data study in 2020,

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30 269 there may be deviations in the inclusion of patients in the centre, thus affecting the interpretation of the

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33 270 follow-up prospective results. Finally, given the low incidence of severe AKI and the great difference in

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35 271 the proportion of positive and negative samples, the data may be accidental. The diagnostic performance

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38 272 of severe AKI is good with the sensitivity as high as 0.85 in model construction and external validation.

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41 273 however, the sensitivity decreases to 0.72 in the prospective validation, and the overall PPV effect is

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43 274 general. Our model seems to be superior to diagnostic non-AKI patients rather than AKI because of the

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46 275 proportion of positive data that we include. A large number of negative data will increase the specificity

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48 276 and reduce the sensitivity. In the retrospective study, we reduced the proportion of negative data by

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51 277 randomization but retain all data in prospective phase with the sensitivity decreases. We believe that such

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54 278 results are still acceptable and need to be viewed by the reader as a whole.

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58 280 **Conclusion:**

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4 281 Based on databases of patients of different races from different countries, we constructed stable
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6 282 machine learning models to predict the occurrence of AKI in the next 48 hours. Prospective validation
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9 283 through the implementation of an updated local database is an effective exploration of further research.
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14 285 Data Availability Statement:

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17 286 The model code can be obtained by email if readers need it, but we cannot guarantee that all the
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19 287 code will be provided. Two public databases can be applied from the official website of their respective
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22 288 databases.

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25 289 Ethics approval:

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27 290 Our research was approved by the ethics committee of the Second Affiliated Hospital of Zhejiang
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29
30 291 University School of Medicine.

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32 292 Competing interests for authors:

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35 293 The authors declare that they have no competing interests.
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40 295 **Reference:**

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32 358 **Footnotes**

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35 359 Contributions: Conceptualization, QL and MH; Methodology, YX; Software, YX; Validation, YZ, and
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38 360 YX.; Formal Analysis, JC and XC; Resources, MH; Data Curation, QL; Writing – Original Draft
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41 361 Preparation, QL; Writing – Review & Editing, MH; Visualization, YX; Supervision, YZ and QL; Project
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43 362 Administration, QL;

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45 363 **Funding:** This research received no specific grant from any funding agency in the public, commercial
46
47
48 364 or not-for-profit sectors.

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50 365 Conflicts of Interest: Not Applicable.

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53 366 Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or
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56 367 reporting, or dissemination plans of this research.

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58 368 Provenance and peer review Not commissioned; externally peer reviewed.
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4 369 Acknowledgements: Thank my colleagues in general ICU for cooperating with us in our prospective
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6 370 study. Thanks to two public databases namely MIMIC and AmsterdamUMC for providing important
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14 373 **Supplemental Figure:**

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19 375 Title and Description of data: The variable importance parameter histogram of early diagnosis prediction
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22 376 models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.

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27 378 Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative
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30 379 diagnosis of early diagnosis prediction models of severe AKI.

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35 381 Title of data: The visual interface for prospective studies of the AKI early diagnosis prediction models.

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37 382 Description of data: Different patients have independent card display information, in which the last line
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40 383 of the card is the AKI diagnosis. The visual interface was not available to doctors during the prospective
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43 384 study and was used only by the researchers to verify the diagnosis and for sampling verification.

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48 386 Title and of Description data: Missing data between three databases in the study and values included in
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56 389 Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model
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6 392 Title of data: TRIPOD Checklist of Prediction Model Development and Validation

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9 393 Description of data: Writing norms of this type of research.

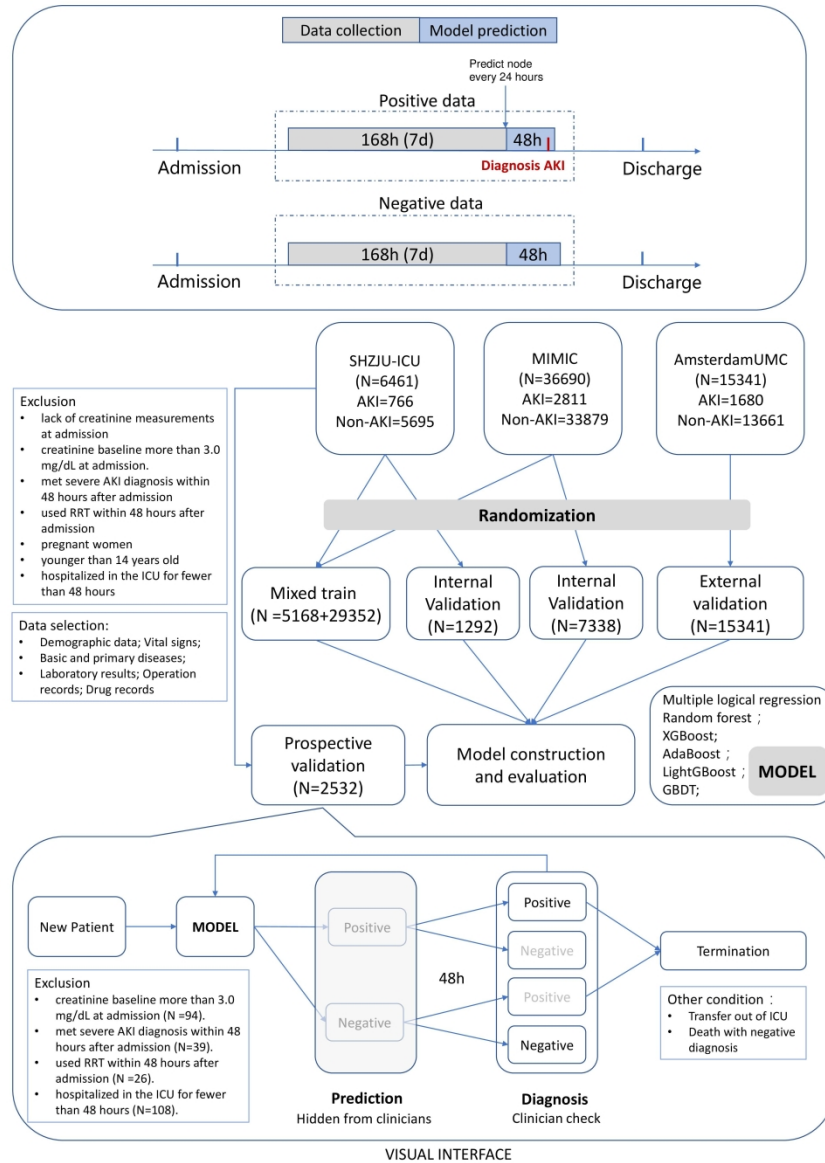
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14 395 **Figure Legend:**

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17 396 Figure 1: The research flow chart. The data collection time interval of the study was 7 days before
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19 397 diagnosis and the prediction interval was 48 hours. The early prediction model of AKI diagnosis was
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22 398 constructed and verified by our database and the MIMIC database and incorporated into the
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25 399 AmsterdamUMC database for external validation. We carried out a one-year prospective validation
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28 400 through the database of the centre.

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30 401 Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC
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33 402 database.

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35 403 Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and
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38 404 the prospective validation in our center for 3B.



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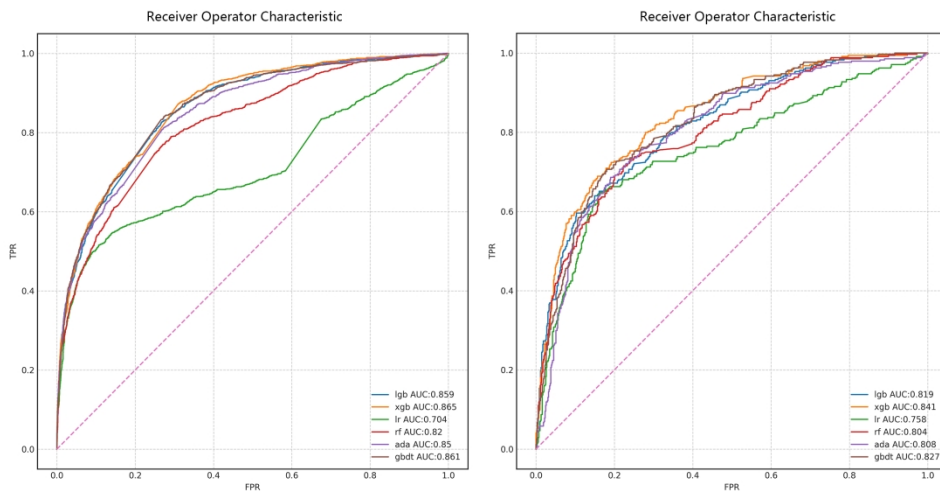
Internal validation set ROC curves



External and prospective validation set ROC curves

A: AmsterdamUMC database external validation set

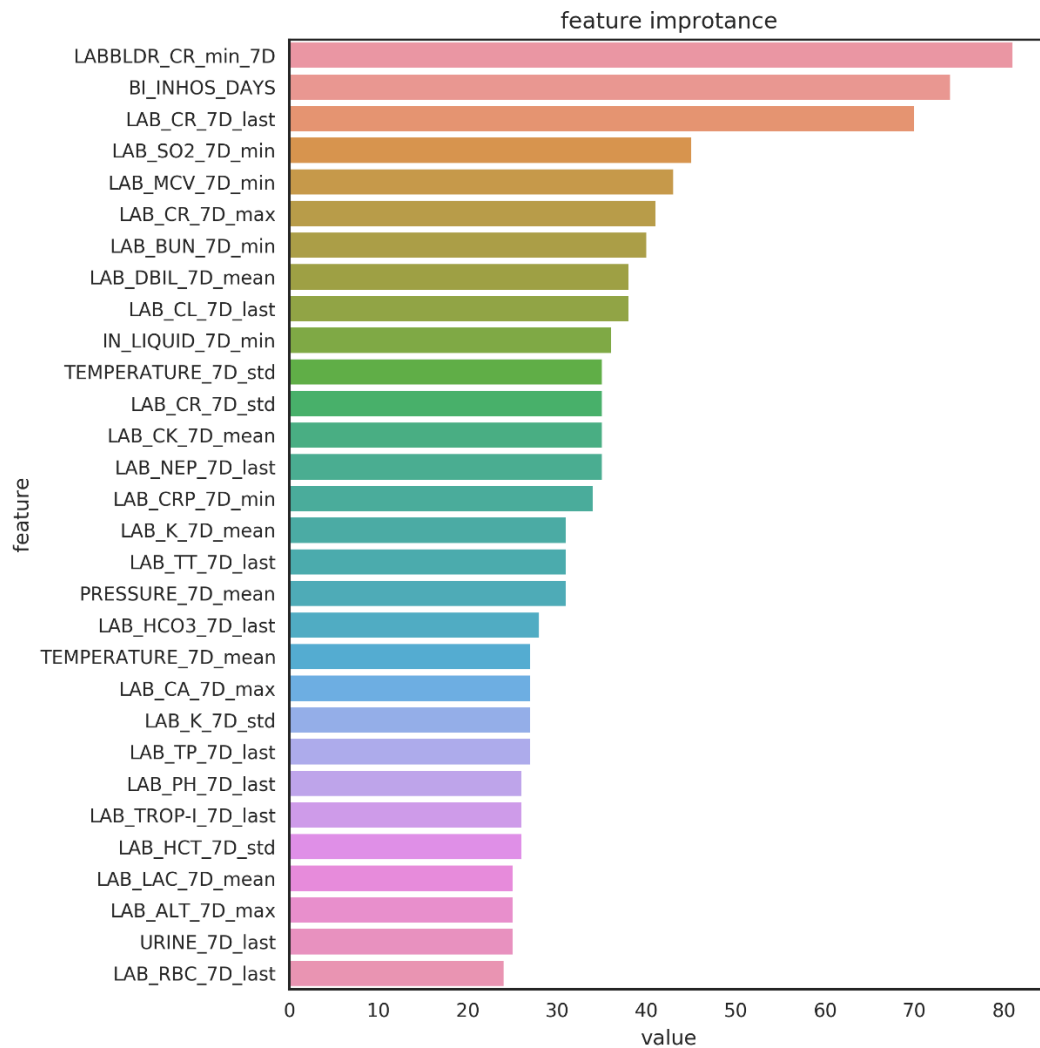
B: SHZJU-ICU database prospective validation set



Supplemental Figure:

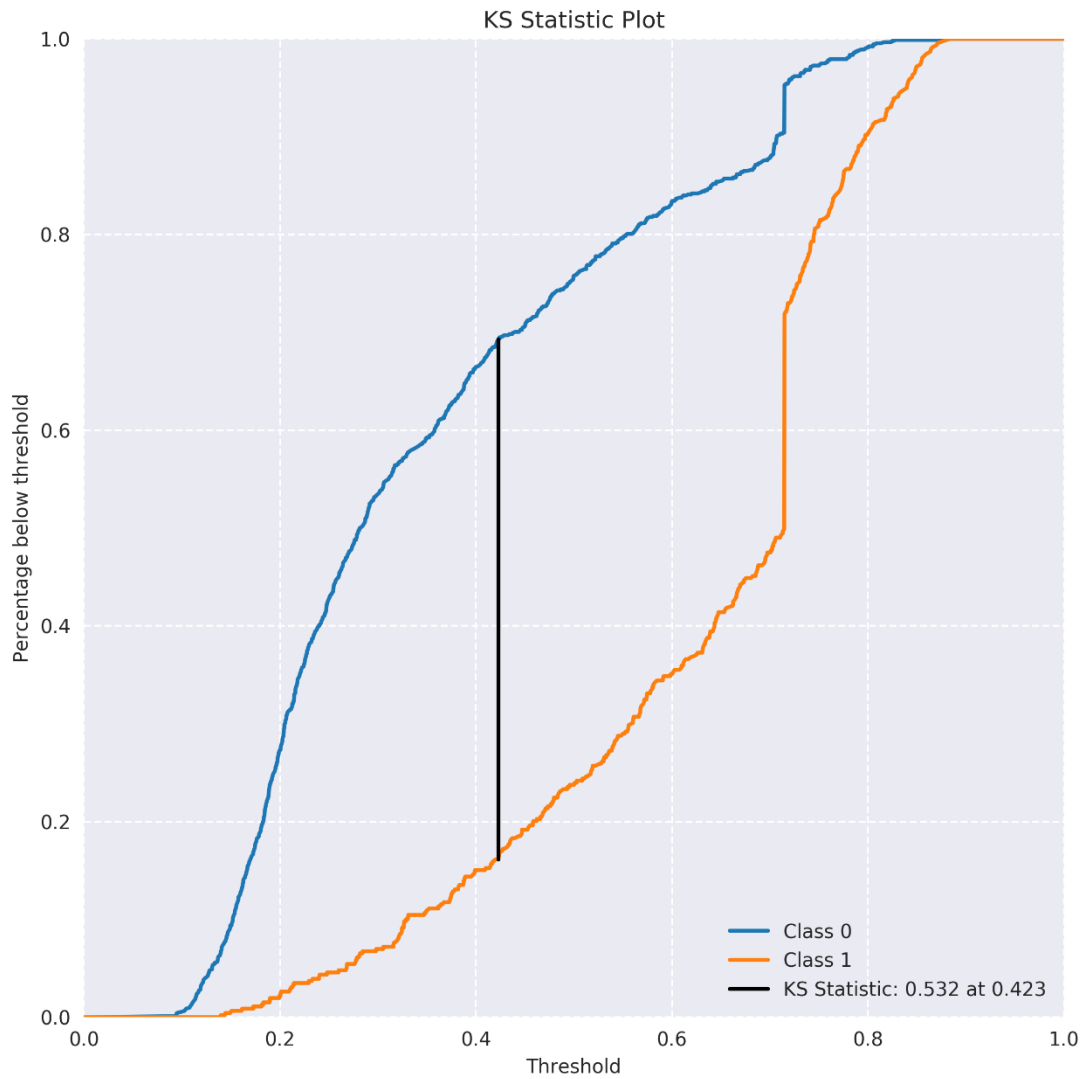
File name: **Figure S1.tif**

Title and Description of data: The variable importance parameter histogram of early diagnosis prediction models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.



File name: **Figure S2.tif**

Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative diagnosis of early diagnosis prediction models of severe AKI.



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47 of the card is the AKI diagnosis. The visual interface was not available to doctors during the prospective
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50 study and was used only by the researchers to verify the diagnosis and for sampling verification.

<p>A002 床 [redacted]</p> <p>1.烧伤2.低容量性休克3.气管切开后4.高血压</p> <p>APACHE II 27 SOFA 缺失参数, 无法评估 Sepsis 已发生sepsis ▲ AKI 非AKI ▲</p>	<p>疑似转床</p> <p>A002 床 [redacted]</p> <p>APACHE II 缺失参数, 无法评估 SOFA 缺失参数, 无法评估 Sepsis 低风险 AKI 缺失参数, 无法评估</p>	<p>A003 床 [redacted]</p> <p>1.累及体表45%的烧伤; 2.低蛋白血症; 3.低钠血症; 4.慢性支气管炎</p> <p>APACHE II 34 SOFA 缺失参数, 无法评估 Sepsis 低风险 AKI 高肌酐型AKI ▲</p>
<p>疑似转床</p> <p>A004 床 [redacted]</p> <p>APACHE II 缺失参数, 无法评估 SOFA 缺失参数, 无法评估 Sepsis 低风险 AKI 缺失参数, 无法评估</p>	<p>疑似转床</p> <p>A004 床 [redacted]</p> <p>APACHE II 缺失参数, 无法评估 SOFA 缺失参数, 无法评估 Sepsis 低风险 AKI 缺失参数, 无法评估</p>	<p>A005 床 [redacted]</p> <p>1.烧伤 体表 > 90%的烧伤 2.呼吸衰竭</p> <p>APACHE II 37 SOFA 缺失参数, 无法评估 Sepsis 已发生sepsis ▲ AKI 非AKI ▲</p>

File name: **Table S1.docx**

Title and of Description data: Missing data between three databases in the study and values included in the model.

	SHZJU-ICU	MIMIC	AmsterdamUMC	Including in Model
Age	√	√	√	√
Gender	√	√	√	√
Race	√	√	×	×
Primary disease	√	√	×	×
Comorbidity	√	√	×	×
Ventilation	√	√	√	√
Operation	√	√	×	×
ICU hours	√	√	√	√
Survived	√	√	√	√
Vital sign				
Temperature	√	√	√	√
Systolic pressure	√	√	√	√
Diastolic pressure	√	√	√	√
Respiratory rate	√	√	√	√
Heart rate	√	√	√	√
Oxygen saturation	√	√	√	√
Urine	√	√	√	√
GCS score	√	×	×	×
Laboratory results				

1				
2				
3	Scr	√	√	√
4	BUN	√	√	√
5	RBC	√	√	√
6	MCV	√	√	√
7	Hb	√	√	√
8	WBC	√	√	√
9	NEUT	√	√	√
10	PLT	√	√	√
11	HCV	√	√	×
12	TBLB	√	√	√
13	DBLB	√	√	√
14	IBLB	√	√	√
15	CRP	√	√	√
16	PCT	√	×	×
17	Serum kalium	√	√	√
18	Serum natrium	√	√	√
19	Serum chlorine	√	√	√
20	PT	√	√	√
21	APTT	√	√	√
22	INR	√	√	√
23	CK	√	√	√
24	LDH	√	√	√
25	Troponin	√	√	√
26	Blood glucose	√	√	√
27	PH	√	√	√
28	Lactic acid	√	√	√
29	Anion gap	√	√	√
30	ABC	√	√	√
31	SBC	√	√	√
32	PaCO₂	√	√	√
33	PaO₂	√	√	√
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SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; APTT: Activated partial thromboplastin time; INR: International normalized ratio; LDH: Lactate dehydrogenase; PaCO₂: Partial pressure of carbon dioxide; PaO₂ Partial pressure of oxygen; MCV: Mean corpuscular volume; PH: Potential of hydrogen; WBC: White blood cell count; NEUT: Proportion of neutrophils; CK: Creatine kinase; Scr: Serum Creatinine; BUN: Blood urea nitrogen; RBC: Red blood cell count; Hb: Hemoglobin; PT: Prothrombin time; TBLB: Total bilirubin; DBLB: Direct bilirubin; IBLB: Indirect bilirubin; CRP: C-reactive protein; HCV: Hematocrit value; PCT: Procalcitonin; ABC: Actual Bicarbonate Radical; SBC: Standard Bicarbonate Radical; PLT: Platelet count

File name: **Table S2.docx**

Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model

building set and prospective validation.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P-value	SHZJU-ICU Prospective Negative (N=2188)	SHZJU-ICU Prospective Positive (N=344)	P-value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.004	61.3 [47.5-73.4]	62.1 [51.2-70.5]	0.03
Gender, male (%)	3561 (64.9)	438 (59.8)	0.007	1365 (62.4)	207 (60.2)	0.438
Race						
White	3 (0.05)	1 (0.1)	1	2 (0.001)	0	1
Black	1 (0.02)	0	1	0	0	1
Asian	5691(99.9)	764 (99.7)	1	2185 (99.9)	344(100)	1
Other	0	1 (0.1)	1	1 (0.001)	0	1
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.001	0.8 (0.32)	0.9 (0.35)	<0.001
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.001	17 (11)	20 (10)	0.007
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.001	230 (10.5)	26 (7.6)	0.102
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	15 (0.7)	3 (0.8)	0.726
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	98 (4.5)	19 (5.7)	0.403
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.002	142 (6.5)	29 (8.6)	0.203
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	324(14.8)	56 (16.4)	0.466
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.001	1102 (50.4)	239 (69.5)	<0.001
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	1234(56.4)	160 (46.7)	0.001
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	58.7 [34.2-160.4]	145.6 [68.5-314.8]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	1868 (85.4)	178 (51.9)	<0.001

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood urea nitrogen.

File name: **Table S3.docx**

Title of data: TRIPOD Checklist of Prediction Model Development and Validation

Description of data: Writing norms of this type of research.

1Section/Topic		Checklist Item		Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Yes; P1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Yes; P2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Yes; P3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Yes; P4, L76-79
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Yes; P4, L80
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Yes; P4, L84-86
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Yes
	5b	D;V	Describe eligibility criteria for participants.	Yes; P5, L104
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Yes; P6, L111
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Yes; P6, L116
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Yes; P6, L127
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Yes; P6, L116
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Yes; P6, L119
	10c	V	For validation, describe how the predictions were calculated.	Yes; P6, L126
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Yes; P6, L159
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Yes; P6, L111

Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results				
Participants	3a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	3b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, Table2
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Yes
Model specification	5a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	5b	D	Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L236
Interpretation	9a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L217
	9b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L198
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Yes, P9, L193
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	NA

BMJ Open

Severe Acute Kidney Injury Predicting Model based on transcontinental databases: a single-center perspective study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054092.R2
Article Type:	Original research
Date Submitted by the Author:	21-Nov-2021
Complete List of Authors:	Liang, Qiqiang; Zhejiang University School of Medicine Second Affiliated Hospital Xu, Yongfeng; HealSci Technology Co Zhou, Yu; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Xinyi; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Juan; Zhejiang University School of Medicine Second Affiliated Hospital Huang, Man; Zhejiang University School of Medicine Second Affiliated Hospital,
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics
Keywords:	Acute renal failure < NEPHROLOGY, INTENSIVE & CRITICAL CARE, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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4 **1 Severe Acute Kidney Injury Predicting Model based on transcontinental**
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6 **2 databases: a single-center perspective study**
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8

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4 **23 Abstract:**

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6 **24 Objectives:** There are many studies of acute kidney injury (AKI) diagnosis models lack of external
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9 **25 validation and prospective validation.** We constructed the models using three databases to predict severe
10
11
12 **26 AKI within 48 hours in intensive care unit (ICU) patients.**

13
14 **27 Design:** A retrospective and prospective cohort study.

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16
17 **28 Setting:** We studied critically ill patients in our database (SHZJU-ICU) and two other public databases,
18
19
20 **29 the Medical Information Mart for Intensive Care (MIMIC) and AmsterdamUMC databases, including**
21
22
23 **30 basic demographics, vital signs, and laboratory results.** We predicted the diagnosis of severe AKI in
24
25 **31 patients in the next 48 hours using machine-learning algorithms with the three databases.** Then, we
26
27 **32 carried out real-time severe AKI prediction in the prospective validation study at our centre for one year.**

28
29
30 **33 Participants:** All patients included in three databases with uniform exclusion criteria.

31
32
33 **34 Primary and secondary outcome measures:** Effect evaluation index of prediction models.

34
35
36 **35 Results:** We included 58492 patients, and a total of 5257 (9.0%) patients met the definition of severe
37
38 **36 AKI.** In the internal validation of the SHZJU-ICU and MIMIC databases, the best area under the receiver
39
40
41 **37 operating characteristic curve (AUROC) of the model was 0.86.** The external validation results by
42
43 **38 AmsterdamUMC database were also satisfactory, with the best AUROC of 0.86.** A total of 2532 patients
44
45
46 **39 were admitted to the center for prospective validation; 358 positive results were predicted, and 344**
47
48
49 **40 patients were diagnosed with severe AKI, with the best sensitivity of 0.72, the specificity of 0.80, and**
50
51 **41 the AUROC of 0.84.**

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54 **42 Conclusion:** The prediction model of severe AKI exhibits promises as a clinical application based on
55
56
57 **43 dynamic vital signs and laboratory results of multi-center databases with prospective and external**
58
59 **44 validation.**

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4 45 **Keywords:** Machine learning; Acute kidney injury; Real-time prospective validation; External
5
6 46 validation.

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8
9 47 **Strengths and limitations of this study:**

10
11 48 A prospective validation in machine learning of AKI research rather than other studies;

12
13 49 Three large database containing different national populations and regions;

14
15 50 Variable's sampling limited by the monitoring frequency of clinical data;

16
17 51 Differences in the samples proportion of three databases;

18
19 52 The dimensions of variables are not rich enough.

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21 53

22
23 54 **Introduction:**

24
25 55 Acute kidney injury (AKI), as a common clinical complication in the intensive care unit (ICU),

26
27 56 significantly increases the duration of hospitalization and mortality[1]. AKI is divided into three types

28
29 57 according to the various aetiologies: prerenal (renal hypoperfusion), intrarenal (vascular, glomerular, or

30
31 58 tubulointerstitial lesions), and postrenal (urinary tract obstruction)[2]. Although nearly all diseases

32
33 59 associated with ICU admission may cause AKI, acute tubular necrosis (ATN) and prerenal azotaemia

34
35 60 are the most common causes[3].

36
37 61 All AKI diagnostic criteria including the latest Kidney Disease: Improving Global Outcomes (KDIGO)

38
39 62 standard are currently based on the creatinine level and urine volume[4]. However, the increase in the

40
41 63 creatinine level or decrease in the urine volume lags the onset of AKI[2]. Many studies have suggested

42
43 64 that early diagnosis and treatment of reversible AKI can reduce mortality[5]. Therefore, the creatinine

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45 65 level and urine volume are not satisfactory to meet clinical diagnostic demands. Consequently, many

46
47 66 researchers have tried to develop an early warning model by analysing the risk factors for AKI[6].

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4 67 Patient complications, such as diabetes, hypertension, cardiovascular disease, chronic liver disease,
5
6 68 sepsis, and trauma, are identified as important risk factors for AKI[7]. The AKI prediction model and
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9 69 scoring system developed based on high-risk factors has gradually become the focus of research
10
11 70 considering the lower clinical application threshold compared with that of new biomarkers[6]. Although
12
13
14 71 most previous prediction models use the multiple logistic regression model, a variety of AKI prediction
15
16
17 72 models based on machine learning have resulted in satisfactory outcomes[6]. Since the first AKI
18
19 73 prediction model study based on artificial intelligence was published in 2016, researchers have built more
20
21
22 74 than 20 published AKI prediction models successively by using local or multi-centre databases[6,8-14].
23
24
25 75 The results indicate that these models can predict the occurrence of AKI and the need for renal
26
27 76 replacement therapy (RRT) within 24 or 48 hours, with accuracies ranging from 81% to 97%[6,15]. In
28
29
30 77 addition, many studies have focused on subspecialized conditions, including cardiac surgery, trauma,
31
32
33 78 and burns[14-16]. However, the common defect in these studies is the lack of external validation and
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35
36 79 prospective validation, which causes the prediction model to deviate from the clinical scenarios and limits
37
38 80 extrapolation beyond the scope of the data.

39
40 81 In this study, we built models to predict AKI within 48 hours in critically ill patients by using
41
42
43 82 transcontinental three databases. Then, we evaluated the clinical effect of the model through a one-year
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45
46 83 prospective validation at our centre.

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48 84

49 50 85 **Methods:**

51 52 86 **Study design and setting**

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55 87 We collected patients using three ICU databases and prospectively validated the models in our centre.

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58 88 The first database was our centre general ICU database (SHZJU-ICU) of the Second Affiliated Hospital
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4 89 of Zhejiang University School of Medicine, an academic teaching hospital. Since its establishment in
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6 90 2017, it has included 12000 ICU patients' data and is updated daily. The Medical Information Mart for
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8
9 91 Intensive Care (MIMIC) III database, the second one, is an open ICU database provided by the
10
11 92 Massachusetts Institute of Technology and includes nearly 60000 ICU patients from North America[17].
12
13
14 93 Lastly, the AmsterdamUMC database is an available European ICU database with health data related to
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16
17 94 23000 patients admitted to ICUs in parts of Europe[18]. The research flow chart is shown in Figure 1.
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21 22 96 **Study definition**

23
24
25 97 In this study, the diagnosis of AKI was confirmed based on three stages according to the KDIGO
26
27 98 criteria[4]. We defined the patients who met the KDIGO AKI II and III criteria as severe AKI groups
28
29
30 99 and the others as negative groups. We excluded patients with lack of creatinine measurements during
31
32
33 100 admission, patients with creatinine baseline more than 3.0 mg/dL at admission, patients who met severe
34
35 101 AKI diagnosis within 24 hours, and patients who used RRT within 48 hours after admission[19]. In
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37
38 102 addition, we excluded pregnant women, patients younger than 14 years old, and patients hospitalized in
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40 103 the ICU for fewer than 48 hours. After the patient was admitted to ICU, we performed a prediction every
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42
43 104 24 hours and recorded a prediction time. If the patient was diagnosed with severe AKI within 48 hours,
44
45 105 the predictive time was defined as a positive predictive point, and the others were defined as a negative
46
47
48 106 point. The study was evaluated and approved by the Ethics Committee of the Second Affiliated Hospital
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50
51 107 of Zhejiang University School of Medicine as study number 2019-078.

52 53 108 **Data Collection**

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55
56 109 The variables included demographic data, vital signs, basic and primary diseases, laboratory results,
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58 110 important operation records, and drug records. Comorbidity included hypertension, diabetes, cardiopathy,
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4 111 liver disease, and malignant tumors. The primary disease was the main cause of admission to the ICU
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6 112 following the ICD-10 codes. The vital signs and clinical laboratory results were transformed into
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9 113 different variables according to the average, variance, maximum, minimum, and final value before
10
11 114 diagnosis. We use a method similar to the forward incremental method in the multivariate logic
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14 115 regression model, that is, the combination of embedded feature selection and forward addition for feature
15
16
17 116 selection. First of all, all variables are trained in the model, then list by variables importance. variables
18
19 117 are added to the model one by one according to the variable importance. a variable is retained if it causes
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22 118 the AUC growth to be greater than 0.01, otherwise delete it. We transformed the MIMIC and
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25 119 AmsterdamUMC databases according to our centre database structure, unifying the unit and diagnostic
26
27 120 codes. We deleted variables missing more than 50%. Variables missing more than 30% but less than 50%
28
29
30 121 are listed to clinicians who determine the potential correlation between these variables and AKI. We
31
32 122 carry out multiple interpolation for these variables which clinicians require to be retained, and the others
33
34
35 123 deleted. Variables missing less than 30% are fill in multiple interpolation. All Missing data between three
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37 124 databases and values included in the model shown in supplementation file Table S1.

125 **Model construction and external validation**

126 The ratio of the training and internal validation sets was 4:1. The SHZJU and MIMIC databases
127 training sets were mixed into a new training set. There were more negative data than positive data, so we
128 randomly sampled the negative datasets and constructed a new data subset with a sampling ratio of
129 positive and negative data of 1:5 in model building in order to extract the importance variables. In the
130 subsequent model validation, we adopted the original data set. We used multiple logistic regression,
131 random forest, XGBoost, AdaBoost, LightGBoost, gradient boosting decision tree (GBDT), and debug
132 to assess the variables and model-related parameters by the fivefold cross-validation method. After the

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4 133 models were built, we used the SHZJU-ICU and MIMIC test sets for internal validation of the model and
5
6 134 the AmsterdamUMC database for external validation. The most appropriate cut-off value was determined
7
8
9 135 according to the K-S curve. The prediction model represents the results of each prediction with a
10
11
12 136 probability between 0 to 1.0. We define results more than 0.4 as high-risk, that is, positive results, and
13
14 137 the rest as negative results. Through internal validation and external validation, we calibrated the model
15
16
17 138 by adjusting the super-parameters and using the Platt calibration algorithm and compared the calibration
18
19
20 139 effect by drawing a reliability diagram. All model building and validation processes were performed in
21
22 140 Python 3.6.

23 24 25 141 **Prospective validation**

26
27 142 The prospective research period was 2020.01.01 to 2020.12.31. We collected real-time data when
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29
30 143 patients were admitted to the ICU, transformed the data according to the requirements, and formed a
31
32
33 144 complete sample for the prediction model after passing the integrity test. We had established a
34
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36 145 visualization scheme and allowed researchers to review the predictions daily. The daily prediction results
37
38 146 were not publicly accessible during the study to avoid affecting clinicians' decisions, but the diagnosis
39
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41 147 results were available to the researchers as visual graphics. We sampled the 20% predicted data every
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44 148 month and deleted samples with more than 50% missing values to ensure data correctness. When a patient
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47 149 has the following conditions, AKI prediction system will end the patient's prospective prediction: A. a
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50 150 positive diagnosis; B. Transfer out of ICU or death with negative diagnosis. All diagnosis of severe AKI
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53 151 needs to be reviewed by two ICU attending physicians independently, and if the they have different
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56 152 opinion, the third one will be appealed.

57 58 59 153 **Statistical analysis:**

60 154 The population characteristics were reported as the medians and inter-quartile ranges (IQRs) for

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4 155 skewed data and the means and standard deviations for normally distributed data. The independent
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6 156 sample T-test was used for normally distributed data, and the rank-sum test was used for the rest.
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9 157 Dichotomous variables were assessed by the chi-square test, and a P value less than 0.05 was considered
10
11 158 statistically significant. The non-normally distributed data were analyzed by exponential transformation
12
13
14 159 and logarithmic transformation. The effect of the model was evaluated by parameters such as the
15
16
17 160 AUROC, accuracy, specificity, and F1-score.

19 161 **Patient and Public Involvement:**

22 162 The information of cases in three databases was in a state of complete desensitization in the process
23
24 163 of building the model. During the prospective study, all the patients signed an informed consent form at
25
26
27 164 the beginning of admission to ICU. The real-time data discussed and used by only the study members,
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29
30 165 and were not made public during the study period. All data were anonymized before the authors accessed
31
32 166 them for the purpose of this study. Therefore, patients' priorities, experience, and preferences will not
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35 167 affect the development of the research question and outcome measures. If necessary, we will inform
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38 168 patients of relevant research results by telephone.

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43 170 **Results:**

45 171 According to the inclusion criteria and exclusion criteria, we selected 58492 patients from three
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48 172 databases who met the requirements of the study, including 6461 patients from the SHZJU-ICU database,
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51 173 36690 patients from the MIMIC database, and 15341 patients from the AmsterdamUMC database. A
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53 174 total of 5257 (9.0%) patients met the definition of severe AKI (11.8% in SHZJU-ICU, 7.6% in MIMIC,
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56 175 and 10.9% in AmsterdamUMC). The distributions of age and sex in the three centers were similar, but
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59 176 the differences in race were large. Asian patients accounted for more than 99% in the SHZJU-ICU

177 database, and only approximately 2.5% in the MIMIC database. White people accounted for more than
 178 70% of the MIMIC database. In addition, patients from the MIMIC database had a higher incidence of
 179 the tumor, liver cirrhosis, diabetes, and hypertension. Patients in the AmsterdamUMC and SHZJU-ICU
 180 databases had a higher proportion of mechanical ventilation and overall survival rate. Severe AKI
 181 patients had longer ICU hospital stays and higher mortality. More details are presented in Table 1.
 182 Table 1: Clinical Demographics and Outcomes in patients with or without severe acute
 183 kidney injury.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P- valu e	MIMIC Negative (N=33879)	MIMIC Severe AKI (N=2811)	P- value	AmsterdamUMC Negative (N=13661)	AmsterdamUMC severe AKI (N=1680)	P- value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.00 4	62.0 [45.0-76.0]	64.0 [52.0-76.0]	<0.001	64.5 [54.5,74.5]	64.3 [52.5,78.5]	0.04
Gender, male (%)	3561 (64.9)	438 (59.8)	0.00 7	18976 (56.0)	1524 (54.2)	0.06	8920 (65.3)	1054 (63.9)	0.03
Race							/	/	/
White	3 (0.05)	1 (0.1)	1	23796 (70.2)	2005 (71.3)	0.23	/	/	/
Black	1 (0.02)	0	1	2455 (7.2)	199 (7.1)	0.45	/	/	/
Asian	5691(99.9)	764 (99.7)	1	918 (2.7)	70 (2.5)	0.54	/	/	/
Other	0	1 (0.1)	1	6710 (19.8)	537 (19.1)	0.34	/	/	/
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.0 01	1.1 (0.41)	1.1 (0.50)	0.04	1.2 (0.35)	1.1 (0.38)	<0.00 1
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.0 01	17 (12)	23 (12)	<0.001	18 (13)	23 (10)	<0.00 1
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.0 01	6652 (19.6)	752 (26.8)	<0.001	/	/	/
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	1180 (3.5)	426 (15.2)	<0.001	/	/	/
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	4840 (14.3)	336 (12.0)	0.001	/	/	/
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.00 2	7250 (21.4)	789 (28.1)	<0.001	/	/	/
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	16328 (48.2)	1513 (53.8)	<0.001	/	/	/
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.0 01	13009 (38.4)	1503(53.5)	<0.001	7718(56.5)	1248(74.3)	<0.00 1
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.0 01	12455 (36.7)	1430 (50.8)	<0.001	/	/	/

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ICU	Hours,	50.8	164.4	<0.0	51.0	103.4	<0.001	24.0	142.0	<0.00
median [IQR]		[23.0-139.5]	[70.3-328.6]	01	[28.5-110.3]	[50.1-261.3]		[19.8,63.5]	[45.4,394.2]	1
Survived, n (%)		4997 (87.7)	380 (49.6)	<0.0	25648 (75.7)	1356 (48.2)	<0.001	10942(80.1)	1033 (61.5)	<0.00
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184 *SHZJU-ICU*: The general ICU database of the second affiliated hospital of Zhejiang university
185 school of medicine; *MIMIC*: Medical Information Mart for Intensive Care; *IQR*: Inter-Quartile
186 Range; *ICU*: Intensive Care Unit; *AKI*: Acute Kidney Injury. *Scr*: serum creatinine; *BUN*: blood
187 urea nitrogen.

188 There were significant differences in the important parameters of the variables among the different
189 models (see Figure S1). However, the trend of the creatinine level in the past week was still an important
190 variable, followed by urine volume, blood urea nitrogen level, temperature, and length of ICU stay. The
191 cut-off value used to distinguish between a negative and positive prediction was determined by the K-S
192 curve, with value of 0.423 (see Figure S2). The GBDT model had the best prediction effect in the test
193 set, followed by XGBoost and LightGBoost. In the two central internal validation sets, the two best-
194 performing machine learning algorithms with great AUROC are LightGBoost (*SHZJU-ICU* of 83.2%,
195 *MIMIC* of 86.0%) and XGBoost (*SHZJU-ICU* 85.9%, *MIMIC* 85.6%), as detailed in Figure 2. Overall,
196 the sensitivity (*SHZJU-ICU* 0.84, *MIMIC* 0.83) and the negative predictive value (*SHZJU-ICU* 0.90,
197 *MIMIC* 0.90) of the predictive model were high, but the specificity was general (*SHZJU-ICU* 0.79,
198 *MIMIC* 0.75), as shown in Table 2. In the external validation based on AmsterdamUMC database, the
199 overall model validation effect results were satisfactory, and XGBoost had the best performance, with
200 an AUROC of 0.84, as shown in Figure 2 and Table 2. We built a visual prediction interface based on
201 the prediction model (supplementation file Figure S3).

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203 Table 2: Model validation results by three databases with machine learning algorithm

Model	AUROC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1
Internal validation with SHZJU-ICU database							
Logistic regression	0.748	0.662	0.834	0.576	0.496	0.874	0.622
LightGBoost	0.832	0.741	0.839	0.692	0.576	0.896	0.683

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GBDT	0.845	0.765	0.843	0.725	0.606	0.902	0.705
AdaBoost	0.806	0.721	0.824	0.67	0.555	0.884	0.663
Random Forest	0.821	0.763	0.71	0.789	0.627	0.845	0.666
XGBoost	0.859	0.779	0.81	0.763	0.631	0.889	0.709
Internal validation with MIMIC database							
Logistic regression	0.733	0.695	0.643	0.72	0.535	0.801	0.584
LightGBost	0.86	0.768	0.822	0.741	0.613	0.893	0.702
GBDT	0.846	0.765	0.786	0.755	0.616	0.876	0.691
AdaBoost	0.837	0.732	0.831	0.683	0.567	0.89	0.674
Random Forest	0.832	0.738	0.791	0.712	0.578	0.872	0.668
XGBoost	0.856	0.758	0.833	0.721	0.598	0.895	0.695
External validation with AmsterdamUMC database							
Logistic regression	0.704	0.767	0.516	0.893	0.706	0.787	0.596
LightGBost	0.859	0.763	0.827	0.731	0.606	0.894	0.7
GBDT	0.861	0.764	0.84	0.727	0.606	0.901	0.704
AdaBoost	0.85	0.755	0.813	0.726	0.597	0.886	0.689
Random Forest	0.82	0.743	0.77	0.729	0.587	0.864	0.666
XGBoost	0.865	0.75	0.873	0.688	0.584	0.916	0.7
Prospective validation with SHZJU-ICU							
Logistic regression	0.758	0.772	0.648	0.834	0.662	0.826	0.655
LightGBost	0.819	0.796	0.596	0.895	0.74	0.816	0.66
GBDT	0.827	0.781	0.706	0.818	0.66	0.848	0.683
AdaBoost	0.808	0.766	0.686	0.805	0.638	0.837	0.661
Random Forest	0.804	0.755	0.715	0.775	0.613	0.845	0.66
XGBoost	0.841	0.779	0.724	0.807	0.652	0.854	0.686

204 AUROC: Area Under Receiver Operating Characteristic; PPV: Positive Predictive Value; NPV:
 205 Negative Predictive Value; SHZJU-ICU: The general ICU database of the second affiliated
 206 hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for
 207 Intensive Care; GBDT: Gradient Boosted Decision Tree.

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209 According to the inclusion and exclusion criteria, we delete 267 patients among 94 patients with
 210 creatinine baseline more than 3.0 mg/dL at admission, 39 patients met severe AKI diagnosis within 24
 211 hours, and 26 patients who used RRT within 48 hours after admission, 108 patients hospitalized in the
 212 ICU for fewer than 48 hours. A total of 2532 patients were admitted to our centre for prospective
 213 validation, and the prediction model made 16858 times predictions. In the prospective cohort, there was
 214 no significant difference in age, gender, baseline creatinine and urea nitrogen, and complications. The

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4 215 proportion of mechanical ventilation and the ICU stay time in AKI patients were longer with higher
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6 216 mortality. Above all, there was no significant difference between the prospective and the retrospective
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9 217 cohort. More detail sees in supplementation file Table S2. In the end, 358 positive results were predicted,
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11 218 and the rest were negative results. There are 344 patients with severe AKI were diagnosed and the
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14 219 prediction accuracy was 83.5%. The model with the highest area under the curve was XGBoost, 0.84
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17 220 with the best sensitivity of 0.72, the specificity of 0.80. The results of the prospective study are similar
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19 221 to those of the external validation of the model, and are relatively stable. More detail is presented in
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22 222 Figure 3 and Table 2.
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27 224 **Discussion:**

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30 225 In this study, we built predictive models by machine learning to predict the incidence of severe AKI
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32 226 with three databases in different regions and in the next 48 hours. After internal and external validation,
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35 227 prospective validation over one year was carried out to verify the model effects. The three databases
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38 228 come from three countries that are in Asia, Europe, and North America, which proves that the model is
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40 229 universal to some extent.

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43 230 Despite the huge amount of data, many databases are still not suitable for prospective research
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45 231 because they are not updated promptly. Tomasev, N and colleagues have provided research on AKI
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48 232 prediction models with a large amount of data[10]. The study covered 703782 adult patients with 6 billion
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51 233 individual items, including 620000 elements. In this study, a depth neural network model was used for
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53 234 real-time prediction. A total of 55.8% of severe AKI patients were predicted within the first 48 hours,
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56 235 although each accurate prediction was accompanied by two mispredictions[10]. This study provided a
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59 236 new scheme for real-time prediction and indicated that we should prospectively evaluate and
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4 237 independently validate models to explore their effectiveness. In a prospective study, Flechet, M et al
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6 238 compared an AKI prediction model with clinicians in 252 patients and found that the clinical effect of
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9 239 the random forest model for predicting AKI-II/III was equivalent to that of clinicians. Our prediction
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11 240 model graphical visualization of the model was installed in the centre's database for better usage. In
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14 241 addition, our database is updated daily to achieve daily predictions and present the results to researchers.
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17 242 In the prospective validation of our study, the stability of the prediction model confirmed its promise,
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19 243 which provides a basis for future research.

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22 244 There are many studies of artificial intelligence for predicting the occurrence of AKI, but most of them
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24 245 are single-centre studies, and the extrapolation effect has been controversial. In 2016, Koyner, J, and his
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27 246 colleague published the first study of an AKI prediction model based on multi-centre data. In all 202961
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30 247 patients, 17541 (8.6%) had AKI, 4251 (3.5%) had AKI-II, and 1242 (0.6%) had AKI-III. A multivariate
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32 248 logistic regression model was used to predict AKI in this study with an AUROC of 0.74 (95% CI=0.74).
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35 249 With the classification of AKI, the AUROC of the prediction model gradually increased to 0.84[8].
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38 250 Subsequently, the study team used a new machine learning algorithm, to build a more accurate model to
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40 251 predict the occurrence of AKI-II, with an AUROC of 0.9 within 24 hours and 0.87 within 48 hours[19].
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43 252 Recently, the research team included data from two other centres, namely, LUMC (N=200613) and NUS
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45 253 (N=246895), to externally validate the AKI-II prediction model with AUROCs reaching 0.85 to 0.86,
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48 254 suggesting that the artificial intelligence model has stable predictive ability[12]. This series of studies
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51 255 included many data points, suggesting the feasibility of artificial intelligence in the diagnosis of AKI,
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53 256 but the proportion of positive patients (3.5%) and ICU patients (30%) was too low to properly predict
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56 257 AKI. Our research is similar to the above. The SAHZJU-ICU database is a single-centre database
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58 258 representing south-eastern China, and the MIMIC database is a well-known open ICU database in the
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4 259 United States. The AmsterdamUMC database is a public database located in Europe. The population
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6 260 structure and diseases in the three databases are complete but different in the distribution of complications
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9 261 and race. Therefore, it provides a prediction model with unparalleled stability compared with other
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11 262 studies.

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17 264 **Limitations:**

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19 265 This retrospective multi-centre study was unable to carry out more clinical feature mining and
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22 266 comparison because of different data structures. The differences between the three databases partly
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25 267 reflect some demographic differences between Europe, the United States and China, resulting in a decline
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28 268 in the accuracy of the prediction model. There are some differences in the number of patients included
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31 269 in the three databases, which may affect the choice of variables. As a result of the study design, we
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34 270 deleted patients with ICU hospitalization of less than 48 hours, which may result in the exclusion of most
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37 271 relatively mild patients and may reduce false positives. Second, in the prospective data study in 2020,
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40 272 there may be deviations in the inclusion of patients in the centre, thus affecting the interpretation of the
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43 273 follow-up prospective results. Finally, given the low incidence of severe AKI and the great difference in
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46 274 the proportion of positive and negative samples, the data may be accidental. Our model seems to be
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49 275 superior to diagnostic non-AKI patients rather than AKI because of the proportion of positive data that
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52 276 we include. In the retrospective study, we reduced the proportion of negative data by randomization but
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55 277 retain all data in prospective phase with the sensitivity decreases.

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59 279 **Conclusion:**

60 280 Based on databases of patients of different races from different countries, we constructed stable

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4 281 machine learning models to predict the occurrence of AKI in the next 48 hours. Prospective validation
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6 282 through the implementation of an updated local database is an effective exploration of further research.
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11 284 Data Availability Statement:

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14 285 The model code can be obtained by email if readers need it, but we cannot guarantee that all the
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17 286 code will be provided. Two public databases can be applied from the official website of their respective
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19 287 databases.
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22 288 Ethics approval:

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25 289 Our research was approved by the ethics committee of the Second Affiliated Hospital of Zhejiang
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27 290 University School of Medicine.
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30 291 Competing interests for authors:

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32 292 The authors declare that they have no competing interests.
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37 294 **Reference:**

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30 357 **Footnotes**

31
32 358 Contributions: Conceptualization, QL and MH; Methodology, YX; Software, YX; Validation, YZ, and
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35 359 YX.; Formal Analysis, JC and XC; Resources, MH; Data Curation, QL; Writing – Original Draft
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38 360 Preparation, QL; Writing – Review & Editing, MH; Visualization, YX; Supervision, YZ and QL; Project
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41 361 Administration, QL;

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43 362 **Funding:** This research received no specific grant from any funding agency in the public, commercial
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45
46 363 or not-for-profit sectors.

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48 364 Conflicts of Interest: Not Applicable.

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51 365 Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or
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54 366 reporting, or dissemination plans of this research.

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56 367 Provenance and peer review Not commissioned; externally peer reviewed.

57
58 368 Acknowledgements: Thank my colleagues in general ICU for cooperating with us in our prospective
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4 369 study. Thanks to two public databases namely MIMIC and AmsterdamUMC for providing important
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6 370 data. Thanks for all patient advisers.
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11 372 **Supplemental Figure:**

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14 373 File name: **Figure S1.tif**

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17 374 Title and Description of data: The variable importance parameter histogram of early diagnosis prediction
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19 375 models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.
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25 377 Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative
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27 378 diagnosis of early diagnosis prediction models of severe AKI.
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32 380 Title and of Description data: Missing data between three databases in the study and values included in
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40 383 Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model
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48 386 Title of data: TRIPOD Checklist of Prediction Model Development and Validation

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50 387 Description of data: Writing norms of this type of research.
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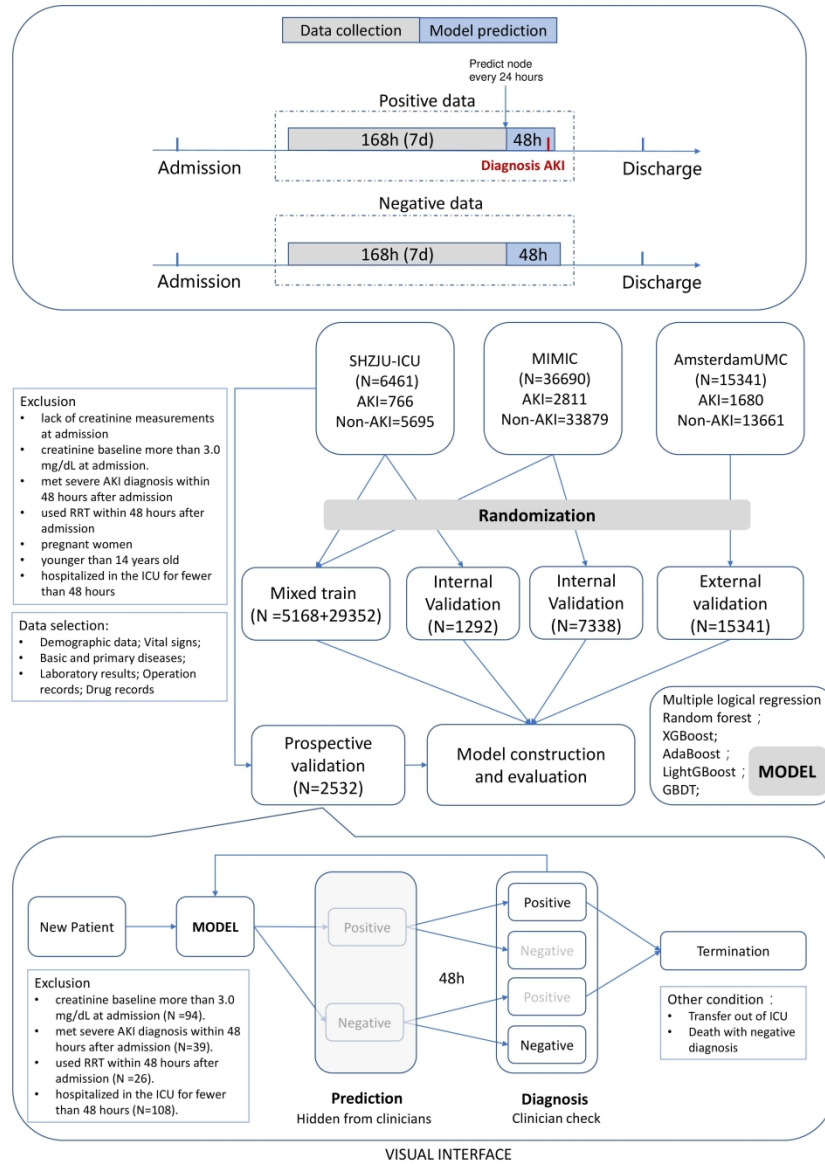
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56 389 **Figure Legend:**

57
58 390 Figure 1: The research flow chart. The data collection time interval of the study was 7 days before
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4 391 diagnosis and the prediction interval was 48 hours. The early prediction model of AKI diagnosis was
5
6 392 constructed and verified by our database and the MIMIC database and incorporated into the
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8
9 393 AmsterdamUMC database for external validation. We carried out a one-year prospective validation
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11
12 394 through the database of the centre.

13
14 395 Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC
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16
17 396 database.

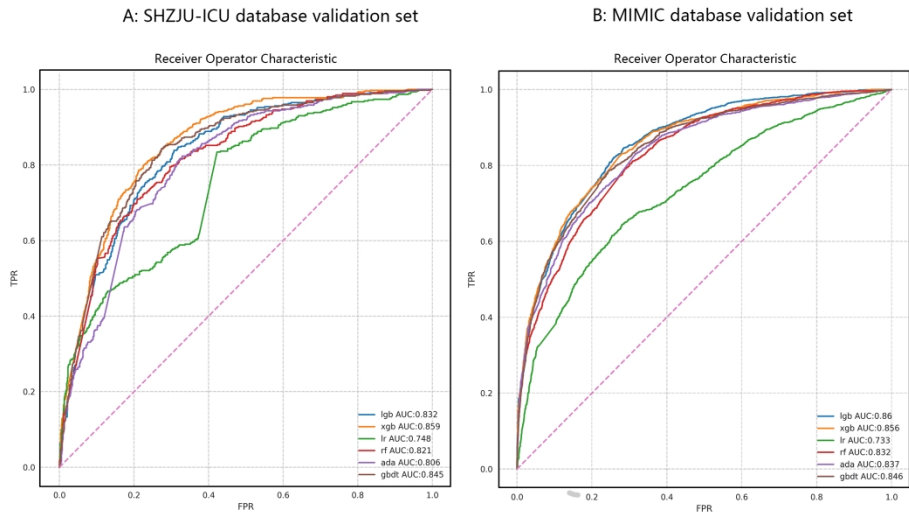
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19 397 Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and
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22 398 the prospective validation in our center for 3B.
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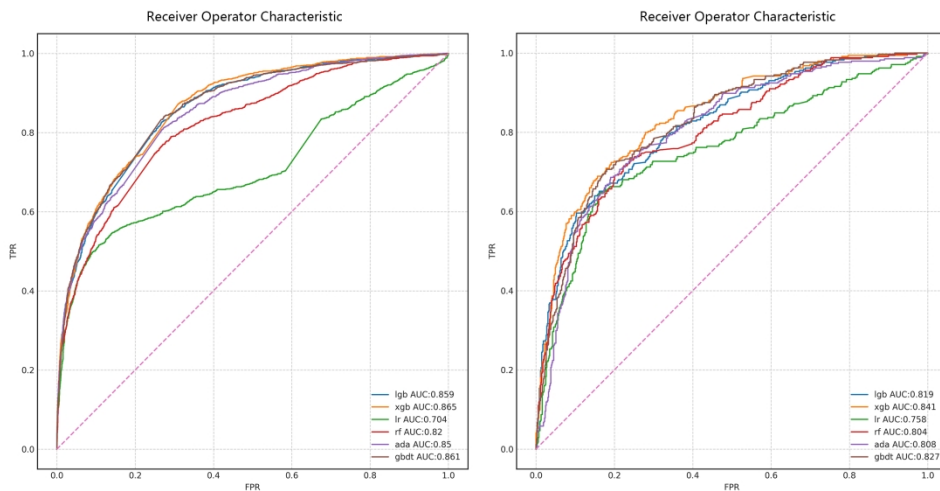
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Internal validation set ROC curves



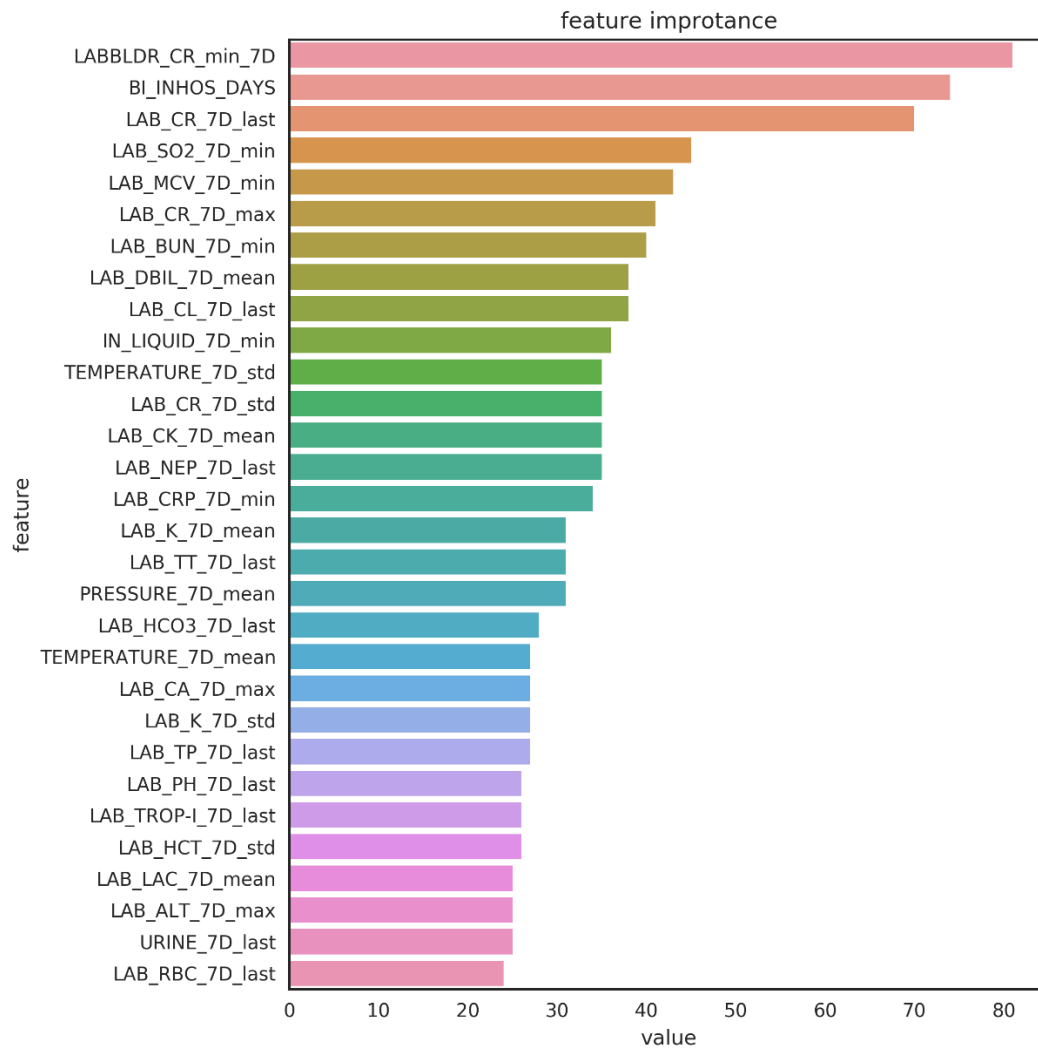
External and prospective validation set ROC curves

A: AmsterdamUMC database external validation set B: SHZJU-ICU database prospective validation set

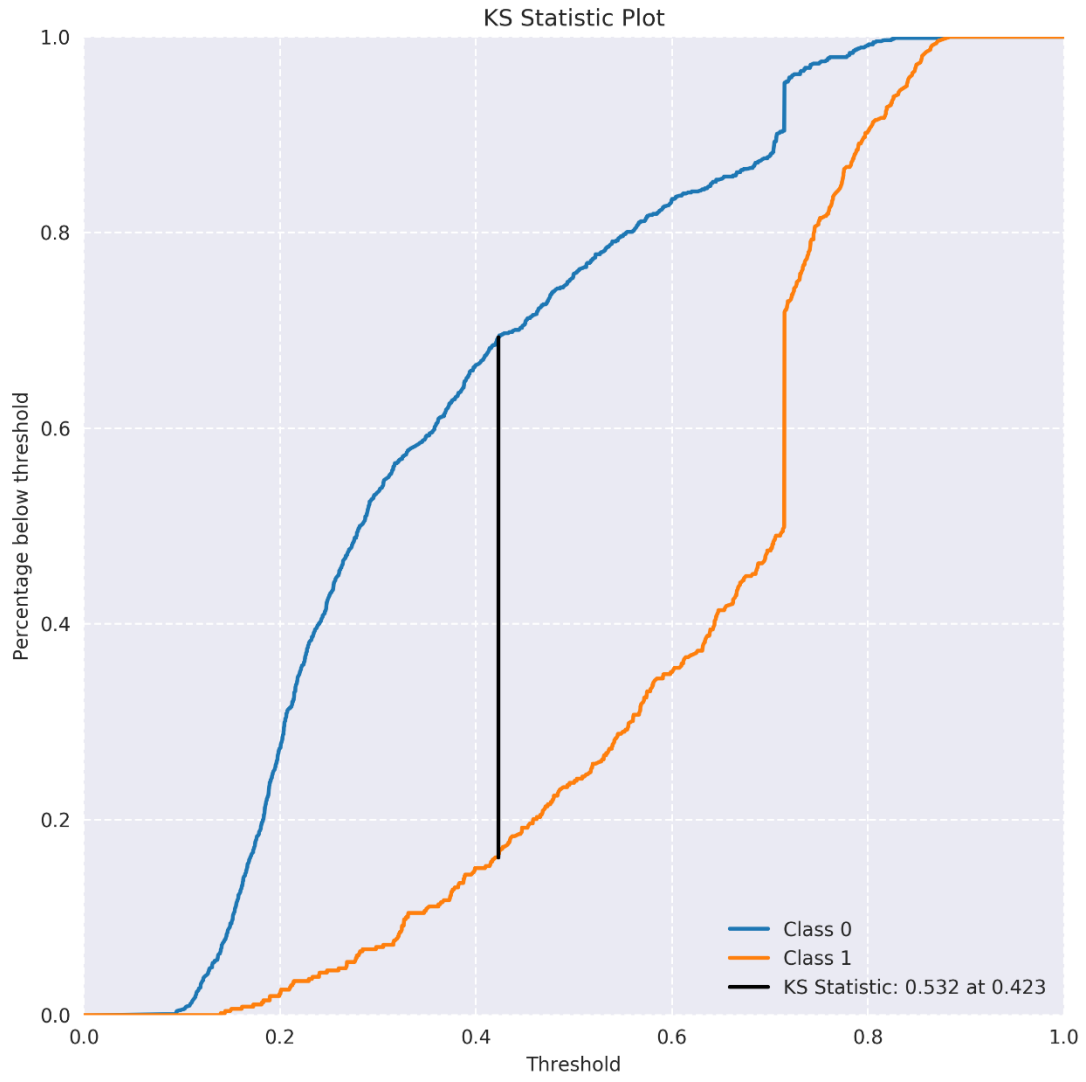


Supplemental Figure:File name: **Figure S1.tif**

Title and Description of data: The variable importance parameter histogram of early diagnosis prediction models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.

File name: **Figure S2.tif**

Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative diagnosis of early diagnosis prediction models of severe AKI.



For peer review only

File name: **Table S1.docx**

Title and of Description data: Missing data between three databases in the study and values included in the model.

	SHZJU-ICU	MIMIC	AmsterdamUMC	Including in Model
Age	√	√	√	√
Gender	√	√	√	√
Race	√	√	×	×
Primary disease	√	√	×	×
Comorbidity	√	√	×	×
Ventilation	√	√	√	√
Operation	√	√	×	×
ICU hours	√	√	√	√
Survived	√	√	√	√
Vital sign				
Temperature	√	√	√	√
Systolic pressure	√	√	√	√
Diastolic pressure	√	√	√	√
Respiratory rate	√	√	√	√
Heart rate	√	√	√	√
Oxygen saturation	√	√	√	√
Urine	√	√	√	√
GCS score	√	×	×	×
Laboratory results				
Scr	√	√	√	√
BUN	√	√	√	√
RBC	√	√	√	√
MCV	√	√	√	√
Hb	√	√	√	√
WBC	√	√	√	√
NEUT	√	√	√	√
PLT	√	√	√	√
HCV	√	√	×	×
TBLB	√	√	√	√
DBLB	√	√	√	√
IBLB	√	√	√	√
CRP	√	√	√	√
PCT	√	×	×	×
Serum kalium	√	√	√	√
Serum natrium	√	√	√	√
Serum chlorine	√	√	√	√

PT	√	√	√	√
APTT	√	√	√	√
INR	√	√	√	√
CK	√	√	√	√
LDH	√	√	√	√
Troponin	√	√	√	√
Blood glucose	√	√	√	√
PH	√	√	√	√
Lactic acid	√	√	√	√
Anion gap	√	√	√	√
ABC	√	√	√	√
SBC	√	√	√	√
PaCO ₂	√	√	√	√
PaO ₂	√	√	√	√

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; APTT: Activated partial thromboplastin time; INR: International normalized ratio; LDH: Lactate dehydrogenase; PaCO₂: Partial pressure of carbon dioxide; PaO₂: Partial pressure of oxygen; MCV: Mean corpuscular volume; PH: Potential of hydrogen; WBC: White blood cell count; NEUT: Proportion of neutrophils; CK: Creatine kinase; Scr: Serum Creatinine; BUN: Blood urea nitrogen; RBC: Red blood cell count; Hb: Hemoglobin; PT: Prothrombin time; TBLB: Total bilirubin; DBLB: Direct bilirubin; IBLB: Indirect bilirubin; CRP: C-reactive protein; HCV: Hematocrit value; PCT: Procalcitonin; ABC: Actual Bicarbonate Radical; SBC: Standard Bicarbonate Radical; PLT: Platelet count

File name: **Table S2.docx**

Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model

building set and prospective validation.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P-value	SHZJU-ICU Prospective Negative (N=2188)	SHZJU-ICU Prospective Positive (N=344)	P-value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.004	61.3 [47.5-73.4]	62.1 [51.2-70.5]	0.03
Gender, male (%)	3561 (64.9)	438 (59.8)	0.007	1365 (62.4)	207 (60.2)	0.438
Race						
White	3 (0.05)	1 (0.1)	1	2 (0.001)	0	1
Black	1 (0.02)	0	1	0	0	1
Asian	5691(99.9)	764 (99.7)	1	2185 (99.9)	344(100)	1
Other	0	1 (0.1)	1	1 (0.001)	0	1
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.001	0.8 (0.32)	0.9 (0.35)	<0.001
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.001	17 (11)	20 (10)	0.007
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.001	230 (10.5)	26 (7.6)	0.102
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	15 (0.7)	3 (0.8)	0.726
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	98 (4.5)	19 (5.7)	0.403
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.002	142 (6.5)	29 (8.6)	0.203
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	324(14.8)	56 (16.4)	0.466
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.001	1102 (50.4)	239 (69.5)	<0.001
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	1234(56.4)	160 (46.7)	0.001
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	58.7 [34.2-160.4]	145.6 [68.5-314.8]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	1868 (85.4)	178 (51.9)	<0.001

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood urea nitrogen.

File name: **Table S3.docx**

Title of data: TRIPOD Checklist of Prediction Model Development and Validation

Description of data: Writing norms of this type of research.

1Section/Topic	Checklist Item		Page
Title and abstract			
Title	1	Y;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. Yes; P1
Abstract	2	Y;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. Yes; P2
Introduction			
Background and objectives	3a	Y;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. Yes; P3
	3b	Y;V	Specify the objectives, including whether the study describes the development or validation of the model or both. Yes; P4, L76-79
Methods			
Source of data	4a	Y;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. Yes; P4, L80
	4b	Y;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. Yes; P4, L84-86
Participants	5a	Y;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. Yes
	5b	Y;V	Describe eligibility criteria for participants. Yes; P5, L104
	5c	Y;V	Give details of treatments received, if relevant. NA
Outcome	6a	Y;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed. Yes; P6, L111
	6b	Y;V	Report any actions to blind assessment of the outcome to be predicted. NA
Predictors	7a	Y;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. Yes; P6, L116
	7b	Y;V	Report any actions to blind assessment of predictors for the outcome and other predictors. NA
Sample size	8	Y;V	Explain how the study size was arrived at. NA
Missing data	9	Y;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. Yes; P6, L127
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses. Yes; P6, L116
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. Yes; P6, L119
	10c	V	For validation, describe how the predictions were calculated. Yes; P6, L126
	10d	Y;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models. Yes; P6, L159

	0e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	P;V	Provide details on how risk groups were created, if done.	Yes; P6, L111
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results				
Participants	3a	P;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	3b	P;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, Table2
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Yes
Model specification	5a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	5b	D	Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	P;V	Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	P;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L236
Interpretation	9a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L217
	9b	P;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L198
Implications	20	P;V	Discuss the potential clinical use of the model and implications for future research.	Yes, P9, L193
Other information				
Supplementary information	21	P;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	P;V	Give the source of funding and the role of the funders for the present study.	NA



TRIPOD Checklist: Prediction Model Development and Validation

1Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Yes; P1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Yes; P2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Yes; P3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Yes; P4, L76-79
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Yes; P4, L83-92
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Yes; P4, L83-100
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Yes
	5b	D;V	Describe eligibility criteria for participants.	Yes; P4, L103
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Yes; P6, L111
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Yes; P6, L116
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Yes; P6, L127
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Yes; P6, L125
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Yes; P6, L130-138
	10c	V	For validation, describe how the predictions were calculated.	Yes; P6, L139
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Yes; P7, L159
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Yes; P7, L137
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Yes; P6, L111
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180 and SupTable2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, SupTable3
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Yes, SupTable1
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	15b	D	Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L246
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L237
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L210-245
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Yes, P12, L254
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	NA

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Severe Acute Kidney Injury Predicting Model based on transcontinental databases: a single-center prospective study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054092.R3
Article Type:	Original research
Date Submitted by the Author:	11-Dec-2021
Complete List of Authors:	Liang, Qiqiang; Zhejiang University School of Medicine Second Affiliated Hospital Xu, Yongfeng; Zhejiang University School of Medicine Second Affiliated Hospital Zhou, Yu; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Xinyi; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Juan; Zhejiang University School of Medicine Second Affiliated Hospital Huang, Man; Zhejiang University School of Medicine Second Affiliated Hospital,
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics
Keywords:	Acute renal failure < NEPHROLOGY, INTENSIVE & CRITICAL CARE, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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4 **1 Severe Acute Kidney Injury Predicting Model based on transcontinental**
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6 **2 databases: a single-center prospective study**
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9 **3** Qiqiang Liang¹; Yongfeng Xu¹; Yu Zhou²; Xinyi Chen², MM; Juan Chen²; Man Huang^{1*}
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14 **5** China.
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4 **23 Abstract:**

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6 **24 Objectives:** There are many studies of acute kidney injury (AKI) diagnosis models lack of external
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9 **25 validation and prospective validation.** We constructed the models using three databases to predict severe
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11 **26 AKI within 48 hours in intensive care unit (ICU) patients.**

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14 **27 Design:** A retrospective and prospective cohort study.

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17 **28 Setting:** We studied critically ill patients in our database (SHZJU-ICU) and two other public databases,
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19 **29 the Medical Information Mart for Intensive Care (MIMIC) and AmsterdamUMC databases, including**
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21 **30 basic demographics, vital signs, and laboratory results.** We predicted the diagnosis of severe AKI in
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23 **31 patients in the next 48 hours using machine-learning algorithms with the three databases.** Then, we
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25 **32 carried out real-time severe AKI prediction in the prospective validation study at our center for one year.**

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29 **33 Participants:** All patients included in three databases with uniform exclusion criteria.

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32 **34 Primary and secondary outcome measures:** Effect evaluation index of prediction models.

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35 **35 Results:** We included 58492 patients, and a total of 5257 (9.0%) patients met the definition of severe
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37 **36 AKI.** In the internal validation of the SHZJU-ICU and MIMIC databases, the best area under the receiver
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39 **37 operating characteristic curve (AUROC) of the model was 0.86.** The external validation results by
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41 **38 AmsterdamUMC database were also satisfactory, with the best AUROC of 0.86.** A total of 2532 patients
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43 **39 were admitted to the center for prospective validation; 358 positive results were predicted, and 344**
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45 **40 patients were diagnosed with severe AKI, with the best sensitivity of 0.72, the specificity of 0.80, and**
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47 **41 the AUROC of 0.84.**

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53 **42 Conclusion:** The prediction model of severe AKI exhibits promises as a clinical application based on
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55 **43 dynamic vital signs and laboratory results of multi-center databases with prospective and external**
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57 **44 validation.**

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4 45 **Keywords:** Machine learning; Acute kidney injury; Real-time prospective validation; External
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6 46 validation.

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8
9 47 **Strengths and limitations of this study:**

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11 48 A prospective validation in machine learning of AKI research rather than other studies;

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13 49 Three large database containing different national populations and regions;

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15 50 Variable's sampling limited by the monitoring frequency of clinical data;

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17 51 Differences in the samples proportion of three databases;

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19 52 The dimensions of variables are not rich enough.

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21 53 **Data sharing statement:** No data available.

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25 55 **Introduction:**

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27 56 Acute kidney injury (AKI), as a common clinical complication in the intensive care unit (ICU),

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29 57 significantly increases the duration of hospitalization and mortality[1]. AKI is divided into three types

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31 58 according to the various aetiologies: prerenal (renal hypoperfusion), intrarenal (vascular, glomerular, or

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33 59 tubulointerstitial lesions), and postrenal (urinary tract obstruction)[2]. Although nearly all diseases

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35 60 associated with ICU admission may cause AKI, acute tubular necrosis (ATN) and prerenal azotaemia

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37 61 are the most common causes[3].

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39 62 All AKI diagnostic criteria including the latest Kidney Disease: Improving Global Outcomes (KDIGO)

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41 63 standard are currently based on the creatinine level and urine volume[4]. However, the increase in the

42
43 64 creatinine level or decrease in the urine volume lags the onset of AKI[2]. Many studies have suggested

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45 65 that early diagnosis and treatment of reversible AKI can reduce mortality[5]. Therefore, the creatinine

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47 66 level and urine volume are not satisfactory to meet clinical diagnostic demands. Consequently, many

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4 67 researchers have tried to develop an early warning model by analysing the risk factors for AKI[6].
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6 68 Patient complications, such as diabetes, hypertension, cardiovascular disease, chronic liver disease,
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9 69 sepsis, and trauma, are identified as important risk factors for AKI[7]. The AKI prediction model and
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11 70 scoring system developed based on high-risk factors has gradually become the focus of research
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14 71 considering the lower clinical application threshold compared with that of new biomarkers[6]. Although
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17 72 most previous prediction models use the multiple logistic regression model, a variety of AKI prediction
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19 73 models based on machine learning have resulted in satisfactory outcomes[6]. Since the first AKI
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22 74 prediction model study based on artificial intelligence was published in 2016, researchers have built more
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25 75 than 20 published AKI prediction models successively by using local or multi-centre databases[6,8-14].
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27 76 The results indicate that these models can predict the occurrence of AKI and the need for renal
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30 77 replacement therapy (RRT) within 24 or 48 hours, with accuracies ranging from 81% to 97%[6,15]. In
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33 78 addition, many studies have focused on subspecialized conditions, including cardiac surgery, trauma,
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36 79 and burns[14-16]. However, the common defect in these studies is the lack of external validation and
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39 80 prospective validation, which causes the prediction model to deviate from the clinical scenarios and limits
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42 81 extrapolation beyond the scope of the data.

43 82 In this study, we built models to predict AKI within 48 hours in critically ill patients by using
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46 83 transcontinental three databases. Then, we evaluated the clinical effect of the model through a one-year
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49 84 prospective validation at our centre.

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52 53 86 **Methods:**

54 55 56 87 **Study design and setting**

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58 88 We collected patients using three ICU databases and prospectively validated the models in our centre.
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4 89 The first database was our centre general ICU database (SHZJU-ICU) of the Second Affiliated Hospital
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6 90 of Zhejiang University School of Medicine, an academic teaching hospital. Since its establishment in
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9 91 2017, it has included 12000 ICU patients' data and is updated daily. The Medical Information Mart for
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11 92 Intensive Care (MIMIC) III database, the second one, is an open ICU database provided by the
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13 93 Massachusetts Institute of Technology and includes nearly 60000 ICU patients from North America[17].
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16 94 Lastly, the AmsterdamUMC database is an available European ICU database with health data related to
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19 95 23000 patients admitted to ICUs in parts of Europe[18]. The research flow chart is shown in Figure 1.
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97 **Study definition**

27 98 In this study, the diagnosis of AKI was confirmed based on three stages according to the KDIGO
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29 99 criteria[4]. We defined the patients who met the KDIGO AKI II and III criteria as severe AKI groups
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31
32 100 and the others as negative groups. We excluded patients with lack of creatinine measurements during
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35 101 admission, patients with creatinine baseline more than 3.0 mg/dL at admission, patients who met severe
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37 102 AKI diagnosis within 24 hours, and patients who used RRT within 48 hours after admission[19]. In
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40 103 addition, we excluded pregnant women, patients younger than 14 years old, and patients hospitalized in
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43 104 the ICU for fewer than 48 hours. After the patient was admitted to ICU, we performed a prediction every
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45 105 24 hours and recorded a prediction time. If the patient was diagnosed with severe AKI within 48 hours,
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48 106 the predictive time was defined as a positive predictive point, and the others were defined as a negative
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51 107 point. The study was evaluated and approved by the Ethics Committee of the Second Affiliated Hospital
52
53 108 of Zhejiang University School of Medicine as study number 2019-078.

56 109 **Data Collection**

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58 110 The variables included demographic data, vital signs, basic and primary diseases, laboratory results,
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4 111 important operation records, and drug records. Comorbidity included hypertension, diabetes, cardiopathy,
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6 112 liver disease, and malignant tumors. The primary disease was the main cause of admission to the ICU
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9 113 following the ICD-10 codes. The vital signs and clinical laboratory results were transformed into
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11 114 different variables according to the average, variance, maximum, minimum, and final value before
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14 115 diagnosis. We use a method similar to the forward incremental method in the multivariate logic
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17 116 regression model, that is, the combination of embedded feature selection and forward addition for feature
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20 117 selection. First of all, all variables are trained in the model, then list by variables importance. variables
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22 118 are added to the model one by one according to the variable importance. a variable is retained if it causes
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25 119 the AUC growth to be greater than 0.01, otherwise delete it. We transformed the MIMIC and
26
27 120 AmsterdamUMC databases according to our centre database structure, unifying the unit and diagnostic
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29
30 121 codes. We deleted variables missing more than 50%. Variables missing more than 30% but less than 50%
31
32 122 are listed to clinicians who determine the potential correlation between these variables and AKI. We
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34
35 123 carry out multiple interpolation for these variables which clinicians require to be retained, and the others
36
37
38 124 deleted. Variables missing less than 30% are fill in multiple interpolation. All Missing data between three
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40 125 databases and values included in the model shown in supplementation file Table S1.

42 126 **Model construction and external validation**

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45 127 The ratio of the training and internal validation sets was 4:1. The SHZJU and MIMIC databases
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48 128 training sets were mixed into a new training set. There were more negative data than positive data, so we
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51 129 randomly sampled the negative datasets and constructed a new data subset with a sampling ratio of
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53 130 positive and negative data of 1:5 in model building in order to extract the importance variables. In the
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56 131 subsequent model validation, we adopted the original data set. We used multiple logistic regression,
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58 132 random forest, XGBoost, AdaBoost, LightGBoost, gradient boosting decision tree (GBDT), and debug
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4 133 to assess the variables and model-related parameters by the fivefold cross-validation method. After the
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6 134 models were built, we used the SHZJU-ICU and MIMIC test sets for internal validation of the model and
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9 135 the AmsterdamUMC database for external validation. The most appropriate cut-off value was determined
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12 136 according to the K-S curve. The prediction model represents the results of each prediction with a
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14 137 probability between 0 to 1.0. We define results more than 0.4 as high-risk, that is, positive results, and
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17 138 the rest as negative results. Through internal validation and external validation, we calibrated the model
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19 139 by adjusting the super-parameters and using the Platt calibration algorithm and compared the calibration
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21
22 140 effect by drawing a reliability diagram. All model building and validation processes were performed in
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25 141 Python 3.6.

27 142 **Prospective validation**

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30 143 The prospective research period was 2020.01.01 to 2020.12.31. We collected real-time data when
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32 144 patients were admitted to the ICU, transformed the data according to the requirements, and formed a
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34 145 complete sample for the prediction model after passing the integrity test. We had established a
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37 146 visualization scheme and allowed researchers to review the predictions daily. The daily prediction results
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40 147 were not publicly accessible during the study to avoid affecting clinicians' decisions, but the diagnosis
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43 148 results were available to the researchers as visual graphics. We sampled the 20% predicted data every
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46 149 month and deleted samples with more than 50% missing values to ensure data correctness. When a patient
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48 150 has the following conditions, AKI prediction system will end the patient's prospective prediction: A. a
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51 151 positive diagnosis; B. Transfer out of ICU or death with negative diagnosis. All diagnosis of severe AKI
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53 152 needs to be reviewed by two ICU attending physicians independently, and if the they have different
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56 153 opinion, the third one will be appealed.

58 154 **Statistical analysis:**

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4 155 The population characteristics were reported as the medians and inter-quartile ranges (IQRs) for
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6 156 skewed data and the means and standard deviations for normally distributed data. The independent
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9 157 sample T-test was used for normally distributed data, and the rank-sum test was used for the rest.
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12 158 Dichotomous variables were assessed by the chi-square test, and a P value less than 0.05 was considered
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14 159 statistically significant. The non-normally distributed data were analyzed by exponential transformation
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17 160 and logarithmic transformation. The effect of the model was evaluated by parameters such as the
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20 161 AUROC, accuracy, specificity, and F1-score.

22 162 **Patient and Public Involvement:**

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25 163 The information of cases in three databases was in a state of complete desensitization in the process
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27 164 of building the model. During the prospective study, all the patients signed an informed consent form at
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30 165 the beginning of admission to ICU. The real-time data discussed and used by only the study members,
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33 166 and were not made public during the study period. All data were anonymized before the authors accessed
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35 167 them for the purpose of this study. Therefore, patients' priorities, experience, and preferences will not
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38 168 affect the development of the research question and outcome measures. If necessary, we will inform
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40 169 patients of relevant research results by telephone.

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45 171 **Results:**

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48 172 According to the inclusion criteria and exclusion criteria, we selected 58492 patients from three
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50 173 databases who met the requirements of the study, including 6461 patients from the SHZJU-ICU database,
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53 174 36690 patients from the MIMIC database, and 15341 patients from the AmsterdamUMC database. A
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56 175 total of 5257 (9.0%) patients met the definition of severe AKI (11.8% in SHZJU-ICU, 7.6% in MIMIC,
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59 176 and 10.9% in AmsterdamUMC). The distributions of age and sex in the three centers were similar, but
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177 the differences in race were large. Asian patients accounted for more than 99% in the SHZJU-ICU
 178 database, and only approximately 2.5% in the MIMIC database. White people accounted for more than
 179 70% of the MIMIC database. In addition, patients from the MIMIC database had a higher incidence of
 180 the tumor, liver cirrhosis, diabetes, and hypertension. Patients in the AmsterdamUMC and SHZJU-ICU
 181 databases had a higher proportion of mechanical ventilation and overall survival rate. Severe AKI
 182 patients had longer ICU hospital stays and higher mortality. More details are presented in Table 1.
 183 Table 1: Clinical Demographics and Outcomes in patients with or without severe acute
 184 kidney injury.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P- valu e	MIMIC Negative (N=33879)	MIMIC Severe AKI (N=2811)	P- value	AmsterdamUMC Negative (N=13661)	AmsterdamUMC severe AKI (N=1680)	P- value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.00 4	62.0 [45.0-76.0]	64.0 [52.0-76.0]	<0.001	64.5 [54.5,74.5]	64.3 [52.5,78.5]	0.04
Gender, male (%)	3561 (64.9)	438 (59.8)	0.00 7	18976 (56.0)	1524 (54.2)	0.06	8920 (65.3)	1054 (63.9)	0.03
Race							/	/	/
White	3 (0.05)	1 (0.1)	1	23796 (70.2)	2005 (71.3)	0.23	/	/	/
Black	1 (0.02)	0	1	2455 (7.2)	199 (7.1)	0.45	/	/	/
Asian	5691(99.9)	764 (99.7)	1	918 (2.7)	70 (2.5)	0.54	/	/	/
Other	0	1 (0.1)	1	6710 (19.8)	537 (19.1)	0.34	/	/	/
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.0 01	1.1 (0.41)	1.1 (0.50)	0.04	1.2 (0.35)	1.1 (0.38)	<0.00 1
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.0 01	17 (12)	23 (12)	<0.001	18 (13)	23 (10)	<0.00 1
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.0 01	6652 (19.6)	752 (26.8)	<0.001	/	/	/
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	1180 (3.5)	426 (15.2)	<0.001	/	/	/
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	4840 (14.3)	336 (12.0)	0.001	/	/	/
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.00 2	7250 (21.4)	789 (28.1)	<0.001	/	/	/
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	16328 (48.2)	1513 (53.8)	<0.001	/	/	/
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.0 01	13009 (38.4)	1503(53.5)	<0.001	7718(56.5)	1248(74.3)	<0.00 1

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Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	12455 (36.7)	1430 (50.8)	<0.001	/	/	/
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	51.0 [28.5-110.3]	103.4 [50.1-261.3]	<0.001	24.0 [19.8,63.5]	142.0 [45.4,394.2]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	25648 (75.7)	1356 (48.2)	<0.001	10942(80.1)	1033 (61.5)	<0.001

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185 SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university
186 school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile
187 Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood
188 urea nitrogen.

189 There were significant differences in the important parameters of the variables among the different
190 models (see Figure S1). However, the trend of the creatinine level in the past week was still an important
191 variable, followed by urine volume, blood urea nitrogen level, temperature, and length of ICU stay. The
192 cut-off value used to distinguish between a negative and positive prediction was determined by the K-S
193 curve, with value of 0.423 (see Figure S2). The GBDT model had the best prediction effect in the test
194 set, followed by XGBoost and LightGBoost. In the two central internal validation sets, the two best-
195 performing machine learning algorithms with great AUROC are LightGBoost (SHZJU-ICU of 83.2%,
196 MIMIC of 86.0%) and XGBoost (SHZJU-ICU 85.9%, MIMIC 85.6%), as detailed in Figure 2. Overall,
197 the sensitivity (SHZJU-ICU 0.84, MIMIC 0.83) and the negative predictive value (SHZJU-ICU 0.90,
198 MIMIC 0.90) of the predictive model were high, but the specificity was general (SHZJU-ICU 0.79,
199 MIMIC 0.75), as shown in Table 2. In the external validation based on AmsterdamUMC database, the
200 overall model validation effect results were satisfactory, and XGBoost had the best performance, with
201 an AUROC of 0.84, as shown in Figure 2 and Table 2.

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203 Table 2: Model validation results by three databases with machine learning algorithm

Model	AUROC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1
Internal validation with SHZJU-ICU database							
Logistic regression	0.748	0.662	0.834	0.576	0.496	0.874	0.622
LightGBoost	0.832	0.741	0.839	0.692	0.576	0.896	0.683

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GBDT	0.845	0.765	0.843	0.725	0.606	0.902	0.705
AdaBoost	0.806	0.721	0.824	0.67	0.555	0.884	0.663
Random Forest	0.821	0.763	0.71	0.789	0.627	0.845	0.666
XGBoost	0.859	0.779	0.81	0.763	0.631	0.889	0.709
Internal validation with MIMIC database							
Logistic regression	0.733	0.695	0.643	0.72	0.535	0.801	0.584
LightGBost	0.86	0.768	0.822	0.741	0.613	0.893	0.702
GBDT	0.846	0.765	0.786	0.755	0.616	0.876	0.691
AdaBoost	0.837	0.732	0.831	0.683	0.567	0.89	0.674
Random Forest	0.832	0.738	0.791	0.712	0.578	0.872	0.668
XGBoost	0.856	0.758	0.833	0.721	0.598	0.895	0.695
External validation with AmsterdamUMC database							
Logistic regression	0.704	0.767	0.516	0.893	0.706	0.787	0.596
LightGBost	0.859	0.763	0.827	0.731	0.606	0.894	0.7
GBDT	0.861	0.764	0.84	0.727	0.606	0.901	0.704
AdaBoost	0.85	0.755	0.813	0.726	0.597	0.886	0.689
Random Forest	0.82	0.743	0.77	0.729	0.587	0.864	0.666
XGBoost	0.865	0.75	0.873	0.688	0.584	0.916	0.7
Prospective validation with SHZJU-ICU							
Logistic regression	0.758	0.772	0.648	0.834	0.662	0.826	0.655
LightGBost	0.819	0.796	0.596	0.895	0.74	0.816	0.66
GBDT	0.827	0.781	0.706	0.818	0.66	0.848	0.683
AdaBoost	0.808	0.766	0.686	0.805	0.638	0.837	0.661
Random Forest	0.804	0.755	0.715	0.775	0.613	0.845	0.66
XGBoost	0.841	0.779	0.724	0.807	0.652	0.854	0.686

204 AUROC: Area Under Receiver Operating Characteristic; PPV: Positive Predictive Value; NPV:
 205 Negative Predictive Value; SHZJU-ICU: The general ICU database of the second affiliated
 206 hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for
 207 Intensive Care; GBDT: Gradient Boosted Decision Tree.

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209 According to the inclusion and exclusion criteria, we delete 267 patients among 94 patients with
 210 creatinine baseline more than 3.0 mg/dL at admission, 39 patients met severe AKI diagnosis within 24
 211 hours, and 26 patients who used RRT within 48 hours after admission, 108 patients hospitalized in the
 212 ICU for fewer than 48 hours. A total of 2532 patients were admitted to our centre for prospective
 213 validation, and the prediction model made 16858 times predictions. In the prospective cohort, there was
 214 no significant difference in age, gender, baseline creatinine and urea nitrogen, and complications. The

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4 215 proportion of mechanical ventilation and the ICU stay time in AKI patients were longer with higher
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6 216 mortality. Above all, there was no significant difference between the prospective and the retrospective
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9 217 cohort. More detail sees in supplementation file Table S2. In the end, 358 positive results were predicted,
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11 218 and the rest were negative results. There are 344 patients with severe AKI were diagnosed and the
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14 219 prediction accuracy was 83.5%. The model with the highest area under the curve was XGBoost, 0.84
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17 220 with the best sensitivity of 0.72, the specificity of 0.80. The results of the prospective study are similar
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19 221 to those of the external validation of the model, and are relatively stable. More detail is presented in
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22 222 Figure 3 and Table 2.
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27 224 **Discussion:**

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30 225 In this study, we built predictive models by machine learning to predict the incidence of severe AKI
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32 226 with three databases in different regions and in the next 48 hours. After internal and external validation,
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35 227 prospective validation over one year was carried out to verify the model effects. The three databases
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38 228 come from three countries that are in Asia, Europe, and North America, which proves that the model is
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40 229 universal to some extent.

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43 230 Despite the huge amount of data, many databases are still not suitable for prospective research
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45 231 because they are not updated promptly. Tomasev, N and colleagues have provided research on AKI
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48 232 prediction models with a large amount of data[10]. The study covered 703782 adult patients with 6 billion
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51 233 individual items, including 620000 elements. In this study, a depth neural network model was used for
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53 234 real-time prediction. A total of 55.8% of severe AKI patients were predicted within the first 48 hours,
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56 235 although each accurate prediction was accompanied by two mispredictions[10]. This study provided a
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59 236 new scheme for real-time prediction and indicated that we should prospectively evaluate and
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4 237 independently validate models to explore their effectiveness. In a prospective study, Flechet, M et al
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6 238 compared an AKI prediction model with clinicians in 252 patients and found that the clinical effect of
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9 239 the random forest model for predicting AKI-II/III was equivalent to that of clinicians. Our prediction
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11 240 model graphical visualization of the model was installed in the centre's database for better usage. In
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14 241 addition, our database is updated daily to achieve daily predictions and present the results to researchers.
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17 242 In the prospective validation of our study, the stability of the prediction model confirmed its promise,
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19 243 which provides a basis for future research.

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22 244 There are many studies of artificial intelligence for predicting the occurrence of AKI, but most of them
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24 245 are single-centre studies, and the extrapolation effect has been controversial. In 2016, Koyner, J, and his
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27 246 colleague published the first study of an AKI prediction model based on multi-centre data. In all 202961
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29 247 patients, 17541 (8.6%) had AKI, 4251 (3.5%) had AKI-II, and 1242 (0.6%) had AKI-III. A multivariate
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31 248 logistic regression model was used to predict AKI in this study with an AUROC of 0.74 (95% CI=0.74).
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33 249 With the classification of AKI, the AUROC of the prediction model gradually increased to 0.84[8].
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36 250 Subsequently, the study team used a new machine learning algorithm, to build a more accurate model to
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38 251 predict the occurrence of AKI-II, with an AUROC of 0.9 within 24 hours and 0.87 within 48 hours[19].
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41 252 Recently, the research team included data from two other centres, namely, LUMC (N=200613) and NUS
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43 253 (N=246895), to externally validate the AKI-II prediction model with AUROCs reaching 0.85 to 0.86,
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45
46 254 suggesting that the artificial intelligence model has stable predictive ability[12]. This series of studies
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49 255 included many data points, suggesting the feasibility of artificial intelligence in the diagnosis of AKI,
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51
52 256 but the proportion of positive patients (3.5%) and ICU patients (30%) was too low to properly predict
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55 257 AKI. Our research is similar to the above. The SAHZJU-ICU database is a single-centre database
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58 258 representing south-eastern China, and the MIMIC database is a well-known open ICU database in the
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4 259 United States. The AmsterdamUMC database is a public database located in Europe. The population
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6 260 structure and diseases in the three databases are complete but different in the distribution of complications
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9 261 and race. Therefore, it provides a prediction model with unparalleled stability compared with other
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11 262 studies.

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17 264 **Limitations:**

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19 265 This retrospective multi-centre study was unable to carry out more clinical feature mining and
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22 266 comparison because of different data structures. The differences between the three databases partly
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25 267 reflect some demographic differences between Europe, the United States and China, resulting in a decline
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28 268 in the accuracy of the prediction model. There are some differences in the number of patients included
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31 269 in the three databases, which may affect the choice of variables. As a result of the study design, we
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34 270 deleted patients with ICU hospitalization of less than 48 hours, which may result in the exclusion of most
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37 271 relatively mild patients and may reduce false positives. Second, in the prospective data study in 2020,
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40 272 there may be deviations in the inclusion of patients in the centre, thus affecting the interpretation of the
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43 273 follow-up prospective results. Finally, given the low incidence of severe AKI and the great difference in
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46 274 the proportion of positive and negative samples, the data may be accidental. Our model seems to be
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49 275 superior to diagnostic non-AKI patients rather than AKI because of the proportion of positive data that
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52 276 we include. In the retrospective study, we reduced the proportion of negative data by randomization but
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55 277 retain all data in prospective phase with the sensitivity decreases.

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59 279 **Conclusion:**

60 280 Based on databases of patients of different races from different countries, we constructed stable

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4 281 machine learning models to predict the occurrence of AKI in the next 48 hours. Prospective validation
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6 282 through the implementation of an updated local database is an effective exploration of further research.
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11 284 Data sharing statement: No data available.

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14 285 Ethics approval: Our research was approved by the ethics committee of the Second Affiliated Hospital
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17 286 of Zhejiang University School of Medicine.

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19 287 Competing interests for authors: The authors declare that they have no competing interests.
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17 352 **Footnotes**

18
19 353 Contributions: Conceptualization, QL and MH; Methodology, YX; Software, YX; Validation, YZ, and
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22 354 YX.; Formal Analysis, JC and XC; Resources, MH; Data Curation, QL; Writing – Original Draft
23
24
25 355 Preparation, QL; Writing – Review & Editing, MH; Visualization, YX; Supervision, YZ and QL; Project
26
27 356 Administration, QL;

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29
30 357 **Funding:** This research received no specific grant from any funding agency in the public, commercial
31
32 358 or not-for-profit sectors.

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35 359 Conflicts of Interest: Not Applicable.

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38 360 Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or
39
40 361 reporting, or dissemination plans of this research.

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43 362 Provenance and peer review Not commissioned; externally peer reviewed.

44
45 363 Acknowledgements: Thank my colleagues in general ICU for cooperating with us in our prospective
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48 364 study. Thanks to two public databases namely MIMIC and AmsterdamUMC for providing important
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50 365 data. Thanks for all patient advisers.

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56 367 **Supplemental Figure:**

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4 369 Title and Description of data: The variable importance parameter histogram of early diagnosis prediction

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6 370 models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.

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11 372 Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative

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13 373 diagnosis of early diagnosis prediction models of severe AKI.

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18 375 Title and of Description data: Missing data between three databases in the study and values included in

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20 376 the model.

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22 377 File name: **Table S2.docx**

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24 378 Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model

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26 379 building set and prospective validation.

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28 380 File name: **Table S3.docx**

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30 381 Title of data: TRIPOD Checklist of Prediction Model Development and Validation

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32 382 Description of data: Writing norms of this type of research.

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36 384 **Figure Legend:**

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38 385 Figure 1: The research flow chart. The data collection time interval of the study was 7 days before

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40 386 diagnosis and the prediction interval was 48 hours. The early prediction model of AKI diagnosis was

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42 387 constructed and verified by our database and the MIMIC database and incorporated into the

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44 388 AmsterdamUMC database for external validation. We carried out a one-year prospective validation

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46 389 through the database of the centre.

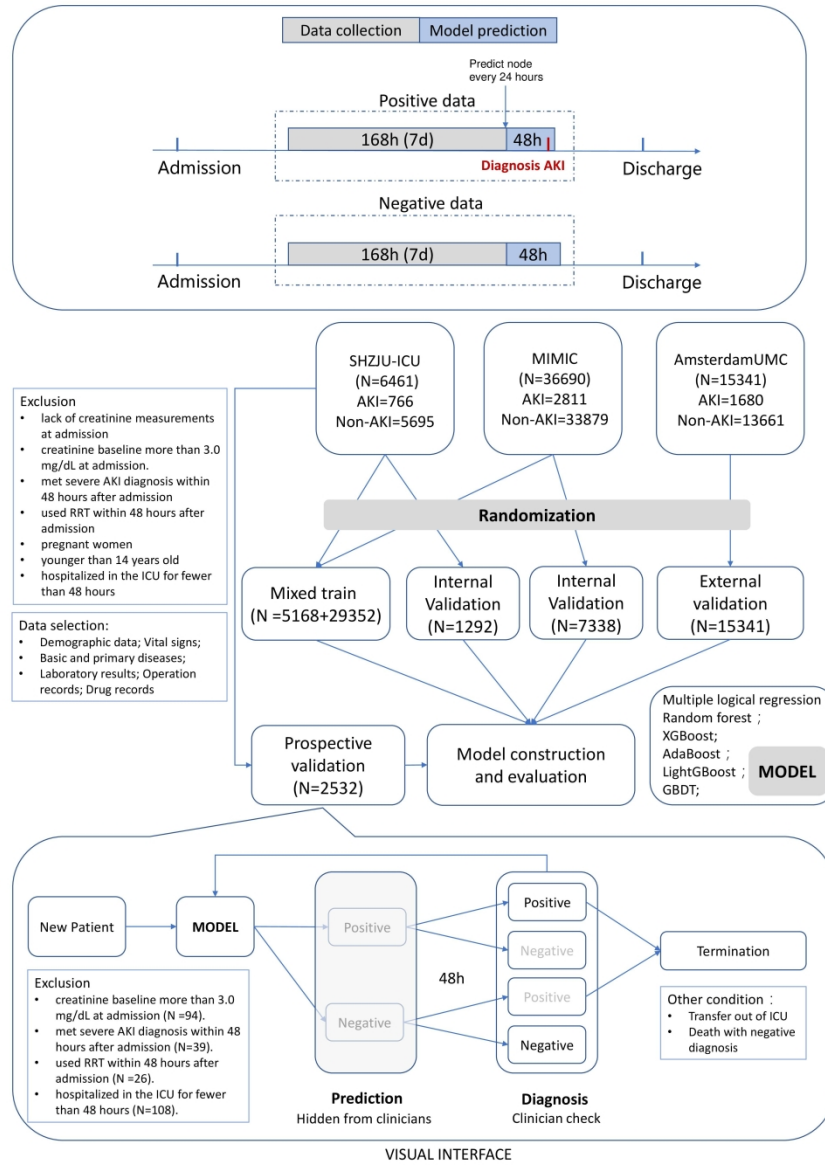
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48 390 Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC

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391 database.

392 Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and
393 the prospective validation in our center for 3B.

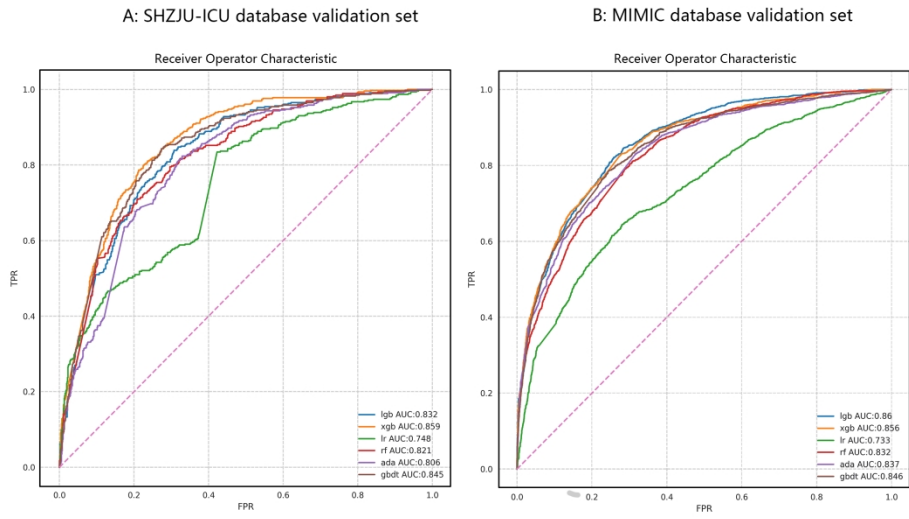
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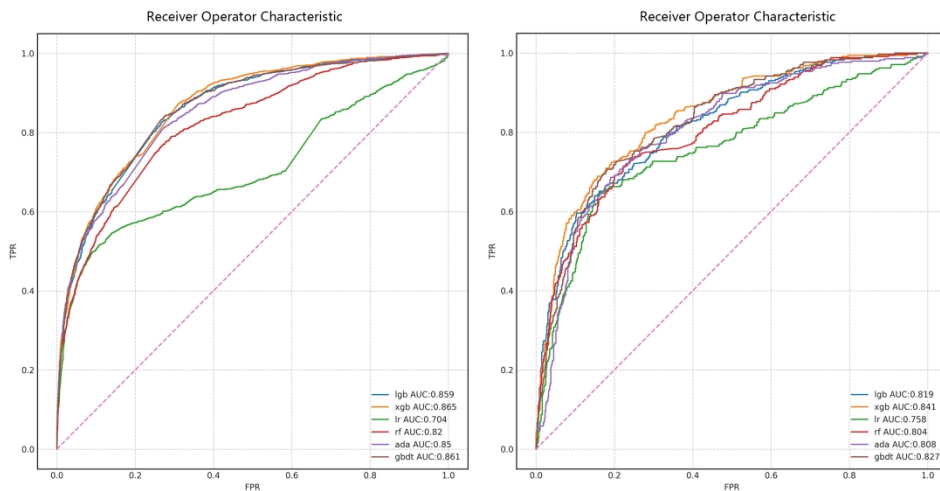
Internal validation set ROC curves



External and prospective validation set ROC curves

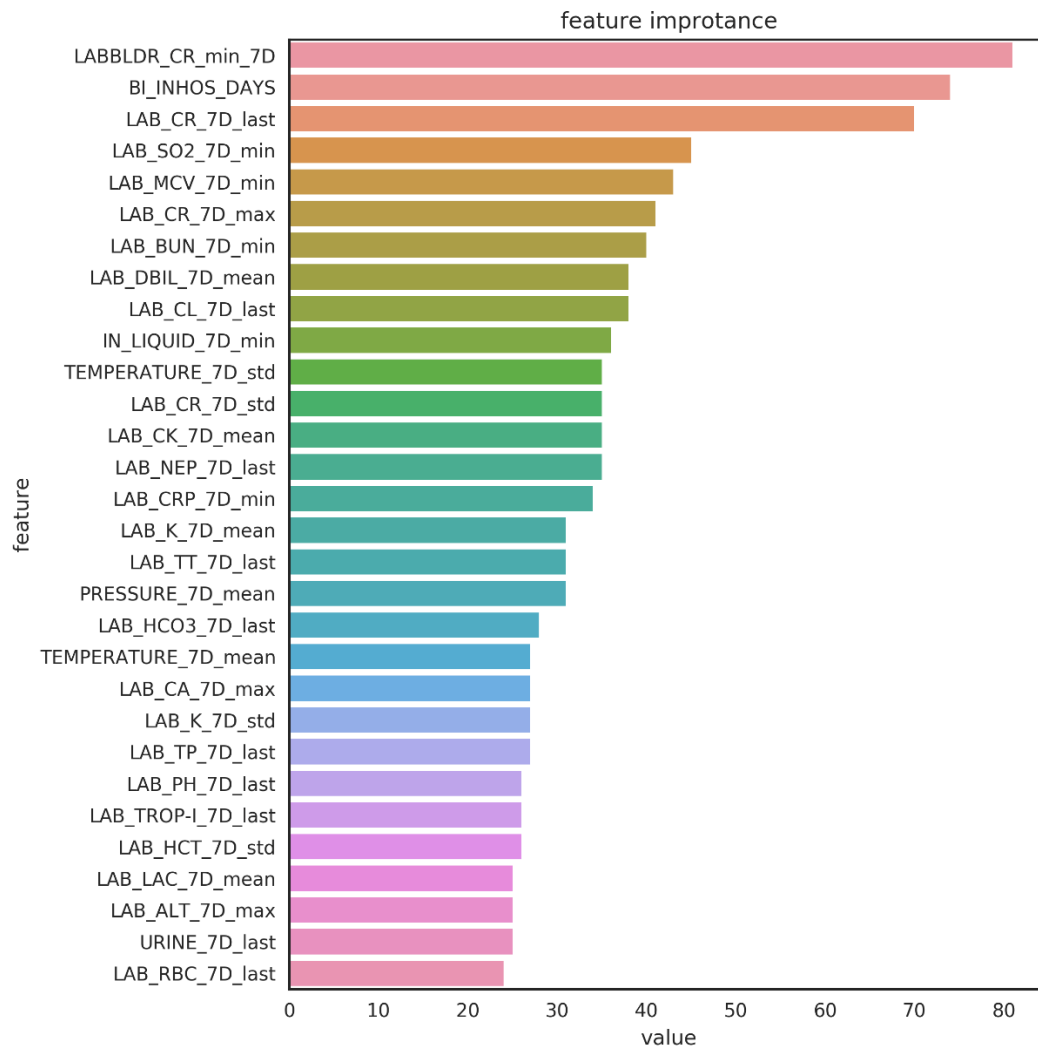
A: AmsterdamUMC database external validation set

B: SHZJU-ICU database prospective validation set

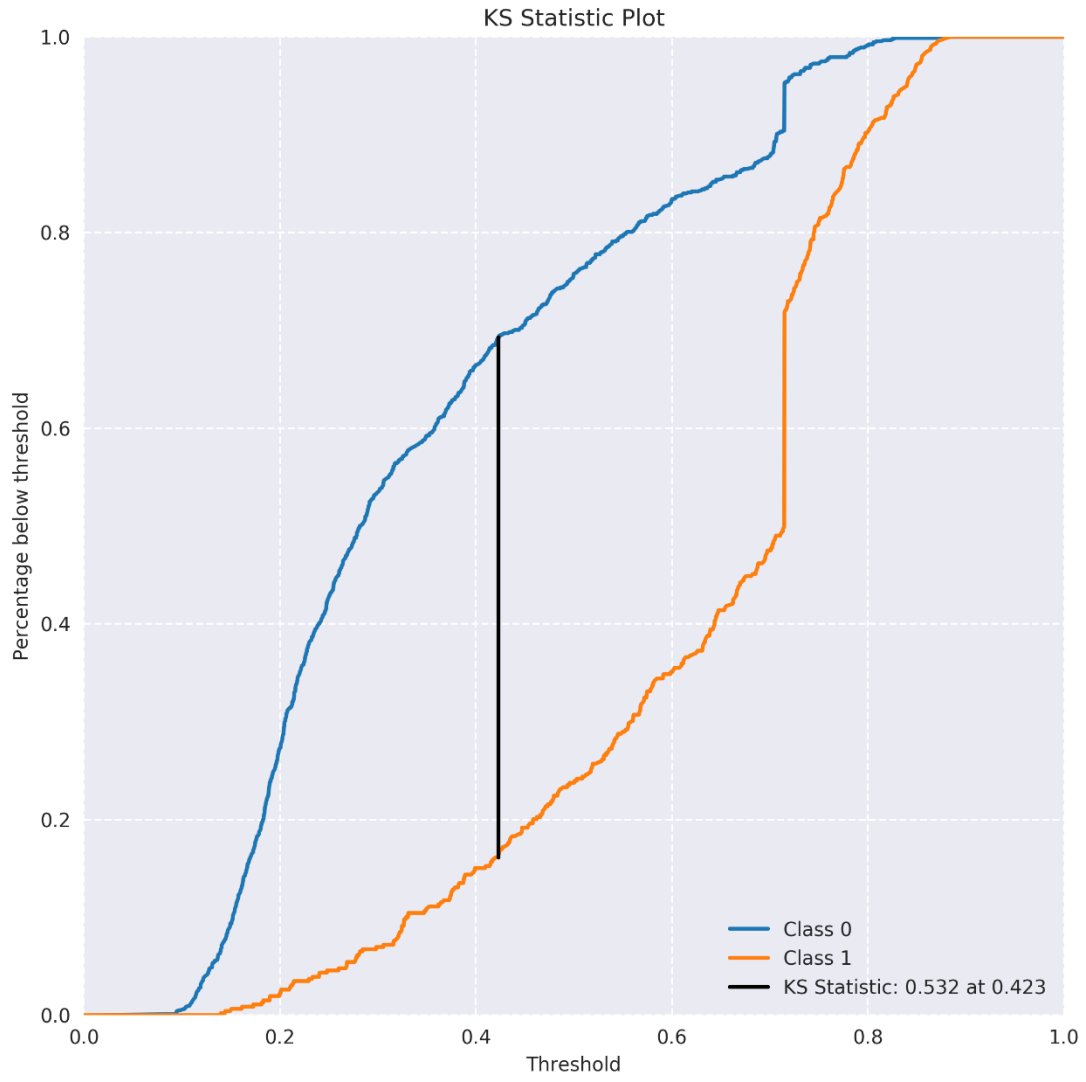


Supplemental Figure:File name: **Figure S1.tif**

Title and Description of data: The variable importance parameter histogram of early diagnosis prediction models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.

File name: **Figure S2.tif**

Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative diagnosis of early diagnosis prediction models of severe AKI.



For peer review only

File name: **Table S1.docx**

Title and of Description data: Missing data between three databases in the study and values included in the model.

	SHZJU-ICU	MIMIC	AmsterdamUMC	Including in Model
Age	√	√	√	√
Gender	√	√	√	√
Race	√	√	×	×
Primary disease	√	√	×	×
Comorbidity	√	√	×	×
Ventilation	√	√	√	√
Operation	√	√	×	×
ICU hours	√	√	√	√
Survived	√	√	√	√
Vital sign				
Temperature	√	√	√	√
Systolic pressure	√	√	√	√
Diastolic pressure	√	√	√	√
Respiratory rate	√	√	√	√
Heart rate	√	√	√	√
Oxygen saturation	√	√	√	√
Urine	√	√	√	√
GCS score	√	×	×	×
Laboratory results				
Scr	√	√	√	√
BUN	√	√	√	√
RBC	√	√	√	√
MCV	√	√	√	√
Hb	√	√	√	√
WBC	√	√	√	√
NEUT	√	√	√	√
PLT	√	√	√	√
HCV	√	√	×	×
TBLB	√	√	√	√
DBLB	√	√	√	√
IBLB	√	√	√	√
CRP	√	√	√	√
PCT	√	×	×	×
Serum kalium	√	√	√	√
Serum natrium	√	√	√	√
Serum chlorine	√	√	√	√

PT	√	√	√	√
APTT	√	√	√	√
INR	√	√	√	√
CK	√	√	√	√
LDH	√	√	√	√
Troponin	√	√	√	√
Blood glucose	√	√	√	√
PH	√	√	√	√
Lactic acid	√	√	√	√
Anion gap	√	√	√	√
ABC	√	√	√	√
SBC	√	√	√	√
PaCO ₂	√	√	√	√
PaO ₂	√	√	√	√

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; APTT: Activated partial thromboplastin time; INR: International normalized ratio; LDH: Lactate dehydrogenase; PaCO₂: Partial pressure of carbon dioxide; PaO₂ Partial pressure of oxygen; MCV: Mean corpuscular volume; PH: Potential of hydrogen; WBC: White blood cell count; NEUT: Proportion of neutrophils; CK: Creatine kinase; Scr: Serum Creatinine; BUN: Blood urea nitrogen; RBC: Red blood cell count; Hb: Hemoglobin; PT: Prothrombin time; TBLB: Total bilirubin; DBLB: Direct bilirubin; IBLB: Indirect bilirubin; CRP: C-reactive protein; HCV: Hematocrit value; PCT: Procalcitonin; ABC: Actual Bicarbonate Radical; SBC: Standard Bicarbonate Radical; PLT: Platelet count

File name: **Table S2.docx**

Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model

building set and prospective validation.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P-value	SHZJU-ICU Prospective Negative (N=2188)	SHZJU-ICU Prospective Positive (N=344)	P-value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.004	61.3 [47.5-73.4]	62.1 [51.2-70.5]	0.03
Gender, male (%)	3561 (64.9)	438 (59.8)	0.007	1365 (62.4)	207 (60.2)	0.438
Race						
White	3 (0.05)	1 (0.1)	1	2 (0.001)	0	1
Black	1 (0.02)	0	1	0	0	1
Asian	5691(99.9)	764 (99.7)	1	2185 (99.9)	344(100)	1
Other	0	1 (0.1)	1	1 (0.001)	0	1
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.001	0.8 (0.32)	0.9 (0.35)	<0.001
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.001	17 (11)	20 (10)	0.007
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.001	230 (10.5)	26 (7.6)	0.102
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	15 (0.7)	3 (0.8)	0.726
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	98 (4.5)	19 (5.7)	0.403
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.002	142 (6.5)	29 (8.6)	0.203
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	324(14.8)	56 (16.4)	0.466
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.001	1102 (50.4)	239 (69.5)	<0.001
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	1234(56.4)	160 (46.7)	0.001
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	58.7 [34.2-160.4]	145.6 [68.5-314.8]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	1868 (85.4)	178 (51.9)	<0.001

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood urea nitrogen.

File name: **Table S3.docx**

Title of data: TRIPOD Checklist of Prediction Model Development and Validation

Description of data: Writing norms of this type of research.

1Section/Topic	Checklist Item		Page
Title and abstract			
Title	1	Y;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. Yes; P1
Abstract	2	Y;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. Yes; P2
Introduction			
Background and objectives	3a	Y;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. Yes; P3
	3b	Y;V	Specify the objectives, including whether the study describes the development or validation of the model or both. Yes; P4, L76-79
Methods			
Source of data	4a	Y;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. Yes; P4, L80
	4b	Y;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. Yes; P4, L84-86
Participants	5a	Y;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. Yes
	5b	Y;V	Describe eligibility criteria for participants. Yes; P5, L104
	5c	Y;V	Give details of treatments received, if relevant. NA
Outcome	6a	Y;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed. Yes; P6, L111
	6b	Y;V	Report any actions to blind assessment of the outcome to be predicted. NA
Predictors	7a	Y;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. Yes; P6, L116
	7b	Y;V	Report any actions to blind assessment of predictors for the outcome and other predictors. NA
Sample size	8	Y;V	Explain how the study size was arrived at. NA
Missing data	9	Y;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. Yes; P6, L127
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses. Yes; P6, L116
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. Yes; P6, L119
	10c	V	For validation, describe how the predictions were calculated. Yes; P6, L126
	10d	Y;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models. Yes; P6, L159

	0e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	P;V	Provide details on how risk groups were created, if done.	Yes; P6, L111
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results				
Participants	3a	P;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	3b	P;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180
	3c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, Table2
Model development	4a	D	Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	4b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Yes
Model specification	5a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	5b	D	Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	P;V	Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	P;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L236
Interpretation	9a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L217
	9b	P;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L198
Implications	20	P;V	Discuss the potential clinical use of the model and implications for future research.	Yes, P9, L193
Other information				
Supplementary information	21	P;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	P;V	Give the source of funding and the role of the funders for the present study.	NA



TRIPOD Checklist: Prediction Model Development and Validation

1Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Yes; P1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Yes; P2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Yes; P3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Yes; P4, L76-79
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Yes; P4, L83-92
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Yes; P4, L83-100
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Yes
	5b	D;V	Describe eligibility criteria for participants.	Yes; P4, L103
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Yes; P6, L111
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Yes; P6, L116
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Yes; P6, L127
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Yes; P6, L125
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Yes; P6, L130-138
	10c	V	For validation, describe how the predictions were calculated.	Yes; P6, L139
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Yes; P7, L159
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Yes; P7, L137
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Yes; P6, L111
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180 and SupTable2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, SupTable3
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Yes, SupTable1
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	15b	D	Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L246
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L237
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L210-245
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Yes, P12, L254
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	NA

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Severe Acute Kidney Injury Predicting Model based on transcontinental databases: a single-center prospective study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054092.R4
Article Type:	Original research
Date Submitted by the Author:	04-Feb-2022
Complete List of Authors:	Liang, Qiqiang; Zhejiang University School of Medicine Second Affiliated Hospital Xu, Yongfeng; Zhejiang University School of Medicine Second Affiliated Hospital Zhou, Yu; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Xinyi; Zhejiang University School of Medicine Second Affiliated Hospital Chen, Juan; Zhejiang University School of Medicine Second Affiliated Hospital Huang, Man; Zhejiang University School of Medicine Second Affiliated Hospital,
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Diagnostics
Keywords:	Acute renal failure < NEPHROLOGY, INTENSIVE & CRITICAL CARE, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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4 **1 Severe Acute Kidney Injury Predicting Model based on transcontinental**
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6 **2 databases: a single-center prospective study**
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4 **23 Abstract:**

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6 **24 Objectives:** There are many studies of acute kidney injury (AKI) diagnosis models lack of external
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9 **25 validation and prospective validation.** We constructed the models using three databases to predict severe
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12 **26 AKI within 48 hours in intensive care unit (ICU) patients.**

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14 **27 Design:** A retrospective and prospective cohort study.

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17 **28 Setting:** We studied critically ill patients in our database (SHZJU-ICU) and two other public databases,
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19
20 **29 the Medical Information Mart for Intensive Care (MIMIC) and AmsterdamUMC databases, including**
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22 **30 basic demographics, vital signs, and laboratory results.** We predicted the diagnosis of severe AKI in
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25 **31 patients in the next 48 hours using machine-learning algorithms with the three databases.** Then, we
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27
28 **32 carried out real-time severe AKI prediction in the prospective validation study at our center for one year.**

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30 **33 Participants:** All patients included in three databases with uniform exclusion criteria.

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32 **34 Primary and secondary outcome measures:** Effect evaluation index of prediction models.

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34
35 **35 Results:** We included 58492 patients, and a total of 5257 (9.0%) patients met the definition of severe
36
37
38 **36 AKI.** In the internal validation of the SHZJU-ICU and MIMIC databases, the best area under the receiver
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40
41 **37 operating characteristic curve (AUROC) of the model was 0.86.** The external validation results by
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44 **38 AmsterdamUMC database were also satisfactory, with the best AUROC of 0.86.** A total of 2532 patients
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46
47 **39 were admitted to the center for prospective validation; 358 positive results were predicted, and 344**
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50 **40 patients were diagnosed with severe AKI, with the best sensitivity of 0.72, the specificity of 0.80, and**
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53 **41 the AUROC of 0.84.**

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56 **42 Conclusion:** The prediction model of severe AKI exhibits promises as a clinical application based on
57
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59 **43 dynamic vital signs and laboratory results of multi-center databases with prospective and external**
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44 validation.

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4 45 **Keywords:** Machine learning; Acute kidney injury; Real-time prospective validation; External
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6 46 validation.

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9 47 **Strengths and limitations of this study:**

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11 48 A prospective validation in machine learning of AKI research rather than other studies;

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13 49 Three large database containing different national populations and regions;

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15 50 Variable's sampling limited by the monitoring frequency of clinical data;

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17 51 Differences in the samples proportion of three databases;

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19 52 The dimensions of variables are not rich enough.

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21 53 **Data sharing statement:** No data available.

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25 55 **Introduction:**

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27 56 Acute kidney injury (AKI), as a common clinical complication in the intensive care unit (ICU),

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29 57 significantly increases the duration of hospitalization and mortality[1]. AKI is divided into three types

30
31 58 according to the various aetiologies: prerenal (renal hypoperfusion), intrarenal (vascular, glomerular, or

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33 59 tubulointerstitial lesions), and postrenal (urinary tract obstruction)[2]. Although nearly all diseases

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35 60 associated with ICU admission may cause AKI, acute tubular necrosis (ATN) and prerenal azotaemia

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37 61 are the most common causes[3].

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39 62 All AKI diagnostic criteria including the latest Kidney Disease: Improving Global Outcomes (KDIGO)

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41 63 standard are currently based on the creatinine level and urine volume[4]. However, the increase in the

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43 64 creatinine level or decrease in the urine volume lags the onset of AKI[2]. Many studies have suggested

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45 65 that early diagnosis and treatment of reversible AKI can reduce mortality[5]. Therefore, the creatinine

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47 66 level and urine volume are not satisfactory to meet clinical diagnostic demands. Consequently, many

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4 67 researchers have tried to develop an early warning model by analysing the risk factors for AKI[6].
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6 68 Patient complications, such as diabetes, hypertension, cardiovascular disease, chronic liver disease,
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9 69 sepsis, and trauma, are identified as important risk factors for AKI[7]. The AKI prediction model and
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11 70 scoring system developed based on high-risk factors has gradually become the focus of research
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14 71 considering the lower clinical application threshold compared with that of new biomarkers[6]. Although
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17 72 most previous prediction models use the multiple logistic regression model, a variety of AKI prediction
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19 73 models based on machine learning have resulted in satisfactory outcomes[6]. Since the first AKI
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22 74 prediction model study based on artificial intelligence was published in 2016, researchers have built more
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25 75 than 20 published AKI prediction models successively by using local or multi-centre databases[6,8-14].
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27 76 The results indicate that these models can predict the occurrence of AKI and the need for renal
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30 77 replacement therapy (RRT) within 24 or 48 hours, with accuracies ranging from 81% to 97%[6,15]. In
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33 78 addition, many studies have focused on subspecialized conditions, including cardiac surgery, trauma,
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36 79 and burns[14-16]. However, the common defect in these studies is the lack of external validation and
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39 80 prospective validation, which causes the prediction model to deviate from the clinical scenarios and limits
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42 81 extrapolation beyond the scope of the data.

43 82 In this study, we built models to predict AKI within 48 hours in critically ill patients by using
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46 83 transcontinental three databases. Then, we evaluated the clinical effect of the model through a one-year
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49 84 prospective validation at our centre.

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52 53 86 **Methods:**

54 55 56 87 **Study design and setting**

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58 88 We collected patients using three ICU databases and prospectively validated the models in our centre.
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4 89 The first database was our centre general ICU database (SHZJU-ICU) of the Second Affiliated Hospital
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6 90 of Zhejiang University School of Medicine, an academic teaching hospital. Since its establishment in
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9 91 2017, it has included 12000 ICU patients' data and is updated daily. The Medical Information Mart for
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11 92 Intensive Care (MIMIC) III database, the second one, is an open ICU database provided by the
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13 93 Massachusetts Institute of Technology and includes nearly 60000 ICU patients from North America[17].
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16 94 Lastly, the AmsterdamUMC database is an available European ICU database with health data related to
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19 95 23000 patients admitted to ICUs in parts of Europe[18]. The research flow chart is shown in Figure 1.
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97 **Study definition**

26
27 98 In this study, the diagnosis of AKI was confirmed based on three stages according to the KDIGO
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30 99 criteria[4]. We defined the patients who met the KDIGO AKI II and III criteria as severe AKI groups
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33 100 and the others as negative groups. We excluded patients with lack of creatinine measurements during
34
35 101 admission, patients with creatinine baseline more than 3.0 mg/dL at admission, patients who met severe
36
37 102 AKI diagnosis within 24 hours, and patients who used RRT within 48 hours after admission[19]. In
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40 103 addition, we excluded pregnant women, patients younger than 14 years old, and patients hospitalized in
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42 104 the ICU for fewer than 48 hours. After the patient was admitted to ICU, we performed a prediction every
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44 105 24 hours and recorded a prediction time. If the patient was diagnosed with severe AKI within 48 hours,
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46 106 the predictive time was defined as a positive predictive point, and the others were defined as a negative
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48
49 107 point. The study was evaluated and approved by the Ethics Committee of the Second Affiliated Hospital
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51
52 108 of Zhejiang University School of Medicine as study number 2019-078.

55 109 **Data Collection**

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58 110 The variables included demographic data, vital signs, basic and primary diseases, laboratory results,
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4 111 important operation records, and drug records. Comorbidity included hypertension, diabetes, cardiopathy,
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6 112 liver disease, and malignant tumors. The primary disease was the main cause of admission to the ICU
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9 113 following the ICD-10 codes. The vital signs and clinical laboratory results were transformed into
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11 114 different variables according to the average, variance, maximum, minimum, and final value before
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14 115 diagnosis. We use a method similar to the forward incremental method in the multivariate logic
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17 116 regression model, that is, the combination of embedded feature selection and forward addition for feature
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19 117 selection. First of all, all variables are trained in the model, then list by variables importance. variables
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22 118 are added to the model one by one according to the variable importance. a variable is retained if it causes
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25 119 the AUC growth to be greater than 0.01, otherwise delete it. We transformed the MIMIC and
26
27 120 AmsterdamUMC databases according to our centre database structure, unifying the unit and diagnostic
28
29
30 121 codes. We deleted variables missing more than 50%. Variables missing more than 30% but less than 50%
31
32 122 are listed to clinicians who determine the potential correlation between these variables and AKI. We
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34
35 123 carry out multiple interpolation for these variables which clinicians require to be retained, and the others
36
37
38 124 deleted. Variables missing less than 30% are fill in multiple interpolation. All Missing data between three
39
40 125 databases and values included in the model shown in supplementation file Table S1.

42 43 126 **Model construction and external validation**

44
45 127 The ratio of the training and internal validation sets was 4:1. The SHZJU and MIMIC databases
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48 128 training sets were mixed into a new training set. There were more negative data than positive data, so we
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51 129 randomly sampled the negative datasets and constructed a new data subset with a sampling ratio of
52
53 130 positive and negative data of 1:5 in model building in order to extract the importance variables. In the
54
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56 131 subsequent model validation, we adopted the original data set. We used multiple logistic regression,
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58 132 random forest, XGBoost, AdaBoost, LightGBoost, gradient boosting decision tree (GBDT), and debug
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4 133 to assess the variables and model-related parameters by the fivefold cross-validation method. After the
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6 134 models were built, we used the SHZJU-ICU and MIMIC test sets for internal validation of the model and
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9 135 the AmsterdamUMC database for external validation. The most appropriate cut-off value was determined
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12 136 according to the K-S curve. The prediction model represents the results of each prediction with a
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15 137 probability between 0 to 1.0. We define results more than 0.4 as high-risk, that is, positive results, and
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18 138 the rest as negative results. Through internal validation and external validation, we calibrated the model
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20
21 139 by adjusting the super-parameters and using the Platt calibration algorithm and compared the calibration
22
23
24 140 effect by drawing a reliability diagram. All model building and validation processes were performed in
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27 141 Python 3.6.

27 142 **Prospective validation**

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30 143 The prospective research period was 2020.01.01 to 2020.12.31. We collected real-time data when
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33 144 patients were admitted to the ICU, transformed the data according to the requirements, and formed a
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36 145 complete sample for the prediction model after passing the integrity test. We had established a
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39 146 visualization scheme and allowed researchers to review the predictions daily. The daily prediction results
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42 147 were not publicly accessible during the study to avoid affecting clinicians' decisions, but the diagnosis
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45 148 results were available to the researchers as visual graphics. We sampled the 20% predicted data every
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48 149 month and deleted samples with more than 50% missing values to ensure data correctness. When a patient
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51 150 has the following conditions, AKI prediction system will end the patient's prospective prediction: A. a
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54 151 positive diagnosis; B. Transfer out of ICU or death with negative diagnosis. All diagnosis of severe AKI
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57 152 needs to be reviewed by two ICU attending physicians independently, and if the they have different
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60 153 opinion, the third one will be appealed.

58 154 **Statistical analysis:**

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4 155 The population characteristics were reported as the medians and inter-quartile ranges (IQRs) for
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6 156 skewed data and the means and standard deviations for normally distributed data. The independent
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9 157 sample T-test was used for normally distributed data, and the rank-sum test was used for the rest.
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12 158 Dichotomous variables were assessed by the chi-square test, and a P value less than 0.05 was considered
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14 159 statistically significant. The non-normally distributed data were analyzed by exponential transformation
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16
17 160 and logarithmic transformation. The effect of the model was evaluated by parameters such as the
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20 161 AUROC, accuracy, specificity, and F1-score.

22 162 **Patient and Public Involvement:**

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25 163 The information of cases in three databases was in a state of complete desensitization in the process
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27 164 of building the model. During the prospective study, all the patients signed an informed consent form at
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30 165 the beginning of admission to ICU. The real-time data discussed and used by only the study members,
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33 166 and were not made public during the study period. All data were anonymized before the authors accessed
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35 167 them for the purpose of this study. Therefore, patients' priorities, experience, and preferences will not
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38 168 affect the development of the research question and outcome measures. If necessary, we will inform
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40 169 patients of relevant research results by telephone.

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45 171 **Results:**

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48 172 According to the inclusion criteria and exclusion criteria, we selected 58492 patients from three
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50 173 databases who met the requirements of the study, including 6461 patients from the SHZJU-ICU database,
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53 174 36690 patients from the MIMIC database, and 15341 patients from the AmsterdamUMC database. A
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56 175 total of 5257 (9.0%) patients met the definition of severe AKI (11.8% in SHZJU-ICU, 7.6% in MIMIC,
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58
59 176 and 10.9% in AmsterdamUMC). The distributions of age and sex in the three centers were similar, but
60

177 the differences in race were large. Asian patients accounted for more than 99% in the SHZJU-ICU
 178 database, and only approximately 2.5% in the MIMIC database. White people accounted for more than
 179 70% of the MIMIC database. In addition, patients from the MIMIC database had a higher incidence of
 180 the tumor, liver cirrhosis, diabetes, and hypertension. Patients in the AmsterdamUMC and SHZJU-ICU
 181 databases had a higher proportion of mechanical ventilation and overall survival rate. Severe AKI
 182 patients had longer ICU hospital stays and higher mortality. More details are presented in Table 1.
 183 Table 1: Clinical Demographics and Outcomes in patients with or without severe acute
 184 kidney injury.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P- valu e	MIMIC Negative (N=33879)	MIMIC Severe AKI (N=2811)	P- value	AmsterdamUMC Negative (N=13661)	AmsterdamUMC severe AKI (N=1680)	P- value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.00 4	62.0 [45.0-76.0]	64.0 [52.0-76.0]	<0.001	64.5 [54.5,74.5]	64.3 [52.5,78.5]	0.04
Gender, male (%)	3561 (64.9)	438 (59.8)	0.00 7	18976 (56.0)	1524 (54.2)	0.06	8920 (65.3)	1054 (63.9)	0.03
Race							/	/	/
White	3 (0.05)	1 (0.1)	1	23796 (70.2)	2005 (71.3)	0.23	/	/	/
Black	1 (0.02)	0	1	2455 (7.2)	199 (7.1)	0.45	/	/	/
Asian	5691(99.9)	764 (99.7)	1	918 (2.7)	70 (2.5)	0.54	/	/	/
Other	0	1 (0.1)	1	6710 (19.8)	537 (19.1)	0.34	/	/	/
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.0 01	1.1 (0.41)	1.1 (0.50)	0.04	1.2 (0.35)	1.1 (0.38)	<0.00 1
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.0 01	17 (12)	23 (12)	<0.001	18 (13)	23 (10)	<0.00 1
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.0 01	6652 (19.6)	752 (26.8)	<0.001	/	/	/
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	1180 (3.5)	426 (15.2)	<0.001	/	/	/
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	4840 (14.3)	336 (12.0)	0.001	/	/	/
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.00 2	7250 (21.4)	789 (28.1)	<0.001	/	/	/
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	16328 (48.2)	1513 (53.8)	<0.001	/	/	/
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.0 01	13009 (38.4)	1503(53.5)	<0.001	7718(56.5)	1248(74.3)	<0.00 1

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Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	12455 (36.7)	1430 (50.8)	<0.001	/	/	/
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	51.0 [28.5-110.3]	103.4 [50.1-261.3]	<0.001	24.0 [19.8,63.5]	142.0 [45.4,394.2]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	25648 (75.7)	1356 (48.2)	<0.001	10942(80.1)	1033 (61.5)	<0.001

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185 SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university
186 school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile
187 Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood
188 urea nitrogen.

189 There were significant differences in the important parameters of the variables among the different
190 models (see Figure S1). However, the trend of the creatinine level in the past week was still an important
191 variable, followed by urine volume, blood urea nitrogen level, temperature, and length of ICU stay. The
192 cut-off value used to distinguish between a negative and positive prediction was determined by the K-S
193 curve, with value of 0.423 (see Figure S2). The GBDT model had the best prediction effect in the test
194 set, followed by XGBoost and LightGBoost. In the two central internal validation sets, the two best-
195 performing machine learning algorithms with great AUROC are LightGBoost (SHZJU-ICU of 83.2%,
196 MIMIC of 86.0%) and XGBoost (SHZJU-ICU 85.9%, MIMIC 85.6%), as detailed in Figure 2. Overall,
197 the sensitivity (SHZJU-ICU 0.84, MIMIC 0.83) and the negative predictive value (SHZJU-ICU 0.90,
198 MIMIC 0.90) of the predictive model were high, but the specificity was general (SHZJU-ICU 0.79,
199 MIMIC 0.75), as shown in Table 2. In the external validation based on AmsterdamUMC database, the
200 overall model validation effect results were satisfactory, and XGBoost had the best performance, with
201 an AUROC of 0.84, as shown in Figure 2 and Table 2.

202

203 Table 2: Model validation results by three databases with machine learning algorithm

Model	AUROC	Accuracy	Sensitivity	Specificity	PPV	NPV	F1
Internal validation with SHZJU-ICU database							
Logistic regression	0.748	0.662	0.834	0.576	0.496	0.874	0.622
LightGBoost	0.832	0.741	0.839	0.692	0.576	0.896	0.683

10

GBDT	0.845	0.765	0.843	0.725	0.606	0.902	0.705
AdaBoost	0.806	0.721	0.824	0.67	0.555	0.884	0.663
Random Forest	0.821	0.763	0.71	0.789	0.627	0.845	0.666
XGBoost	0.859	0.779	0.81	0.763	0.631	0.889	0.709
Internal validation with MIMIC database							
Logistic regression	0.733	0.695	0.643	0.72	0.535	0.801	0.584
LightGBost	0.86	0.768	0.822	0.741	0.613	0.893	0.702
GBDT	0.846	0.765	0.786	0.755	0.616	0.876	0.691
AdaBoost	0.837	0.732	0.831	0.683	0.567	0.89	0.674
Random Forest	0.832	0.738	0.791	0.712	0.578	0.872	0.668
XGBoost	0.856	0.758	0.833	0.721	0.598	0.895	0.695
External validation with AmsterdamUMC database							
Logistic regression	0.704	0.767	0.516	0.893	0.706	0.787	0.596
LightGBost	0.859	0.763	0.827	0.731	0.606	0.894	0.7
GBDT	0.861	0.764	0.84	0.727	0.606	0.901	0.704
AdaBoost	0.85	0.755	0.813	0.726	0.597	0.886	0.689
Random Forest	0.82	0.743	0.77	0.729	0.587	0.864	0.666
XGBoost	0.865	0.75	0.873	0.688	0.584	0.916	0.7
Prospective validation with SHZJU-ICU							
Logistic regression	0.758	0.772	0.648	0.834	0.662	0.826	0.655
LightGBost	0.819	0.796	0.596	0.895	0.74	0.816	0.66
GBDT	0.827	0.781	0.706	0.818	0.66	0.848	0.683
AdaBoost	0.808	0.766	0.686	0.805	0.638	0.837	0.661
Random Forest	0.804	0.755	0.715	0.775	0.613	0.845	0.66
XGBoost	0.841	0.779	0.724	0.807	0.652	0.854	0.686

204 AUROC: Area Under Receiver Operating Characteristic; PPV: Positive Predictive Value; NPV:
 205 Negative Predictive Value; SHZJU-ICU: The general ICU database of the second affiliated
 206 hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for
 207 Intensive Care; GBDT: Gradient Boosted Decision Tree.

208

209 According to the inclusion and exclusion criteria, we delete 267 patients among 94 patients with
 210 creatinine baseline more than 3.0 mg/dL at admission, 39 patients met severe AKI diagnosis within 24
 211 hours, and 26 patients who used RRT within 48 hours after admission, 108 patients hospitalized in the
 212 ICU for fewer than 48 hours. A total of 2532 patients were admitted to our centre for prospective
 213 validation, and the prediction model made 16858 times predictions. In the prospective cohort, there was
 214 no significant difference in age, gender, baseline creatinine and urea nitrogen, and complications. The

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4 215 proportion of mechanical ventilation and the ICU stay time in AKI patients were longer with higher
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6 216 mortality. Above all, there was no significant difference between the prospective and the retrospective
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8
9 217 cohort. More detail sees in supplementation file Table S2. In the end, 358 positive results were predicted,
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11 218 and the rest were negative results. There are 344 patients with severe AKI were diagnosed and the
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14 219 prediction accuracy was 83.5%. The model with the highest area under the curve was XGBoost, 0.84
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17 220 with the best sensitivity of 0.72, the specificity of 0.80. The results of the prospective study are similar
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19 221 to those of the external validation of the model, and are relatively stable. More detail is presented in
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22 222 Figure 3 and Table 2.
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27 224 **Discussion:**

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30 225 In this study, we built predictive models by machine learning to predict the incidence of severe AKI
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32 226 with three databases in different regions and in the next 48 hours. After internal and external validation,
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35 227 prospective validation over one year was carried out to verify the model effects. The three databases
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38 228 come from three countries that are in Asia, Europe, and North America, which proves that the model is
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40 229 universal to some extent.

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43 230 Despite the huge amount of data, many databases are still not suitable for prospective research
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45 231 because they are not updated promptly. Tomasev, N and colleagues have provided research on AKI
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48 232 prediction models with a large amount of data[10]. The study covered 703782 adult patients with 6 billion
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51 233 individual items, including 620000 elements. In this study, a depth neural network model was used for
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53 234 real-time prediction. A total of 55.8% of severe AKI patients were predicted within the first 48 hours,
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56 235 although each accurate prediction was accompanied by two mispredictions[10]. This study provided a
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59 236 new scheme for real-time prediction and indicated that we should prospectively evaluate and
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4 237 independently validate models to explore their effectiveness. In a prospective study, Flechet, M et al
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6 238 compared an AKI prediction model with clinicians in 252 patients and found that the clinical effect of
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9 239 the random forest model for predicting AKI-II/III was equivalent to that of clinicians. Our prediction
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11 240 model graphical visualization of the model was installed in the centre's database for better usage. In
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14 241 addition, our database is updated daily to achieve daily predictions and present the results to researchers.
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17 242 In the prospective validation of our study, the stability of the prediction model confirmed its promise,
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19 243 which provides a basis for future research.

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21
22 244 There are many studies of artificial intelligence for predicting the occurrence of AKI, but most of them
23
24 245 are single-centre studies, and the extrapolation effect has been controversial. In 2016, Koyner, J, and his
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27 246 colleague published the first study of an AKI prediction model based on multi-centre data. In all 202961
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29 247 patients, 17541 (8.6%) had AKI, 4251 (3.5%) had AKI-II, and 1242 (0.6%) had AKI-III. A multivariate
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31 248 logistic regression model was used to predict AKI in this study with an AUROC of 0.74 (95% CI=0.74).
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33 249 With the classification of AKI, the AUROC of the prediction model gradually increased to 0.84[8].
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36 250 Subsequently, the study team used a new machine learning algorithm, to build a more accurate model to
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38 251 predict the occurrence of AKI-II, with an AUROC of 0.9 within 24 hours and 0.87 within 48 hours[19].
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41 252 Recently, the research team included data from two other centres, namely, LUMC (N=200613) and NUS
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43 253 (N=246895), to externally validate the AKI-II prediction model with AUROCs reaching 0.85 to 0.86,
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45
46 254 suggesting that the artificial intelligence model has stable predictive ability[12]. This series of studies
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49 255 included many data points, suggesting the feasibility of artificial intelligence in the diagnosis of AKI,
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51
52 256 but the proportion of positive patients (3.5%) and ICU patients (30%) was too low to properly predict
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55 257 AKI. Our research is similar to the above. The SAHZJU-ICU database is a single-centre database
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58 258 representing south-eastern China, and the MIMIC database is a well-known open ICU database in the
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4 259 United States. The AmsterdamUMC database is a public database located in Europe. The population
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6 260 structure and diseases in the three databases are complete but different in the distribution of complications
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9 261 and race. Therefore, it provides a prediction model with unparalleled stability compared with other
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12 262 studies.

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17 264 **Limitations:**

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19 265 This retrospective multi-centre study was unable to carry out more clinical feature mining and
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22 266 comparison because of different data structures. The differences between the three databases partly
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25 267 reflect some demographic differences between Europe, the United States and China, resulting in a decline
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28 268 in the accuracy of the prediction model. There are some differences in the number of patients included
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31 269 in the three databases, which may affect the choice of variables. As a result of the study design, we
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34 270 deleted patients with ICU hospitalization of less than 48 hours, which may result in the exclusion of most
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37 271 relatively mild patients and may reduce false positives. Second, in the prospective data study in 2020,
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40 272 there may be deviations in the inclusion of patients in the centre, thus affecting the interpretation of the
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43 273 follow-up prospective results. Finally, given the low incidence of severe AKI and the great difference in
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46 274 the proportion of positive and negative samples, the data may be accidental. Our model seems to be
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49 275 superior to diagnostic non-AKI patients rather than AKI because of the proportion of positive data that
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52 276 we include. In the retrospective study, we reduced the proportion of negative data by randomization but
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55 277 retain all data in prospective phase with the sensitivity decreases.

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59 279 **Conclusion:**

60 280 Based on databases of patients of different races from different countries, we constructed stable

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4 281 machine learning models to predict the occurrence of AKI in the next 48 hours. Prospective validation
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6 282 through the implementation of an updated local database is an effective exploration of further research.
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11 284 Data sharing statement: No data available.
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14 285 Ethics approval: Our research was approved by the ethics committee of the Second Affiliated Hospital
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16
17 286 of Zhejiang University School of Medicine.
18

19 287 Competing interests for authors: There may be some potential competing interests between our
20
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22 288 research and “HealSci Technology Co. Beijing.”. In this study, we jointly complete the work including
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25 289 data integration and transcoding in model construction and model visualization projects based on contract.
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30 291 **Reference:**

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354 **Footnotes**

355 Contributions: Conceptualization, QL and MH; Methodology, YX; Software, YX; Validation, YZ, and
356 YX.; Formal Analysis, JC and XC; Resources, MH; Data Curation, QL; Writing – Original Draft
357 Preparation, QL; Writing – Review & Editing, MH; Visualization, YX; Supervision, YZ and QL; Project
358 Administration, QL;

359 **Funding:** This research received no specific grant from any funding agency in the public, commercial
360 or not-for-profit sectors.

361 Conflicts of Interest: There may be some potential competing interests between our research and
362 “HealSci Technology Co. Beijing.”. In this study, we jointly complete the work including data integration
363 and transcoding in model construction and model visualization projects based on contract.

364 Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or
365 reporting, or dissemination plans of this research.

366 Provenance and peer review Not commissioned; externally peer reviewed.

367 Acknowledgements: Thank my colleagues in general ICU for cooperating with us in our prospective
368 study. Thanks to two public databases namely MIMIC and AmsterdamUMC for providing important

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4 369 data. Thanks for all patient advisers.
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9 371 **Supplemental Figure:**

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11 372 File name: **Figure S1.tif**

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14 373 Title and Description of data: The variable importance parameter histogram of early diagnosis prediction
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16 374 models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.

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22 376 Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative
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24 377 diagnosis of early diagnosis prediction models of severe AKI.

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27 378 File name: **Table S1.docx**

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30 379 Title and of Description data: Missing data between three databases in the study and values included in
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32 380 the model.

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35 381 File name: **Table S2.docx**

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38 382 Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model
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40 383 building set and prospective validation.

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45 385 **Figure Legend:**

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48 386 Figure 1: The research flow chart. The data collection time interval of the study was 7 days before
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50 387 diagnosis and the prediction interval was 48 hours. The early prediction model of AKI diagnosis was
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52 388 constructed and verified by our database and the MIMIC database and incorporated into the
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54 389 AmsterdamUMC database for external validation. We carried out a one-year prospective validation
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57 390 through the database of the centre.
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391 Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC
392 database.

393 Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and
394 the prospective validation in our center for 3B.

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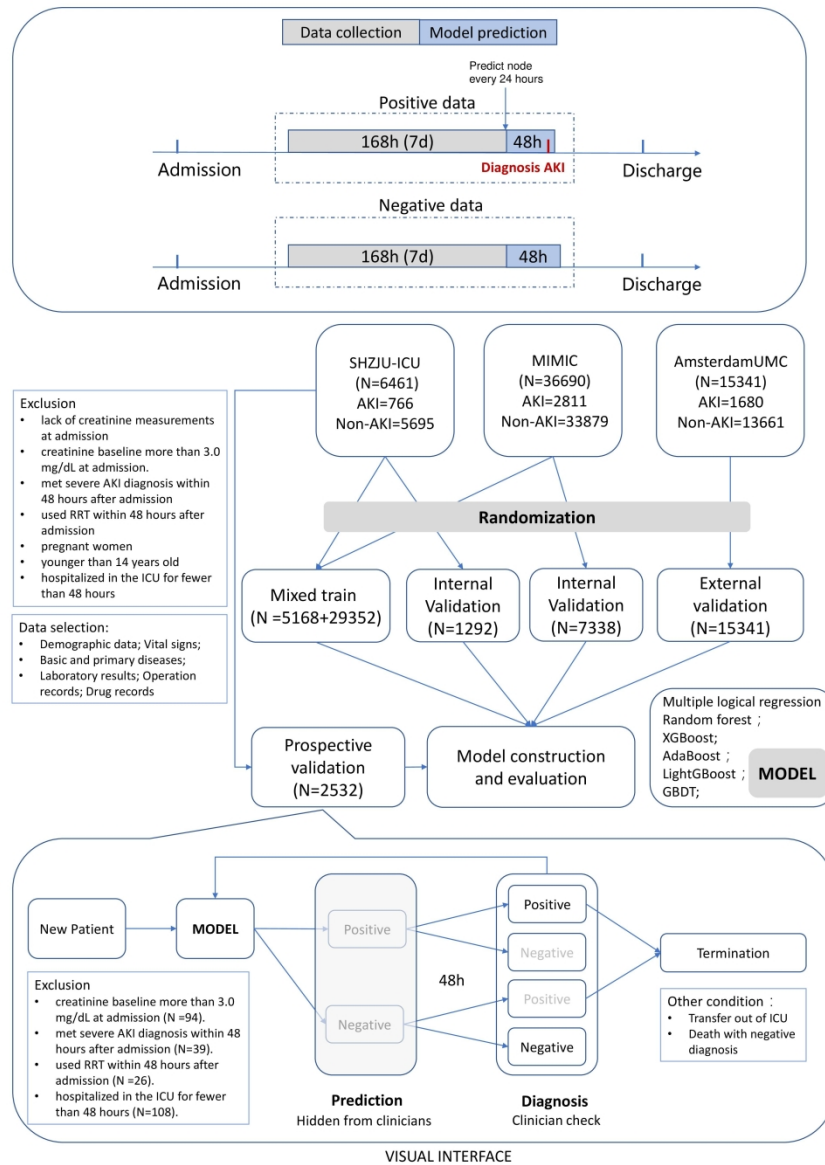


Figure 1: The research flow chart. The data collection time interval of the study was 7 days before diagnosis and the prediction interval was 48 hours. The early prediction model of AKI diagnosis was constructed and verified by our database and the MIMIC database and incorporated into the AmsterdamUMC database for external validation. We carried out a one-year prospective validation through the database of the centre.

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Internal validation set ROC curves

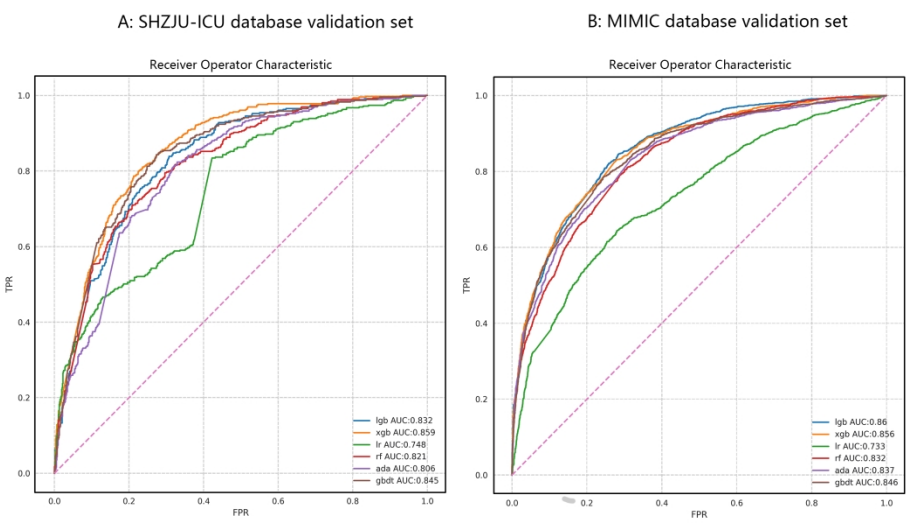


Figure 2: The AUROC curve of the internal validation set of the SHZJU-ICU database and the MIMIC database.

External and prospective validation set ROC curves

A: AmsterdamUMC database external validation set B: SHZJU-ICU database prospective validation set

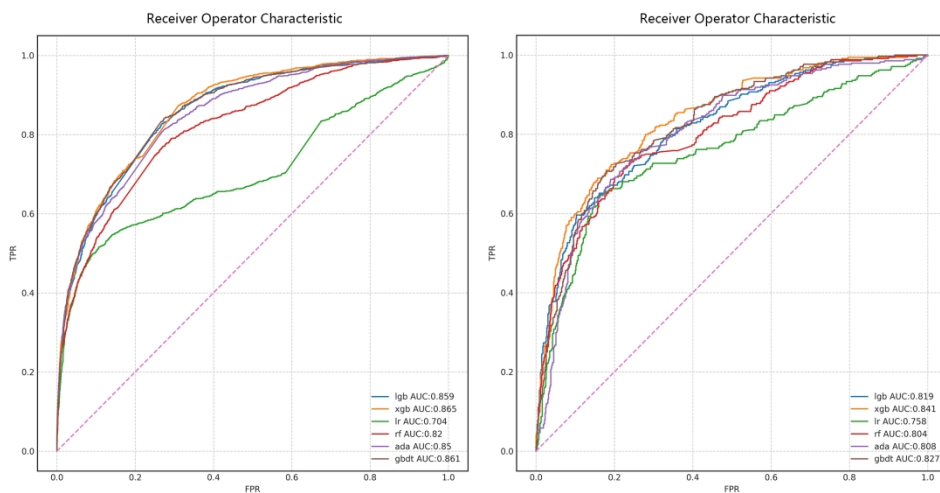


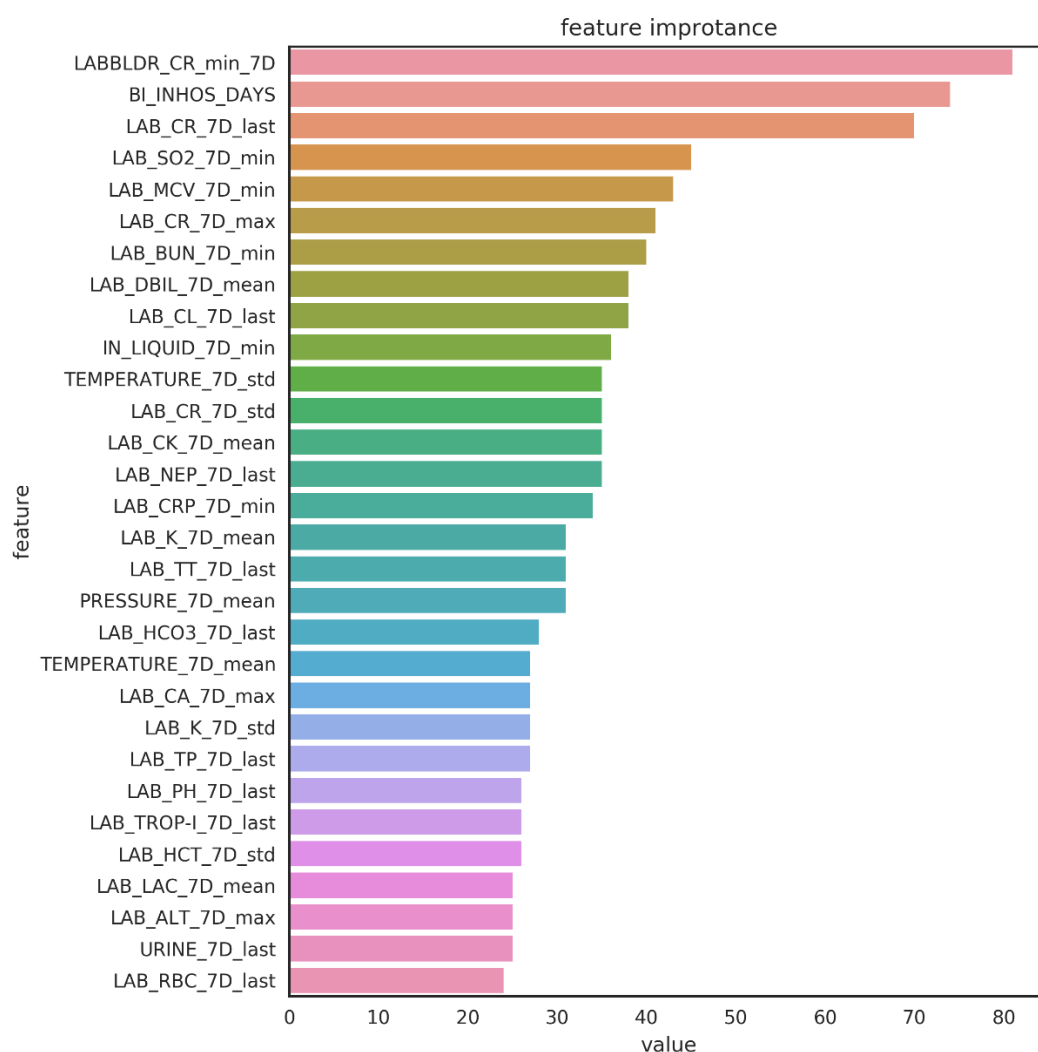
Figure 3: The AUROC curve of the external validation set of the AmsterdamUMC database for 3A and the prospective validation in our center for 3B.

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4 **Supplemental Figure:**

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9 Title and Description of data: The variable importance parameter histogram of early diagnosis prediction

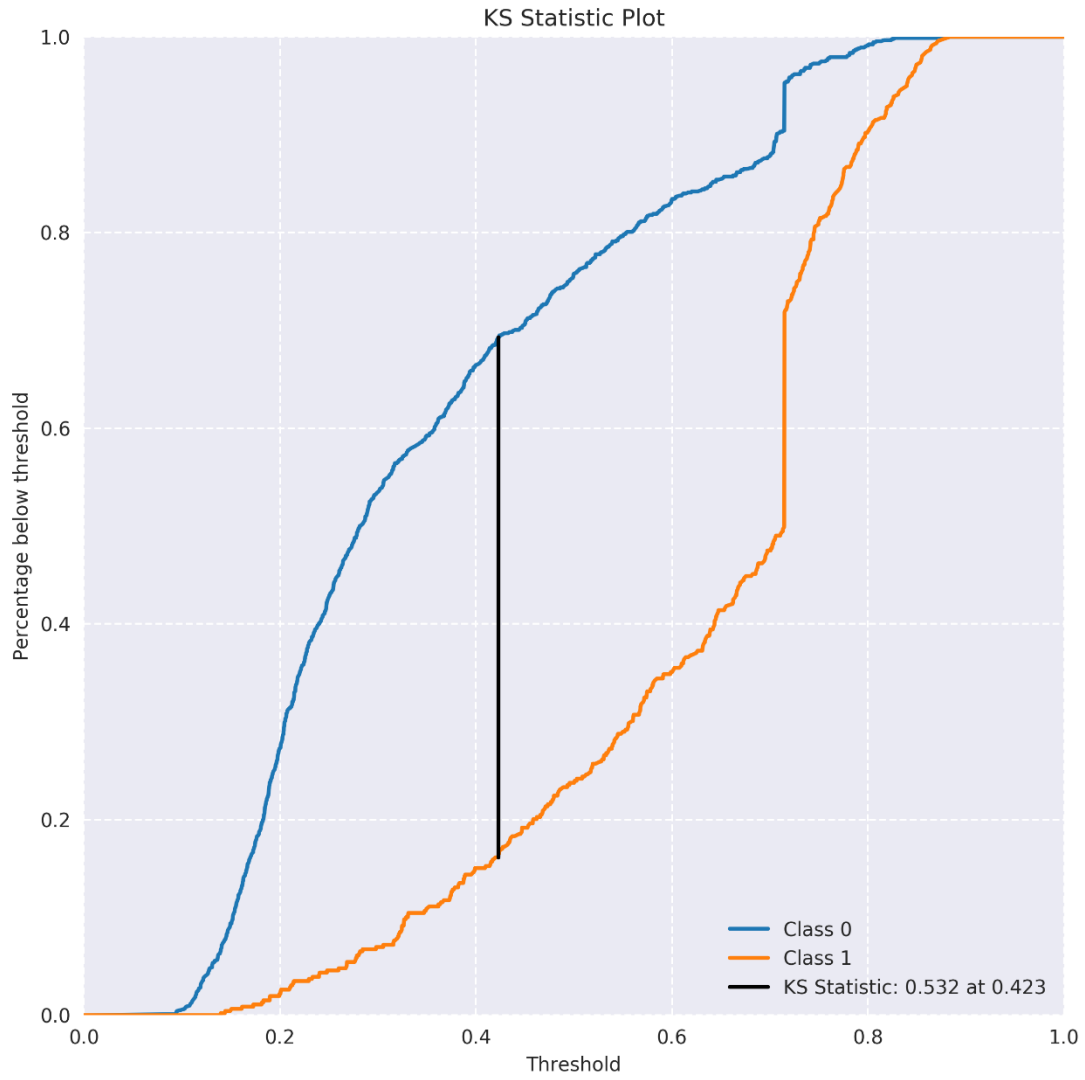
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11 models of severe AKI uses a multiple logistic regression algorithm and five machine learning algorithms.



File name: **Figure S2.tif**

Title and Description of data: The K-S curve used to determine the cut-off value of positive and negative

diagnosis of early diagnosis prediction models of severe AKI.



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Title and of Description data: Missing data between three databases in the study and values included in the model.

	SHZJU-ICU	MIMIC	AmsterdamUMC	Including in Model
Age	√	√	√	√
Gender	√	√	√	√
Race	√	√	×	×
Primary disease	√	√	×	×
Comorbidity	√	√	×	×
Ventilation	√	√	√	√
Operation	√	√	×	×
ICU hours	√	√	√	√
Survived	√	√	√	√
Vital sign				
Temperature	√	√	√	√
Systolic pressure	√	√	√	√
Diastolic pressure	√	√	√	√
Respiratory rate	√	√	√	√
Heart rate	√	√	√	√
Oxygen saturation	√	√	√	√
Urine	√	√	√	√
GCS score	√	×	×	×
Laboratory results				
Scr	√	√	√	√
BUN	√	√	√	√
RBC	√	√	√	√
MCV	√	√	√	√
Hb	√	√	√	√
WBC	√	√	√	√
NEUT	√	√	√	√
PLT	√	√	√	√
HCV	√	√	×	×
TBLB	√	√	√	√
DBLB	√	√	√	√
IBLB	√	√	√	√
CRP	√	√	√	√
PCT	√	×	×	×
Serum kalium	√	√	√	√
Serum natrium	√	√	√	√
Serum chlorine	√	√	√	√

PT	√	√	√	√
APTT	√	√	√	√
INR	√	√	√	√
CK	√	√	√	√
LDH	√	√	√	√
Troponin	√	√	√	√
Blood glucose	√	√	√	√
PH	√	√	√	√
Lactic acid	√	√	√	√
Anion gap	√	√	√	√
ABC	√	√	√	√
SBC	√	√	√	√
PaCO ₂	√	√	√	√
PaO ₂	√	√	√	√

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; APTT: Activated partial thromboplastin time; INR: International normalized ratio; LDH: Lactate dehydrogenase; PaCO₂: Partial pressure of carbon dioxide; PaO₂ Partial pressure of oxygen; MCV: Mean corpuscular volume; PH: Potential of hydrogen; WBC: White blood cell count; NEUT: Proportion of neutrophils; CK: Creatine kinase; Scr: Serum Creatinine; BUN: Blood urea nitrogen; RBC: Red blood cell count; Hb: Hemoglobin; PT: Prothrombin time; TBLB: Total bilirubin; DBLB: Direct bilirubin; IBLB: Indirect bilirubin; CRP: C-reactive protein; HCV: Hematocrit value; PCT: Procalcitonin; ABC: Actual Bicarbonate Radical; SBC: Standard Bicarbonate Radical; PLT: Platelet count

File name: **Table S2.docx**

Title and of Description data: Clinical Demographics and Outcomes of SHZJU-ICU patients in model

building set and prospective validation.

	SHZJU-ICU Negative (N=5695)	SHZJU-ICU Severe AKI (N=766)	P-value	SHZJU-ICU Prospective Negative (N=2188)	SHZJU-ICU Prospective Positive (N=344)	P-value
Age, median [IQR]	60.5 [48.8-70.1]	62.1 [50.1-72.5]	0.004	61.3 [47.5-73.4]	62.1 [51.2-70.5]	0.03
Gender, male (%)	3561 (64.9)	438 (59.8)	0.007	1365 (62.4)	207 (60.2)	0.438
Race						
White	3 (0.05)	1 (0.1)	1	2 (0.001)	0	1
Black	1 (0.02)	0	1	0	0	1
Asian	5691(99.9)	764 (99.7)	1	2185 (99.9)	344(100)	1
Other	0	1 (0.1)	1	1 (0.001)	0	1
Admission Scr (mg/dL), mean (sd)	0.9 (0.34)	1.0 (0.40)	<0.001	0.8 (0.32)	0.9 (0.35)	<0.001
Admission BUN (mg/dL), mean (sd)	18 (11)	21 (9)	<0.001	17 (11)	20 (10)	0.007
Cancer, n (%)	644 (11.3)	48 (6.3)	<0.001	230 (10.5)	26 (7.6)	0.102
Cirrhosis, n (%)	43 (0.8)	6 (0.8)	0.89	15 (0.7)	3 (0.8)	0.726
Cardiopathy, n (%)	231 (4.1)	42 (5.5)	0.08	98 (4.5)	19 (5.7)	0.403
Diabetes, n (%)	305 (5.4)	63 (8.2)	0.002	142 (6.5)	29 (8.6)	0.203
Hypertension, n (%)	889 (15.6)	115 (15.0)	0.70	324(14.8)	56 (16.4)	0.466
Ventilation, n (%)	2569 (45.1)	592 (77.3)	<0.001	1102 (50.4)	239 (69.5)	<0.001
Operation, n (%)	3361 (59.1)	373 (48.7)	<0.001	1234(56.4)	160 (46.7)	0.001
ICU Hours, median [IQR]	50.8 [23.0-139.5]	164.4 [70.3-328.6]	<0.001	58.7 [34.2-160.4]	145.6 [68.5-314.8]	<0.001
Survived, n (%)	4997 (87.7)	380 (49.6)	<0.001	1868 (85.4)	178 (51.9)	<0.001

SHZJU-ICU: The general ICU database of the second affiliated hospital of Zhejiang university school of medicine; MIMIC: Medical Information Mart for Intensive Care; IQR: Inter-Quartile Range; ICU: Intensive Care Unit; AKI: Acute Kidney Injury. Scr: serum creatinine; BUN: blood urea nitrogen.



TRIPOD Checklist: Prediction Model Development and Validation

1Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	D;V Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Yes; P1
Abstract	2	D;V Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Yes; P2
Introduction			
Background and objectives	3a	D;V Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Yes; P3
	3b	D;V Specify the objectives, including whether the study describes the development or validation of the model or both.	Yes; P4, L76-79
Methods			
Source of data	4a	D;V Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Yes; P4, L83-92
	4b	D;V Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Yes; P4, L83-100
Participants	5a	D;V Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Yes
	5b	D;V Describe eligibility criteria for participants.	Yes; P4, L103
	5c	D;V Give details of treatments received, if relevant.	NA
Outcome	6a	D;V Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Yes; P6, L111
	6b	D;V Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	D;V Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Yes; P6, L116
	7b	D;V Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	D;V Explain how the study size was arrived at.	NA
Missing data	9	D;V Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Yes; P6, L127
Statistical analysis methods	10a	D Describe how predictors were handled in the analyses.	Yes; P6, L125
	10b	D Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Yes; P6, L130-138
	10c	V For validation, describe how the predictions were calculated.	Yes; P6, L139
	10d	D;V Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Yes; P7, L159
	10e	V Describe any model updating (e.g., recalibration) arising from the validation, if done.	Yes; P7, L137
Risk groups	11	D;V Provide details on how risk groups were created, if done.	Yes; P6, L111
Development vs. validation	12	V For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Yes; P6, L132
Results			
Participants	13a	D;V Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Yes; Figure 1
	13b	D;V Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Yes, P8, L168-180 and SupTable2
	13c	V For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Yes, SupTable3
Model development	14a	D Specify the number of participants and outcome events in each analysis.	Yes, P8, L168
	14b	D If done, report the unadjusted association between each candidate predictor and outcome.	Yes, SupTable1
Model specification	15a	D Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Yes.
	15b	D Explain how to use the prediction model.	Yes, P9, L196
Model performance	16	D;V Report performance measures (with CIs) for the prediction model.	Yes, P9, L190
Model-updating	17	V If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion			
Limitations	18	D;V Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Yes, P12, L246
Interpretation	19a	V For validation, discuss the results with reference to performance in the development data, and any other validation data.	Yes, P11, L237
	19b	D;V Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Yes, P10 L210-245
Implications	20	D;V Discuss the potential clinical use of the model and implications for future research.	Yes, P12, L254
Other information			
Supplementary information	21	D;V Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Yes
Funding	22	D;V Give the source of funding and the role of the funders for the present study.	NA

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.