REVIEW

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

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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. This systematic review (SR) summarizes the current clinical evidence on machine learning (ML)-based prediction models. After conducting the literature search, nine publications met 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 the Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiology Score II (SAPS II), indicating their promising role in clinical practice.

Keywords: Acute kidney injury; Machine learning; Sepsis.

Introduction

Acute kidney injury (AKI) is a frequent complication in patients admitted to the intensive care unit (ICU) due to sepsis.[1] In these patients, the occurrence and severity of AKI are predictors of poor clinical outcomes.[2] AKI complicates 25-75% of cases in patients associated with sepsis or septic shock, termed sepsis-associated acute kidney injury (SA-AKI).[3-7] Several mechanisms may play a role in this complication, including microvascular dysfunction, inflammation, and metabolic reprogramming.[8] Timely diagnosis, along with prompt and adequate treatment, can effectively render AKI reversible.[9] Various approaches have been tested to anticipate the 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 the Acute Physiology and Chronic Health Evaluation II (APACHE II), have been found inadequate in relia-

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bility predicting SA-AKI.[10-12] An alternative strategy involves identifying important molecules that can aid in predicting AKI.[13-16]

The advent of big-data analysis and machine learning (ML) methods has increasingly influenced the field of healthcare.[17] In recent years, various ML-based methods have been utilized to predict the development of acute kidney injury.[18]

The potential applications of ML-based prediction of SA-AKI in patients admitted to the ICU with sepsis represent a debated and evolving topic.

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

Materials and Methods

This SR was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered in the PROSPERO registry for SRs (No. CRD42023422436, May 9, 2023).

Search Strategy, Data Extraction, and Screening

The systematic search was conducted on the PubMed, Embase, Scopus, and Medline databases, reviewing literature available until July 17, 2023. The clinical literature was searched using the keywords "machine learning acute kidney injury." This keyword was further expanded by screening the references of the included studies to identify possible synonyms. Additionally, we examined the reference sections of potential publications for relevance. The search was limited to articles that meet the inclusion criteria defined by the SR.

The screening process for selecting studies began with an evaluation of the titles, then narrowed down based on the abstracts, and finally, full texts were reviewed for further refinement by two reviewers to identify relevant studies. Full-text articles for potentially eligible studies were obtained and assessed for eligibility. Any discrepancies between reviewers were resolved through discussion and consensus.

Data extraction was conducted using a predefined form that included information on 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 employed some form of ML for the prediction of AKI in adult (over 18 years of age) ICU patients with sepsis. The study is limited to English language publications with full text available.

The exclusion criteria for this review include case reports, comments, letters to the editor, editorials, errata, and replies. Study protocols were also excluded. Furthermore, studies that do not utilize ML algorithms for the prediction of AKI in ICU patients were excluded. Studies evaluating the prediction of SA-AKI in non-ICU settings, studies that do not report on patient outcomes, and studies not published in the English language were also excluded. Additionally, studies conducted on pediatric patients were excluded.

Outcomes

The primary outcome of this SR is to compare and evaluate the ML-based prediction of AKI in patients admitted to the ICU with sepsis, focusing on the accuracy, sensitivity, and specificity of the ML algorithms. This includes predicting the occurrence and mortality of SA-AKI, as well as the occurrence of persistent renal insufficiency after SA-AKI. Outcomes were defined and measured based on the included studies' methodologies, encompassing the models and algorithms used for prediction, the reference standards for AKI diagnosis, and the timing of outcome measurement (e.g., duration of ICU stay, 30-day mortality).

Risk of Bias

The risk of bias was assessed using five parameters: reasonable cohort size, proper cross-validation, the inclusion of an external validation set, blinding of participants and personnel, and the completeness of outcome data (Table 1).

Results

Study Selection and Characteristics

The literature search resulted in 3,680 publications, and after screening for duplicates, irrelevance, or improper records, nine studies were deemed suitable for the current SR (Figure 1).

The total number of patients enrolled in the studies ranged from 718[19] to 45,895.[20] Thirteen different ML-based methodological approaches were evaluated in the

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[21]	L	L	S	L	L
He J. et al., 2021 [19]	L	M	L	L	L
Yue S. et al., 2022 [22]	L	L	S	L	L
Luo X. G. et al., 2022 [27]	L	M	L	L	L
Zhang L. et al., 2022 [20]	L	L	L	L	L
Li X. et al., 2023 [23]	L	M	S	L	L
Zhou H. et al., 2023 [24]	L	M	L	L	L
Yang J. et al., 2023 [25]	L	L	S	L	L
Fan Z. et al., 2023 [26]	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.

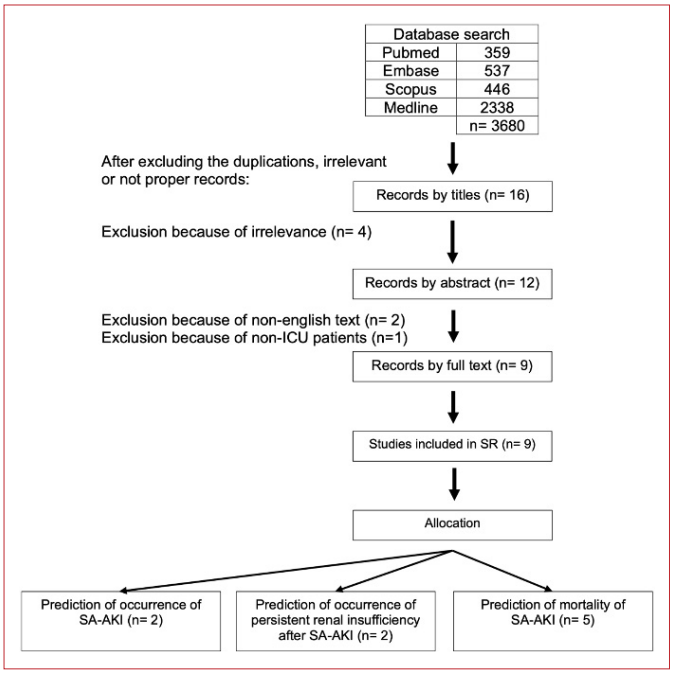

Figure 1. Flow diagram.

studies. Some studies tested a single approach, while others employed different approaches concurrently: logistic regression (LR) was used in seven studies,[19,21,22-26] random forest, extreme gradient boost (XGB), and support vector machine (SVM) in seven studies,[20-26] K-nearest neighbor and decision tree (DT) in four studies,[19,22,23,24] recurrent neural network - long short-term memory (RNN-LSTM), Adaptive Boosting (AdaBoost), Categorical Boosting (CatBoost), multilayer perceptron, naive Bayesian, gradient boosting machine (GBM), and Light Gradient Boosting Machine (LightGBM) in four studies,[19,24-26] and artificial neural network in three studies.[20-22]

The relevant content related to ML-based prediction of AKI in septic patients is summarized into three sections: occurrence of SA-AKI, persistent renal insufficiency, and mortality in patients that developed SA-AKI. The studies meeting the inclusion criteria were arranged in order based on their exact publication dates, so the reference number follows this order when presented.

Prediction of SA-AKI Occurrence

The prediction of SA-AKI in septic patients treated in the ICU was investigated in two retrospective observational studies.

One study analyzed a total of 3,176 septic patients and tested seven different ML-based methods, comparing them with two traditional clinical scores (SOFA, SAPS II).[22] The performance of ML-based methods and clinical scores was evaluated by the area under the curve (AUC) of the receiver operating curve (ROC).[22] The XGBoost model achieved the best predictive value for the occurrence of SA-AKI before the onset of AKI with an AUC of 0.817.[22] Traditional SOFA and SAPS II scores reported AUC values of 0.646 and 0.702, respectively.[22] The sensitive parameters of the XGBoost model for prediction included renal parameters (e.g., urine output, estimated glomerular filtration rate (eGFR), minimum creatinine, and minimum blood urea nitrogen (BUN)), mechanical ventilation, maximum partial thromboplastin time (PTT), and body mass index (BMI).[22]

The other study analyzed a total of 45,895 septic patients and tested four different ML-based methods as part of an ensemble model, with the highest weight given to XGBoost.[20]

The performance of ML-based methods and clinical scores was evaluated by the area under the curve (AUC).[20] These models were applied to predict the occurrence of SA-AKI 48 to 12 hours before the onset of AKI.[20] The XGBoost-weighted ensemble model achieved a predictive value for the occurrence of SA-AKI with AUC ranging from 0.774 to 0.788 and 0.756 to 0.813 (Table 2).[20]

Prediction of Persistent Renal Insufficiency in SA-AKI Patients

Prediction of persistent renal insufficiency was investigated in two retrospective observational studies involving ICU patients with sepsis.[19, 21]

One study analyzed a total of 5,984 septic patients and tested five different ML-based methods.[21] In this study, the artificial neural network (ANN) and logistic regression (LR) models achieved the best performance in predicting persistent renal insufficiency in SA-AKI patients, with an AUC of 0.76.[21] Serum creatinine and urine output at the stage of AKI were strong predictors of persistent AKI is septic patients.[21]

The other study analyzed a total of 718 septic patients and tested three different ML-based methods.[19] The RNN-LSTM method provided the best performance, with an AUC of 1, and the decision tree (DT) method achieved the second-best performance in predicting persistent AKI in septic patients, with an AUC of 0.954.[19] The change in the non-renal SOFA score between the first and third day is an important parameter in predicting the persistence of renal insufficiency (Table 3).[19]

Prediction of Mortality in SA-AKI Patients

The prediction of mortality in SA-AKI patients was investigated in five different studies involving ICUs, with a total of 51,913 septic patients.[23-27] The number of ML-based methods adopted ranged from 3 to 11.[24,27]

One study analyzed 15,873 septic patients and tested three different ML-based methods.[27] The XGBoost model achieved the highest AUC values, ranging from 0.804 to 0.848 and from 0.748 to 0.818, outperforming traditional clinical scores (SOFA, SAPS II) as well.[27] The top five predictor parameters were Glasgow Coma Scale (GCS) score, urine output, ICU length of stay, older age, and higher blood urea nitrogen (BUN).[27] The second study analyzed 8,129 septic patients and tested six different ML-based methods.[23] The XGBoost model had the best performance with an AUC of 0.794, while the score systems (SOFA: AUC=0.701, SAPS II: AUC=0.706) yielded weaker results in this study.[23] The third study analyzed 16,154 septic patients and tested 11 different ML-based methods.[24] The CatBoost model had the best performance with an AUC of 0.827, followed by Gradient Boosting Decision Tree (GBDT) (AUC=0.823) and Light Gradient Boosting Machine (LightGBM) (AUC=0.819).[24] The fourth study analyzed 9,158 septic patients and tested four different ML-based methods.[25] The XGBoost model showed the best performance in predicting 30-day

Table 2. Prediction of occurrence of SA-AKI

Study (First author, year, ref.)	ML-method	Number of patients	Predictive power AUC
Yue S., 2022 [22]	logistic regression (LR), k-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 [20]	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[21]	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[19]	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 1st and 3rd day non renal SOFA score is an important predictive factor

mortality with an AUC of 0.873.[25] The fifth study analyzed 2,599 septic patients and tested five different ML-based methods.[26] The XGBoost model demonstrated the best performance across the 7-day (AUC=0.91), 14-day (AUC=0.78), and 28-day groups (AUC=0.83) (Table 4).[26]

Discussion

This SR reports recent clinical evidence of the role of ML-based prediction models in patients with SA-AKI in the ICU: occurrence of SA-AKI, persistent renal insufficiency,

Table 4. Prediction of mortality of SA-AKI

Study (First author, year, ref.)	Method	Number of patients	Result
Luo X. G. et al., 2022 [27]	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 [23]	logistic regression (LR), support vector machine (SVM), k-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 [24]	Categorical Boosting (CatBoost), k-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 [25]	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 [26]	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).

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, persistent AKI, and mortality in SA-AKI patients. Based on the collected results, the XGBoost method emerged as the most effective in forecasting. Traditional ICU scoring systems such as SOFA and SAPS-II were outperformed by various 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 patients infected with Coronavirus Disease 2019 (COVID-19) as well; however, further validation is needed before its implementation in everyday clinical practice.[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 timing is crucial in the treatment of AKI, rapid diagnosis and prediction have been highly discussed topics in the medical field. Various biomarkers, such as microRNA-22-3p, neutrophil gelatinase-associated lipocalin, urinary miR-26b, or soluble thrombomodulin, have been previously explored, alongside different imaging modality-based techniques.[13-16] However, none of these approaches have yet overcome the challenges of technical and clinical applicability. Traditional scoring systems used among intensive care unit patients, such as APACHE II, SOFA, or SAPS II, suffer from low specificity and sensitivity, making them inadequate 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 the early diagnosis and prediction of AKI.

This SR summarizes all available evidence regarding the prediction of early diagnosis, persistence, and mortality of SA-AKI. The two most significant findings of this SR are that the 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 the potential for redesigning or incorporating ML-based methods either as replacements for or in conjunction with traditional risk scoring systems in the intensive care setting.

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

Conclusion

In conclusion, the available evidence suggests that ML-based prediction models have the potential to serve as predictors of occurrence, persistence, or mortality of SA-AKI in patients treated in intensive care units.

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