

Machine Learning-Based Prediction of Acute Kidney Injury in Patient Admitted to ICU with Sepsis: A Systematic Review of Clinical Evidence

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Cite this article as: Stubnya JD, Marino L, Glaser K, Bilotta F. Machine Learning-Based Prediction of Acute Kidney Injury in Patient Admitted to ICU with Sepsis: A Systematic Review of Clinical Evidence. *J Crit Intensive Care* 2024;15:1–6

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Received: Nov 06, 2023

Accepted: Jan 12, 2024

Available online: Feb 12, 2024

ABSTRACT

Sepsis is a highly prevalent condition in intensive care units, with one of its severe complications being acute kidney injury (AKI). Sepsis-associated acute kidney injury (SA-AKI) can be a reversible process if timely recognition and adequate treatment are provided to the patient. This systematic review (SR) summarizes the current clinical evidence of machine learning (ML) based prediction models. After conducting the literature search, 9 publications meet the inclusion criteria of the SR, categorized into three groups: prediction of SA-AKI occurrence, prediction of persistent AKI in septic patients, and prediction of mortality in SA-AKI patients. In summary, based on the current clinical evidence, ML-based methods show great potential for future clinical applications. They have the ability to outperform conventional scoring systems (such as SOFA and SAPS II), indicating their promising role in clinical practice.

Keywords: machine learning, acute kidney injury, sepsis

Introduction

Acute kidney injury (AKI) is a frequent complication in patients admitted to intensive care unit (ICU) because of sepsis (1). In these patients the occurrence and severity of AKI is a predictor of poor clinical outcome (2). AKI complicates 25-75% cases of patients associated with sepsis or septic shock that is sepsis-associated acute kidney injury (SA-AKI) (3-7). Several mechanisms might take a role in this complication: microvascular dysfunction, inflammation and metabolic reprogramming (8). A timely diagnosis along with prompt and adequate treatment can effectively make AKI a reversible damage (9). Several approaches have been tested to anticipate occurrence and severity of AKI in this subset of patients; ICU scoring systems, such as the Simplified Acute Physiology Score II (SAPS II), the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II), have been proven inadequate in their reliability to predict SA-AKI (10-12). Further alternative test strategy is to find important molecules which can help in the prediction of AKI (13-16).

The development of new technologies of big-data-based analysis and machine learning (ML) methods gained more and more space in the field of healthcare (17). In recent years, various ML-based methods have been used to predict the development of acute kidney injury (18).

Evidence on possible applications of ML-based prediction of SA-AKI in patients admitted to ICU with sepsis is a debated and evolving topic.

The aim of this systematic review (SR) is to report clinical evidence related to ML-based prediction of SA-AKI.

Methods

This SR was conducted based on the recommendations of the Preferred Reporting and Items for Systematic Reviews and Meta-Analyses (PRISMA) and was recorded in the PROSPERO registry for SR (N. CRD42023422436, May 9, 2023).

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Search strategy, data extraction and screening

The systematic search was made on the PubMed, Embase, Scopus, and Medline databases and the literature review was conducted using publications available until 17th of July, 2023. The clinical literature was searched using the following keywords: "machine learning acute kidney injury". The selected keyword was expanded by screening the references of the included studies to find possible synonyms. We have also examined the articles of the potential publication's reference section in terms of suitability. The search was restricted to articles that meet the inclusion criteria defined by the SR.

The screening process for selecting studies involved was initially carried out based on the titles, followed by narrowing down the selection using the abstracts, and finally, the full text was used for further refinement by two reviewers to identify relevant studies. Full-text articles were then obtained for potentially eligible studies and assessed for eligibility. Any discrepancies between the reviewers were resolved through discussion and consensus.

Data extraction was performed using a pre-specified form that included the following information: study design, sample size, patient characteristics, intervention/exposure details, comparator details, outcome measures, effect measures, follow-up time, funding source, and conflicts of interest.

Eligibility criteria

This study includes randomized controlled trials (RCTs), observational studies, cohort studies, and case-control studies that implement some form of ML for the prediction of AKI in adult (over 18 years of age) and septic ICU patients. The study includes only English language publications with full text.

Exclusion criteria for this review includes case reports, comments, letters to the editor, editorials, errata, and replies. Study protocols were also excluded. Additionally, studies that do not involve the use of ML algorithms for the prediction of AKI in ICU patients were excluded. Studies that evaluate the prediction of SA-AKI in non-ICU settings, studies that do not report on patient outcomes, and studies that are not published in English language were also excluded. Studies made on pediatric patients were excluded.

Outcomes

The main outcome of the SR is to compare and evaluate the ML-based prediction of AKI in patients admitted to the ICU with sepsis. The focus was on assessing the accuracy, sensitivity, and specificity of the ML algorithms in predicting the occurrence and the mortality of SA-AKI and the occurrence of persistent renal insufficiency after SA-AKI. The outcome was defined and measured based on the included studies' methodology, including the models and algorithms used for prediction, the reference standards for AKI diagnosis, and the timing of outcome measurement (i.e., duration of ICU stay, 30-day mortality, etc.)

Risk of bias

Risk of bias was examined through five parameters which include reasonable cohort size, proper cross-validation, external validation set, blinding of participants and personnel, and incomplete outcome data (Table 1).

Table 1. Risk of Bias evaluation panel

Study (First author, year)	Reasonable cohort size	Proper Cross-Validation	External Validation Set	Blinding of Participants and Personnel	Incomplete Outcome Data
Luo X. G. et al., 2021 (19)	L	L	S	L	L
He J. et al., 2021 (20)	L	M	L	L	L
Yue S. et al., 2022 (21)	L	L	S	L	L
Luo X. G. et al., 2022 (22)	L	M	L	L	L
Zhang L. et al., 2022 (23)	L	L	L	L	L
Li X. et al., 2023 (24)	L	M	S	L	L
Zhou H. et al., 2023 (25)	L	M	L	L	L
Yang J. et al., 2023 (26)	L	L	S	L	L
Fan Z. et al., 2023 (27)	L	L	L	L	L

L: low risk of bias, M: moderate risk of bias, S: serious risk of bias, C: critical risk of bias, U: unclear risk of bias.

Results

Study selection and characteristics

Literature search led to retrieving a total of 3680 publications and after screening for duplicates, irrelevant or not proper records, 9 studies were found suitable for the present SR (Figure 1).

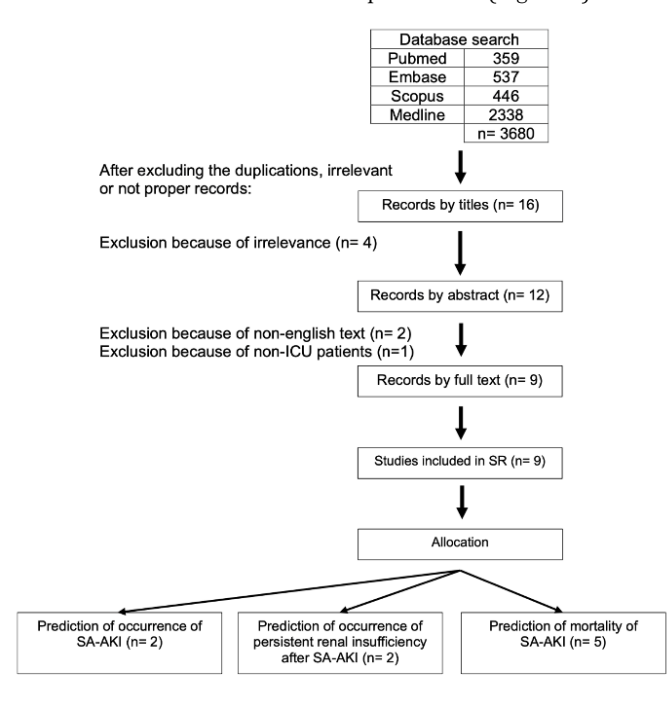


Figure 1. Flow diagram

The total number of enrolled patients in the studies ranged from 718 (20) to 45,895 (23). Thirteen different ML-based methodological approaches were tested in some studies as a single approach, while in others, they included those that used different approaches together: logistic regression (LR) in 7 (19, 20, 21, 24, 25, 26, 27), random forest and extreme gradient Boost (XGB) and support vector machine (SVM) in 7 (19, 21, 23, 24, 25, 26, 27), K-nearest neighbor and decision tree (DT) in 4 (20, 21, 24, 25), recurrent neural network - long short-term memory (RNN-STM), ADABOOST, CATBOOST, multiLayer perceptron, naive bayesian, gradient boosting machine (GBM) and light-XGB in 4 (20, 25, 26, 27), artificial neural network in 3 (19, 21, 23).

Relevant contents related to ML-based prediction of AKI in septic patients are summarized into 3 sections: occurrence of SA-

AKI, persistent renal insufficiency and mortality in patients that developed SA-AKI. The studies that met the inclusion criteria were arranged in order based on their exact publication dates, so the reference number always follows this order when presented.

Prediction of SA-AKI occurrence

Prediction of SA-AKI in septic patients treated on ICU was investigated in 2 retrospective observational studies.

One study analyzed a total of 3176 septic patients and tested seven different ML-based methods comparing them with two traditional clinical scores (SOFA, SAPS II) (21). The performance of ML-based methods and clinical scores were evaluated by the area under the curve (AUC) of the receiver operating curve (ROC) (21). The XGBoost model achieved the best predictive value of the occurrence of SA-AKI before the AKI onset with AUC=0.817. (21). Traditional SOFA and SAPS II scores reported AUC=0.646 and AUC=0.702, respectively (21). The sensitive parameters of XGBoost model for prediction were renal parameters (e.g., urine output, eGFR, minimum creatinine, and minimum BUN), mechanical ventilation, maximum PTT, and BMI (21).

The other study analyzed a total of 45 895 septic patients and tested four different ML-based methods as an ensemble model with the highest weight of XGBoost (23).

The performance of ML-based methods and clinical scores were evaluated by the area under the curve (AUC) (23). The models

were applied to predict occurrence of SA-AKI at 48-12 hours before the onset of AKI (23). The XGBmodel weighted ensemble model achieved the predictive value of the occurrence of SA-AKI with AUC 0.774-0.788 and 0.756-0.813 (23) (Table 2).

Prediction of persistent renal insufficiency in SA-AKI patients

Prediction of persistent renal insufficiency was investigated in two retrospective observational studies on ICU with septic patients (19, 20).

One study analyzed a total of 5 984 septic patients and tested five different ML-based methods (19). In this study the artificial neural network (ANN) and logistic regression (LR) model achieved the best performance of the prediction of persistent renal insufficiency in SA-AKI patients with the AUC of 0.76 (19). The serum creatinine and urine output of the stage of AKI were strong predictors of persistent AKI in septic patients (19).

The other study analyzed a total of 718 septic patients and tested three different ML-based methods (20). RNN-LSTM method gave the best performance with the AUC of 1 and decision tree (DT) achieved the second performance of the prediction of the persistent AKI in septic patients with the AUC of 0.954 (20). The difference of the non-renal SOFA score between the 1st and 3rd day is an important parameter in predicting the persistency of the renal insufficiency (20) (Table 3).

Table 2. Prediction of occurrence of SA-AKI

Study (First author, year, ref.)	ML-method	Number of patients	Predictive power AUC
Yue S., 2022 (21)	logistic regression (LR), <i>k</i> -nearest neighbors (KNN), support vector machine (SVM), decision tree (DT), random forest (RF), Extreme Gradient Boost (XGBoost), artificial neural network (ANN)	3 176	XGBoost: AUC=0.817. LR: AUC= 0.737 KNN: AUC= 0.664 SVM: AUC= 0.735 DT: AUC= 0.749 RF: AUC= 0.779 ANN: AUC= 0.755 SAPS II: AUC= 0.702 SOFA: AUC= 0.646 XGBoost model had the highest sensitivity (0.945), accuracy (0.832), recall (0.852), F1 score (0.895) and the third highest specificity (0.913).
Zhang L., 2022 (23)	Ensemble model of support vector machine (SVM), random forest (RF), artificial neural network (ANN), Extreme Gradient Boost (XGBoost) XGBoost had the highest weight.	45 895	Ensemble model: AUC 0.774-0.788 and 0.756-0.813. The sensitivity of the ensemble model were 0.650-0.724 and 0.685-0.840. The model correctly predicted up 72,4% and 84% of SA-AKI cases.

Table 3. Prediction of occurrence of persistent renal insufficiency in SA-AKI patients

Study (First author, year, ref.)	Method	Number of patients	Predictive power AUC
Luo X. G. et al., 2021 (19)	logistic regression (LR),random forest (RF), support vector machine (SVM), artificial neural network (ANN) Extreme Gradient Boost (XGBoost)	5 984	ANN and LR: AUC=0.76. ANN achieved the highest accuracy of 0.71. XGBoost model showed the highest recall of 0.81. RF model had the highest precision and F1 score of 0.89 and 0.80.
He J. et al., 2021 (20)	Recurrent Neural Network-Long Short-Term Memory (RNN-LSTM), decision tree (DT), logistic regression (LR)	718	RNN-LSTM: AUC=1, DT: AUC=0.954, LR: AUC= 0.728, difference between 1 st and 3 rd day non renal SOFA score is an important predictive factor

Prediction of mortality of SA-AKI patients

The prediction of mortality in SA-AKI patients was investigated in five different studies on ICU with a total of 51,913 septic patients (22, 24-27). The ML-based methods adopted ranged between 3 to 11 (22, 25).

One study analyzed 15 873 septic patients and tested three different ML-based methods (22). The XGBoost model reached the highest AUC value with 0.848-0.804 and 0.818-0.748 and it outperformed the traditional clinical score (SOFA, SAPS II) as well (22). GCS score, urine output, ICU length of stay, older age and higher blood urea nitrogen (BUN) were the top five predictor parameters (22). The second study analyzed 8 129 septic patients and tested six different ML-based methods (24). The XGBoost model had the best performance with the AUC of 0.794 and the score systems had weaker results (SOFA: AUC=0.701, SAPS II: AUC=0.706) in this study as well (24). The third study analyzed 16 154 septic patients and tested eleven different ML-based methods (25). CatBoost model had the best performance with AUC value of 0.827, GBDT achieved the second (AUC=0.823) and LightGBM (AUC=0.819) the third result (25). The fourth study analyzed 9 158 septic patients and tested four different ML-based methods (26). The XGBoost model had the best performance in predicting the 30 day mortality with the AUC value of 0.873 (26). The fifth study analyzed 2 599 septic patients and tested five different ML-based methods (27). The XGBoost model showed the best performance in the 7- (AUC=0.91), 14- (AUC=0.78) and 28-day groups (AUC=0.83) (27) (Table 4).

Discussion

This SR reports the recent clinical evidence of the role of ML-based prediction models in patients with SA-AKI in ICU: occurrence of SA-AKI, persistent renal insufficiency and mortality in patients that developed SA-AKI. The results demonstrate that ML-based methods have significant potential in predicting the early onset of SA-AKI, the persistent AKI and the mortality in SA-AKI patients.

Based on the collected results, XGBoost method emerged as the most effective in forecasting. Traditional ICU scoring systems such as SOFA and SAPS-II were outperformed by different ML-based techniques.

Numerous research findings and comprehensive meta-analyses or systematic reviews confirm that various machine learning-based methods can be reliably utilized in ICU settings (28). Reliable results have been found, for instance, regarding the use of machine learning-based prediction models for early sepsis detection, where XGBoost and random forest techniques were applied (28). There are reliable results in predicting the clinical outcomes of COVID-19-infected patients as well; however, further validation is needed before its implementation in everyday clinical use (29).

The latest research and the growing body of evidence indicate how prominently the duration of AKI and the temporal course of renal recovery are associated with the healing outcomes of critically ill septic patients in the intensive care unit (30, 31).

Since the timing factor is crucial in the treatment of AKI, the rapid diagnosis and prediction of AKI have been a highly discussed topic in the medical field. Various biomarkers, such as microRNA-22-3p, neutrophil gelatinase-associated lipocalin, and urinary miR-26b or soluble thrombomodulin have been previously attempted, along with different imaging modalities-based techniques (13-16). However, none of these approaches have yet met the challenges of technical and clinical applicability. There are certain traditional scoring systems used among intensive care unit patients, such as APACHE-II, SOFA, or SAPS II. However, due to their low specificity and sensitivity, these are not sufficiently adequate for predicting AKI (32).

Therefore, with the continuous advancement of artificial intelligence and machine learning and their increasing adoption in the healthcare domain, there is high potential for early diagnosis and prediction of AKI.

Table 4. Prediction of mortality of SA-AKI

Study (First author, year, ref.)	Method	Number of patients	Result
Luo X. G. et al., 2022 (22)	Extreme Gradient Boost (XGBoost), Random forest (RF), support vector machine (SVM)	15 873	XGBoost: AUC=0.848-0.804 and 0.818-0.748, it outperformed traditional risk score as well. This model achieved a sensitivity of 80,1% and specificity of 72,9% at the cutoff of 0.0349.
Li X. et al., 2023 (24)	logistic regression (LR), support vector machine (SVM), <i>k</i> -nearest neighbors (KNN), decision tree (DT), random forest (RF), Extreme Gradient Boost (XGBoost)	8 129	XGBoost: AUC=0.794. Conventional score systems had weaker performance (SOFA: AUC=0.701, SAPS II: AUC=0.706).
Zhou H. et al., 2023 (25)	Categorical Boosting (CatBoost), <i>k</i> -nearest neighbors (KNN), AdaBoost, multilayer perceptron (MLP), support vector machine (SVM), logistic regression (LR), NaiveBayes, gradient boosting decision tree (GBDT), random forest (RF), light gradient boosting (LightGBM), Extreme Gradient Boost (XGBoost)	16 154	CatBoost outperformed the other models (AUC=0.827, ACC=75%, best cutoff=19,5%, Youden index=50%, sensitivity=75%, specificity=75%, F1-score=56%, PPV=44%, NPV=92%).
Yang J. et al., 2023 (26)	logistic regression (LR), random forest (RF), Gradient Boosting Machine (GBM) and Extreme Gradient Boost (XGBoost)	9 158	XGBoost model achieved the best performance (AUC=0.873, accuracy=0.773, precision=0.724, recall=0.896, F1-score=0.801).
Fan Z. et al., 2023 (27)	random forest (RF), support vector machine (SVM), logistic regression (LR), Extreme Gradient Boost (XGBoost) and multilayer perceptron (MLP)	2 599	The XGBoost model showed the best performance in the 7- (AUC=0.91), 14- (AUC=0.78) and 28-day groups (AUC=0.83).

This SR summarizes all available evidence regarding prediction of early diagnosis, persistence and mortality of SA-AKI. The two most significant findings of this SR are that Extreme Gradient Boost (XGBoost) ML-based method consistently outperformed other machine learning techniques in reliably predicting the onset, progression, and mortality of AKI in critically ill septic patients. Another important result of this research is that ML-based methods, such as XGBoost or random forest, surpassed conventional intensive care risk scoring systems like SOFA or SAPS II. These findings suggest and point towards the redesign or incorporation of ML-based methods in place of, or in conjunction with, traditional risk scoring systems in the intensive care setting.

AUTHOR CONTRIBUTIONS:

Concept: JDS, FB; **Design:** JDS, LM, FB; **Supervision:** FB; **Resources:** JDS; **Materials:** JDS; **Data Collection and/or Processing:** JDS, KG; **Analysis and/or Interpretation:** JDS, KG; **Literature Search:** JDS, KG; **Writing Manuscript:** JDS, LM, KG; **Critical Review:** FB.

Limitations of this SR include the relatively limited number of studies available, all of which were conducted retrospectively. Another limitation is that the different studies were made on the same database. Before the application of ML-based methods, prospective randomized controlled trials are necessary.

In conclusion available evidence suggest that ML-based prediction models have the future potential to be used as a predictor of occurrence, persistence or mortality of SA-AKI in patients treated in intensive care units.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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