



Artificial intelligence and machine learning's role in sepsis-associated acute kidney injury

Wisit Cheungpasitporn¹, Charat Thongprayoon¹, Kianoush B. Kashani^{1,2}

¹Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA

²Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Sepsis-associated acute kidney injury (SA-AKI) is a serious complication in critically ill patients, resulting in higher mortality, morbidity, and cost. The intricate pathophysiology of SA-AKI requires vigilant clinical monitoring and appropriate, prompt intervention. While traditional statistical analyses have identified severe risk factors for SA-AKI, the results have been inconsistent across studies. This has led to growing interest in leveraging artificial intelligence (AI) and machine learning (ML) to predict SA-AKI better. ML can uncover complex patterns beyond human discernment by analyzing vast datasets. Supervised learning models like XGBoost and RNN-LSTM have proven remarkably accurate at predicting SA-AKI onset and subsequent mortality, often surpassing traditional risk scores. Meanwhile, unsupervised learning reveals clinically relevant sub-phenotypes among diverse SA-AKI patients, enabling more tailored care. In addition, it potentially optimizes sepsis treatment to prevent SA-AKI through continual refinement based on patient outcomes. However, utilizing AI/ML presents ethical and practical challenges regarding data privacy, algorithmic biases, and regulatory compliance. AI/ML allows early risk detection, personalized management, optimal treatment strategies, and collaborative learning for SA-AKI management. Future directions include real-time patient monitoring, simulated data generation, and predictive algorithms for timely interventions. However, a smooth transition to clinical practice demands continuous model enhancements and rigorous regulatory oversight. In this article, we outlined the conventional methods used to address SA-AKI and explore how AI and ML can be applied to diagnose and manage SA-AKI, highlighting their potential to revolutionize SA-AKI care.

Keywords: Artificial intelligence, Machine learning, Precision medicine, Acute kidney injury, Sepsis

Introduction

Sepsis-associated acute kidney injury (SA-AKI) is a severe and frequent complication among critically ill septic patients, with reported incidences between 35% and 61% [1-6]. Furthermore, SA-AKI significantly increases the mortality risk, with some studies demonstrating mortality rates of up to 70% in patients with SA-AKI [7-9]. The clinical course of SA-AKI patients tends to deteriorate, with ex-

tended intensive care unit (ICU) stays and increased risks of chronic kidney disease, cardiovascular events, and death [9]. Among acute kidney injury (AKI) patients, sepsis has been identified as the primary cause of death [4,6,10,11]. The complex pathophysiology of SA-AKI and systemic complications make its management challenging [12,13]. Keys to therapeutic measures are the meticulous regulation of renal perfusion, targeted inflammation mitigation, and prompt intervention such as fluid management or medica-

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Correspondence: Kianoush B. Kashani

Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA.

E-mail: kashani.kianoush@mayo.edu

ORCID: <https://orcid.org/0000-0003-2184-3683>

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tion adjustments [14,15]. Given SA-AKI's profound impact, a holistic approach, including preventive protocols, expedited diagnostics, and collaborative treatment, is critical to optimize outcomes [16,17].

Artificial intelligence (AI) and machine learning (ML) are rapidly emerging as transformative tools for diagnosing and managing AKI patients [12–21]. Compared to traditional methods, ML algorithms can reveal patterns beyond human discernment and enhance SA-AKI prediction accuracy by analyzing vast datasets [22–27]. Furthermore, ML enables earlier SA-AKI detection than traditional approaches, allowing timely, appropriate intervention and improved outcomes [12–20,24,28–32]. ML algorithms are designed to accommodate changing patient conditions and integrate new data, continually refining prediction accuracy in a real-time setting [12–20].

Contemporary research increasingly explores AI/ML's capabilities to advance precision medicine and tailored SA-AKI care. The integration of these technologies promises to usher in a new era of early detection and optimized therapeutic interventions for SA-AKI [22–27]. Several state-of-the-art studies and initiatives are currently underway, highlighting the adoption of these technologies in various clinical settings, each aiming to address the profound challenges posed by SA-AKI with a degree of sophistication previously unattainable [12–20]. However, as with all novel technologies, the advent of AI and ML in SA-AKI diagnosis and management is not without its set of challenges and ethical considerations [33]. While AI can analyze vast datasets and identify patterns beyond human capability, ensuring the accuracy, reliability, scalability, and interpretability of these models is vital. Moreover, the black-box nature of certain ML algorithms poses obscurity, making it challenging for clinicians to justify decisions derived from such systems. Ethical concerns warrant thorough scrutiny, including data privacy, potential biases in AI algorithms, and the subsequent impacts on patient care. The collection and utilization of patient data, especially on sensitive subjects such as SA-AKI, necessitates stringent data protection protocols and informed patient consent mechanisms [22–27].

In this article, we first overview the traditional SA-AKI approach, then discuss AI/ML's potential applications, connecting foundational and emerging methodologies to showcase AI/ML's transformative potential for SA-AKI care.

Traditional approach for sepsis-associated acute kidney injury

Predictors and mortality of sepsis-associated acute kidney injury

Traditional statistical analysis has been instrumental in identifying risk factors for SA-AKI across a range of comorbidities, infections, medications, and other determinants [4,34–42]. Key comorbid conditions found to significantly predict SA-AKI include hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, liver disease, and coronary artery disease [4]. A pooled analysis of 47 observational studies with 55,911 sepsis patients revealed that hypertension, diabetes, and chronic kidney disease increased the odds of AKI, with odds ratios (ORs) of 1.43, 1.59, and 3.49, respectively (Fig. 1) [4]. Furthermore, cardiovascular, liver, and coronary artery diseases emerged as risk factors, with ORs of 1.31, 1.68, and 1.27. Regarding infection sources, pulmonary, abdominal, and undetermined infections were significant SA-AKI predictors, with ORs of 0.77, 1.44, and 2.01, respectively. Medications like vasopressors, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and diuretics also correlated with heightened SA-AKI risk, having ORs of 3.15, 1.61, and 1.40. Other notable risk factors included male sex (OR, 1.22), positive blood culture (OR, 1.60), smoking history (OR, 1.60), septic shock (OR, 1.40), Gram-negative bacteria (OR, 2.19), organ transplantation (OR, 1.96), and mechanical ventilation need (OR, 1.64) [4].

While these findings provide valuable insights, traditional statistical approaches have limitations. Despite identifying these predictors, substantial heterogeneity existed across studies, suggesting potential inconsistencies in outcomes depending on the context of SA-AKI [4].

Prediction model for sepsis-associated acute kidney injury by traditional statistical analysis

Traditional statistical approaches to predicting SA-AKI through various studies have been used [34–42]. These studies (Table 1) utilized well-established methods such as logistic regression analysis, least absolute shrinkage and selection operator (LASSO) regression for variable selection, and calibration plots [34–42]. These models identified

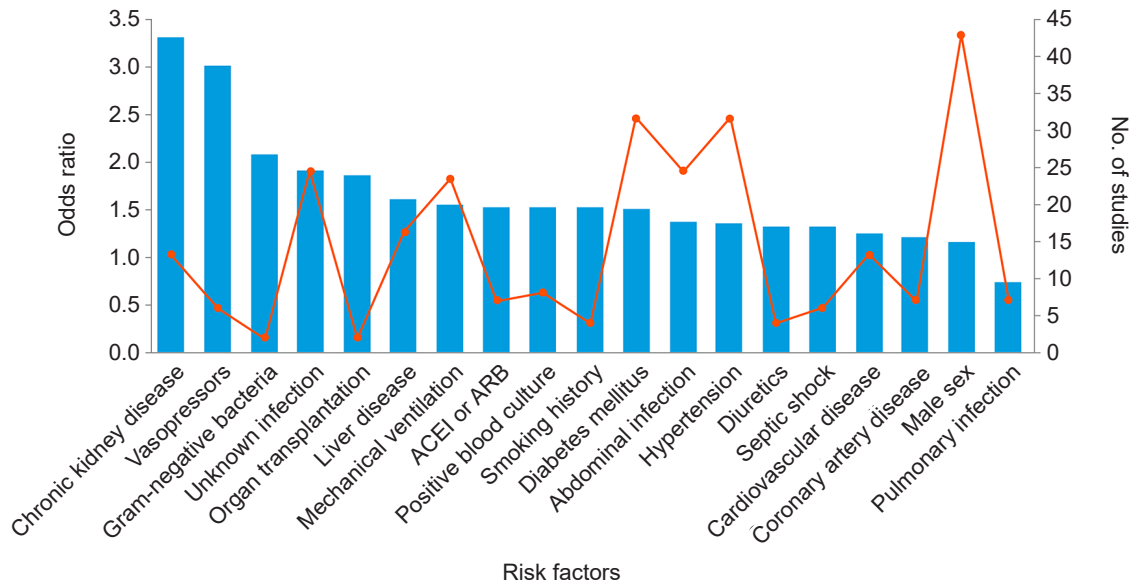


Figure 1. The chart presents the risk factors on the x-axis and their corresponding ORs on the y-axis. The bars represent the ORs, while the red line graph overlaid on the bars indicates the number of studies identifying each risk factor. The risk factors are sorted in descending order based on their OR.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; OR, odd ratio; SA-AKI, sepsis-associated acute kidney injury.

key predictors like diabetes, chronic kidney disease, cardiovascular disease, and specific lab values such as creatinine and procalcitonin. Performance was evaluated using metrics like area under the receiver operating characteristic curve (AUC), sensitivity, and specificity [42].

For instance, Fan et al. [34] developed an SA-AKI prediction model using logistic regression and LASSO, achieving c-statistics of 0.711 and 0.705 in training and validation cohorts. Xin et al. [42] conducted a retrospective cohort study among elderly sepsis patients and achieved an AUC of 0.852 in the training and 0.858 in the validation cohort using logistic regression. Xie et al.'s prospective study [35] of sepsis patients in the ICU resulted in an impressive AUC of 0.9862. In addition, Zhou et al. [36] utilized a randomized clinical trial approach with 16 predictors and achieved an AUC of 0.857 in the validation cohort. While these examples demonstrate traditional statistical methods can effectively predict SA-AKI, recognizing high-risk patients early to guide treatment, these traditional prediction models for SA-AKI come with several limitations (Fig. 2). These limitations include 1) sensitivity to outliers, which may skew results/predictions. Outliers in medical data could be

errors or critical rare events that should not be ignored. 2) Multicollinearity among predictor variables complicates the interpretation of individual predictors' effects on the outcome. 3) Temporal dynamics, as medical time-series data may not meet assumptions of independent and identically distributed points, impacting predictive accuracy. 4) High-dimensional medical data that traditional models can struggle to handle effectively, limiting the identification of complex relationships and predictive capabilities. 5) Calibration, requiring robust procedures to ensure predicted probabilities align closely with observed outcomes, avoiding suboptimal clinical decisions. 6) Potential human bias in feature selection, as choices rely on existing knowledge and practitioner input, possibly introducing limitations.

In essence, while significant, traditional SA-AKI prediction models have inherent challenges around outliers, multicollinearity, temporal dynamics, high-dimensional data, calibration, and bias in feature selection. Continued model updates and refinements alongside technological and research advancements remain important.

Table 1. Prediction model of SA-AKI by traditional statistical analysis

Author	Population	Sample size	Main Predictors	Outcomes	Statistical analysis approach	C-statistics/AUC
Fan et al. [34]	Patients with sepsis in ICU from MIMIC-III database	Training: 11,008 Validation: 4,718	DM, CKD, CHF, CLD, hyperbicaarbonemia, hyperglycemia, low blood pH, prolonged clotting time, hypotension, hyperlactatemia	SA-AKI	LASSO, logistic regression	Original score Training: 0.711 Validation: 0.712 Simplified score Training: 0.712 Validation: 0.705
Xin et al. [42]	Patients aged ≥65 yr with sepsis in one hospital in China	Training: 637 Validation: 212	Low MAP, albumin globulin ratio, prothrombin time activity, platelet, high serum procalcitonin, and creatinine	SA-AKI, MAKE30, and 30-day mortality	Logistic regression	SA-AKI Training: 0.852 Validation: 0.858 30-day mortality 0.813 MAKE30 0.823
Xie et al. [35]	Patients with sepsis in ICU in one hospital in China	Not reported	Male sex, low anti-thrombin III, high creatinine, and BUN	SA-AKI	Logistic regression	0.986
Zhou et al. [36]	Patients with sepsis in ICU	Training: 1,554 Validation: 777	Older age, HTN, CAD, DM, CHF, COPD, acute severe pancreatitis, hypotension, hypoproteinemia, lactic acidosis, ICU length of stay, low hemoglobin, other organ failure	SA-AKI	Logistic regression	Validation: 0.857
Xin et al. [37]	Patients with sepsis in one hospital in China	Training: 787 Validation: 264	Cardiovascular disease, high WBC, procalcitonin, thrombin time, low mean artery pressure, platelet count, prothrombin time activity	SA-AKI, MAKE-30	Logistic regression	SA-AKI Training: 0.872 Validation: 0.888 MAKE30 0.843
Xia et al. [39]	Patients with SA-AKI in ICU from MIMIC-IV database	Not reported	High serum creatinine, change in serum creatinine within 24 hr, CRRT within 48 hr, lactate	Persistent SA-AKI	Logistic regression	Training: 0.80 Validation: 0.81
Hu et al. [40]	Patients with SA-AKI in ICU Training: MIMIC-III Validation: 102	Training: 2,066 Validation: 102	Older age, admission type, liver disease, metastatic cancer, lactate, BUN/creatinine ratio, creatinine, positive culture, and AKI stage	In-hospital mortality	LASSO, Cox regression	Training: 0.73 Validation: 0.72
Jiang et al. [41]	Patients aged ≥65 yr with persistent SA-AKI >48 hr in ICU from MIMIC MIMIC-IV database	Training: 1,065 Validation: 454	Male, sex, cancer, AKI stage, low GCS score, high BUN, respiratory rate, CRRT within 48 hr, mechanical ventilation	In-hospital mortality	Logistic regression	Training: 0.78 Validation: 0.82
Li et al. [38]	Patients with SA-AKI in ICU Training: MIMIC IV Validation: 344	Training: 1,779 Validation: 344	Age, GCS score, SBP, oxygen saturation, platelet count, WBC, bicarbonate	In-hospital mortality	Logistic regression	Training: 0.829 Validation: 0.760

AKD, acute kidney disease; AKI, acute kidney injury; AUC, area under the receiver operating characteristic curve; BUN, blood urea nitrogen; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; DM, diabetes mellitus; GCS, Glasgow coma scale; HTN, hypertension; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator; MAKE30, major adverse kidney event within 30 days; MAP, mean arterial pressure; MIMIC, Medical Information Mart for Intensive Care; SA-AKI, sepsis-associated acute kidney injury; SBP, systolic blood pressure; WBC, white blood cell count.

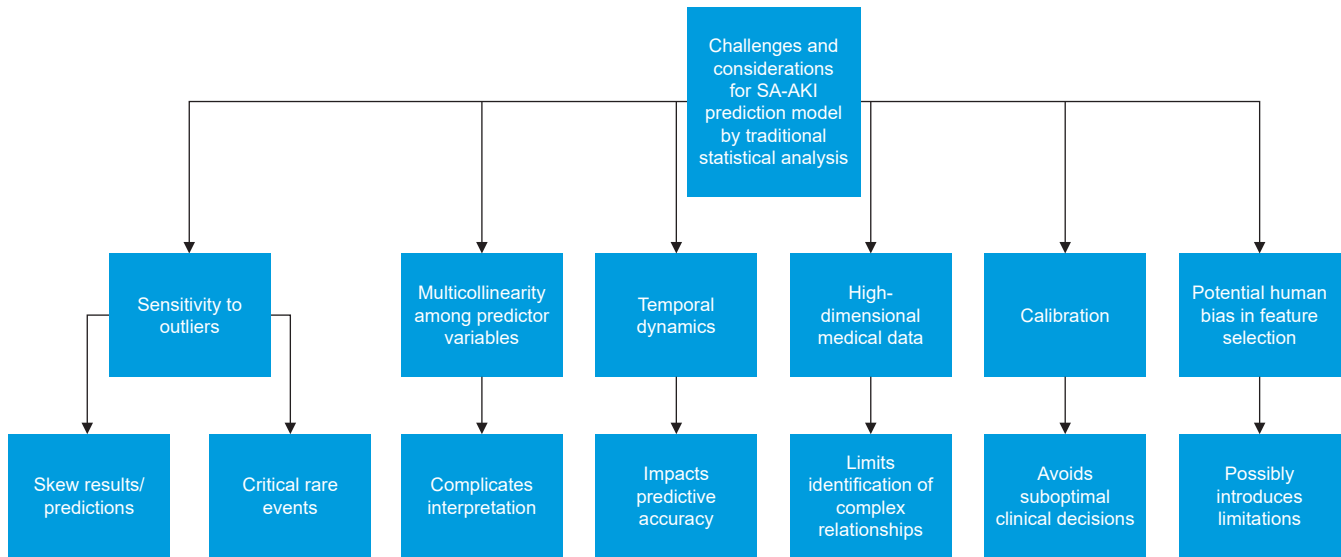


Figure 2. Challenges and considerations for SA-AKI prediction model by traditional statistical analysis.

SA-AKI, sepsis-associated acute kidney injury.

Utilization of novel biomarkers for sepsis-associated acute kidney injury

The timely identification of SA-AKI is crucial for preventing further renal complications. Traditional markers like serum creatinine and urea nitrogen have been primary diagnostic tools but present challenges due to delayed responses and susceptibility to external factors, including age, metabolic rate, and the effects of medications [5,43–49]. As a result, recent investigations have uncovered novel biomarkers with heightened sensitivity and specificity for early SA-AKI detection (Fig. 3) [5,9,43–48,50,51]. The identified biomarkers for SA-AKI have shown varying specificity, sensitivity, and AUC degrees [5,43–48]. For example, neutrophil gelatinase-associated lipocalin in urine/serum has a specificity of 0.84/0.79, sensitivity of 0.87/0.83, and an AUC of 0.92/0.87, kidney injury molecule-1 in urine has a specificity of 0.74, sensitivity of 0.84, and AUC of 0.62, cystatin C in serum has a specificity of 0.84, sensitivity of 0.82, and AUC 0.96, interleukin-18 in urine has an AUC of 0.719, liver fatty acid binding protein in urine has a specificity of 0.74, sensitivity 0.78, and AUC of 0.82, and finally tissue inhibitor metalloproteinase-2/insulin-like growth factor binding protein-7 in urine has a specificity of 0.909, sensitivity of 0.67, and AUC of 0.89.

This diverse range of values for specificity, sensitivity,

and AUC underlines the complexities inherent in AKI diagnosis. Both traditional statistical approaches and biomarker use for SA-AKI diagnosis have numerous challenges. The classic statistical methods, while foundational in many medical research studies, often operate under specific assumptions about data distributions and might not handle outliers or nonlinear patterns effectively. They also might not be adept at deciphering interactions among multiple variables, especially when dealing with high-dimensional datasets, as is common in modern medicine. Biomarkers, while being indispensable tools in the diagnosis and monitoring of many diseases, have their limitations. For sepsis-associated AKI, the main concerns revolve around their sensitivity, specificity, and their overall predictive value. Not all biomarkers perform uniformly across diverse patient populations [9,50,51]. They might also be influenced by a myriad of other factors, such as comorbid conditions, other medications, or even minor variations in sample handling and storage [9,50,51].

These limitations necessitate more advanced methods like the use of AI/ML. Such technologies can overcome traditional challenges by leveraging larger datasets and more intricate analytical tools. Their proficiency in detecting complex nonlinear relationships and discerning patterns in expansive datasets provides insights beyond the reach of conventional methods. AI/ML represents a promising

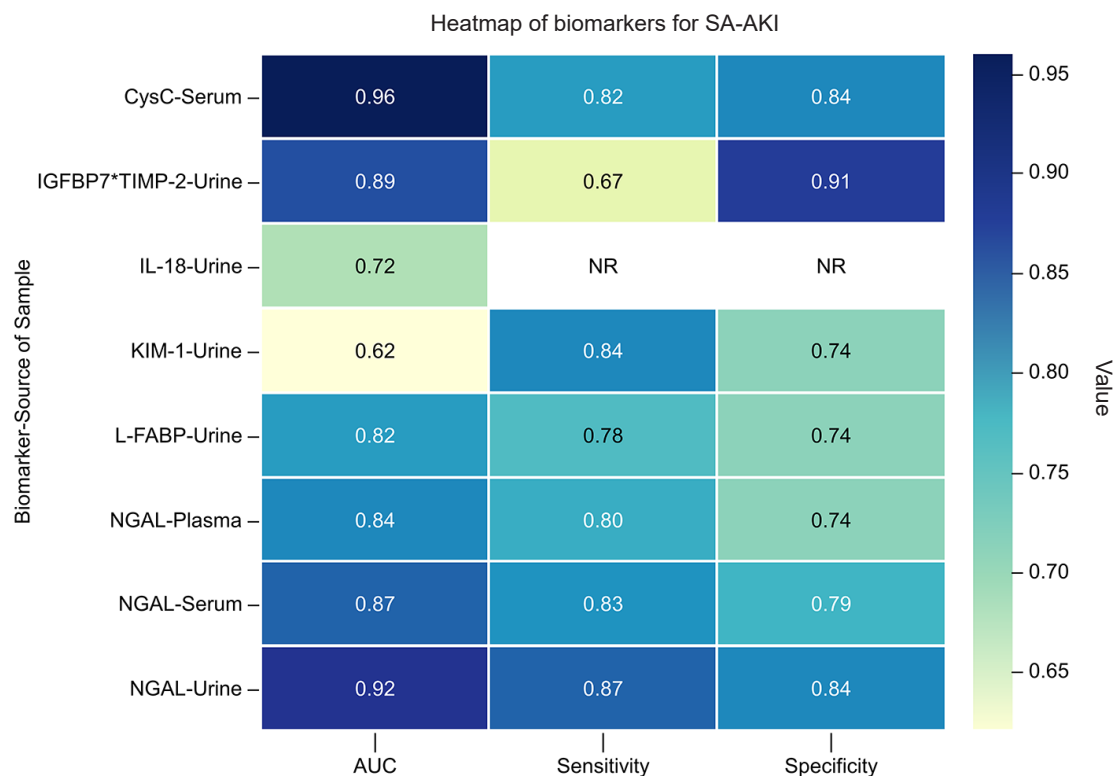


Figure 3. Heatmap of biomarkers for SA-AKI.

AUC, area under the curve; CysC, cystatin C; IGFBP7, insulin-like growth factor binding protein 7; IL-18, interleukin-18; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil-associated lipid transporter protein; NR, not reported; SA-AKI, sepsis-associated acute kidney injury; TIMP-2, tissue inhibitor of metalloproteinase-2.

approach to address the diagnostic complexities of SA-AKI.

Artificial intelligence and machine learning applications in sepsis-associated acute kidney injury

Recent developments in ML have significantly surpassed traditional AKI prediction methods [17,52,53]. Key developments include a deep learning model by Rank et al. [17], which effectively uses electronic health records data to predict AKI with high accuracy (AUC, up to 0.893), all while keeping the physician's workload unchanged. Another study introduced a range of ML models that apply different approaches to estimate baseline serum creatinine, showcasing the importance of error analysis and explainable AI to aid in clinical decisions and prompt AKI treatment [52]. Furthermore, a systematic review underlined the value of externally validated ML models that are effective across

various patient groups, focusing on the necessity of interpretable models and strong predictors. These advances highlight how ML can be seamlessly integrated into clinical practices, significantly improving the early detection and treatment of AKI, marking a substantial shift from theoretical models to actual clinical use [53].

For SA-AKI, ML has emerged as a promising tool in healthcare, presenting innovative solutions to the complexities of medical challenges [22–27]. Three key ML branches play pivotal roles: supervised learning, unsupervised learning, and reinforcement learning (Fig. 4). Each approach leverages abundant patient data to address unique aspects of SA-AKI management, including 1) supervised learning, which facilitates risk prediction; 2) unsupervised learning, which enables patient subgroup identification; and 3) reinforcement learning, which optimizes treatment strategy.

These methodologies equip healthcare professionals to enhance precision and efficiency in prediction, identifi-

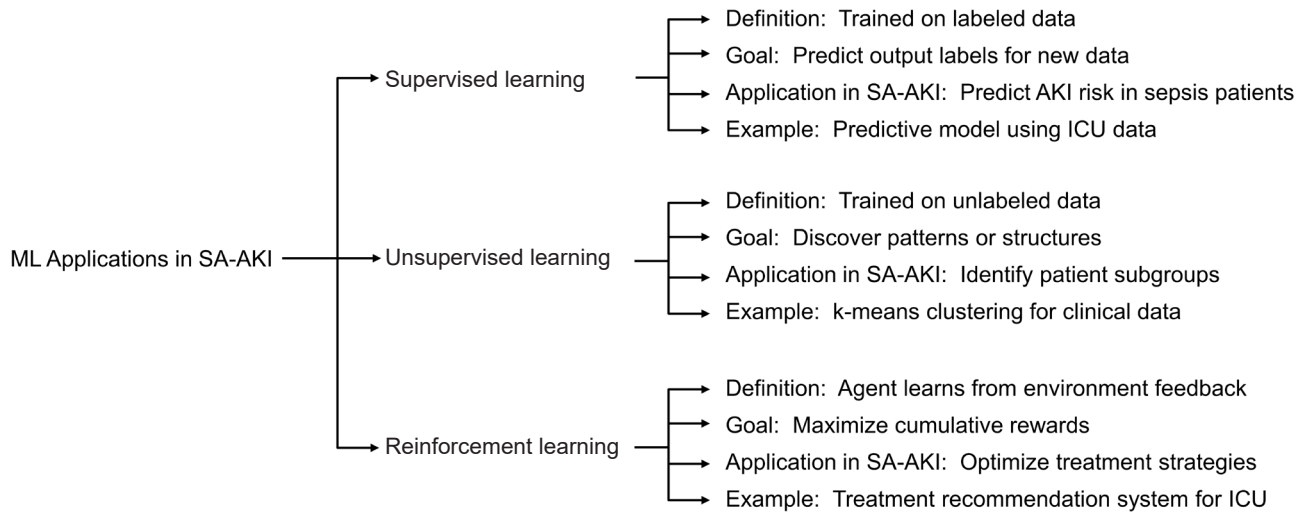


Figure 4. A structured overview of the three primary ML methodologies and their applications in the realm of SA-AKI.

AKI, associated acute kidney injury; ICU, intensive care unit; ML, machine learning; SA-AKI, sepsis-associated AKI.

cation, and optimization for SA-AKI patients. We explore how integrating ML empowers SA-AKI management, from discerning risks early to guiding tailored interventions through continuously optimized protocols. AI/ML represents a transformative approach to tackling the multifaceted difficulties of SA-AKI.

Supervised learning

Supervised learning is a type of ML where the algorithm is trained on labeled data, meaning the input data is paired with corresponding output labels [54]. The primary goal is to learn a mapping function that can accurately predict the output labels for new, unseen data. In the context of SA-AKI, supervised learning can be utilized to predict the risk of AKI in sepsis patients [16,23-31,55]. Researchers can gather historical patient data, including clinical parameters such as vital signs, laboratory results, and patient demographics, as well as information about whether AKI developed during their hospital stay. This data is then used to train a supervised learning model, such as random forest, XGBoost, or artificial neural networks, to predict the likelihood of AKI in sepsis patients [16,23-31]. An example application of supervised learning in SA-AKI is the development of a predictive model that uses patient data from the ICU to identify individuals at high risk of developing AKI as a result of sepsis. The model can provide real-time risk

scores, allowing clinicians to intervene early with appropriate interventions, such as fluid management or medication adjustments, to mitigate the risk of AKI [16,23-31].

Supervised learning has emerged as a pivotal tool in predicting outcomes and characteristics related to SA-AKI, according to published studies (Table 2) [16,23-31]. Researchers have successfully employed ML models to predict the onset of S-AKI, differentiate between persistent and transient AKI, and anticipate in-hospital mortality and acute kidney disease (AKD) occurrence. Notably, models like XGBoost and recurrent neural network (RNN)-long short-term memory (LSTM) were recurrently highlighted for their exceptional performance [16,23-31]. These algorithms often surpassed traditional risk scores such as SOFA (Sequential Organ Failure Assessment) and SAPS II (Simplified Acute Physiology Score II), achieving commendable discrimination metrics [16,23-31]. For instance, in predicting AKI risk in septic patients, an XGBoost model was found to outperform conventional scoring systems, emphasizing the model's utility in pinpointing high-risk patients for proactive interventions [30]. Furthermore, in another instance, an RNN-LSTM model showcased exemplary predictive ability, with a remarkable AUC of 1.0 (Fig. 5), emphasizing its potential in guiding early AKD interventions [31]. Moreover, the application of ML was not limited to SA-AKI. Zhou et al. [30] explored sepsis-associated acute respiratory distress syndrome patients, aiming

Table 2. Examples of Published Supervised Learning for SA-AKI prediction

Author	Population	Sample size	Outcomes	Machine learning techniques	C-statistics/AUC
Zhang et al. [29]	Patient with sepsis in ICU Training: MIMIC-IV Validation: eICU-CRD, ZG	Training: 21,308 Validation eICU-CRD: 24,352 ZG: 505	SA-AKI within 12–48 hr	Ensemble model, combining support vector machine, random forest, neural network, XGBoost via stacking algorithm	eICU-CRD: 0.774–0.788 ZG: 0.756–0.813
Zhou et al. [30]	Patient with SA-ARDS from MIMIC-III database	1,085	SA-AKI	Logistic regression, support vector machine, random forest, XGBoost	Highest C-statistics: XGBoost (0.86)
Yue et al. [26]	Patient with sepsis in ICU from MIMIC-III database	3,176	SA-AKI	Logistic regression, KNN, support vector machine, decision tree, random forest, XGBoost, artificial neural network	Logistic regression: 0.737 KNN: 0.664 Support vector machine: 0.735 Decision tree: 0.749 Random forest: 0.779 XGBoost: 0.817 Artificial neural network: 0.755
Yu et al. [16]	Various hospitalized patients populations from multiple studies.	87 to over 1 million (varying across studies)	Acute kidney injury	Regression, ensemble tree methods, SVM, neural networks, etc.	AUC ranged from 0.69 to 0.98 across studies.
Luo et al. [23]	Patients with SA-AKI in ICU from MIMIC-III database	5,984 (70% training, 30% validation set)	Persistent SA-AKI > 48 hours	Logistic regression, random forest, support vector machine, artificial neural network, XGBoost	Logistic regression: 0.76 Random forest: 0.75 Support vector machine: 0.74 Artificial neural network: 0.76 XGBoost: 0.75
He et al. [31]	Patients with SA-AKI in ICU Training: one hospital in China Validation: MIMIC-III	Training: 209 Validation: 509	Acute kidney disease	RNN-LSTM, decision trees, logistic regression	RNN-LSTM Training: 1.0 Validation: 1.0 Decision trees Training: 0.954 Validation: 0.872 Logistic regression Training: 0.728 Validation: 0.717
Li et al. [24]	Patients with SA-AKI in ICU from MIMIC IV database	Training: 6,503 Validation: 1,626	In-hospital mortality	Logistic regression, support vector machine, KNN, decision tree, random forest, XGBoost	Logistic regression: 0.730 Support vector machine: 0.680 KNN: 0.601 Decision tree: 0.585 Random forest: 0.778 XGBoost: 0.794
Zhou et al. [25]	Patients with SA-AKI in ICU Training/validation: MIMIC-IV External Validation: 2 hospitals in China	16,154 (80% training, 20% validation set) external validation set: 132	In-hospital mortality	Categorical boosting, gradient boosting decision tree, light gradient boosting, adaptive boosting, XGBoost, KNN, multilayer perception, logistic regression, naive Bayes, support vector machine	Categorical boosting: 0.83, ext - 0.75 Gradient boosting decision tree: 0.82, ext - 0.62 Light gradient boosting: 0.8, ext - 0.61 Adaptive boosting: 0.82, ext - 0.60 XGBoost: 0.81, ext - 0.57 KNN: 0.80, ext - 0.63 Multilayer perception: 0.79, ext - 0.63 Logistic regression: 0.79, ext - 0.71 Naive Bayes: 0.76, ext - 0.60 Support vector machine: 0.76, ext - 0.68

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Table 2. Continued

Author	Population	Sample size	Outcomes	Machine learning techniques	C-statistics/AUC
Fan et al. [28]	Patients with SA-AKI in ICU Training: MIMIC IV Validation: one hospital in China	Training: 2,499 External validation: 100	7- day mortality	Logistic regression, random forest, XGBoost, multilayer perception, support vector machine	Logistic regression: 0.75, ext - 0.70 Random forest: 0.84, ext - 0.78 XGBoost: 0.91, ext - 0.81 Multilayer perception: 0.75, ext - 0.72 Support vector machine: 0.80, ext - 0.64
Yang et al. [27]	Patients with SA-AKI in ICU from MIMIC IV database	9,158 (70% training, 30% validation set)	28-day mortality	Logistic regression, random forest, gradient boosting machine, XGBoost	Logistic regression: 0.850 Random forest: 0.849 Gradient boosting machine: 0.865 XGBoost: 0.873

AUC, area under the receiver operating characteristic curve; eICU-CRD, eICU Collaborative Research Database; Ext, external validation; ICUs, intensive care units; KNN, *k*-nearest neighbors; MIMIC, Medical Information Mart for Intensive Care; RNN-LSTM, recurrent neural network-long short-term memory; SA-AKI, sepsis-associated acute kidney injury; SA-ARDS, sepsis-associated acute respiratory distress syndrome; SVM, support vector machine; XGBoost, eXtreme Gradient Boosting; ZG, Zhejiang University's Affiliated Hospitals' database.

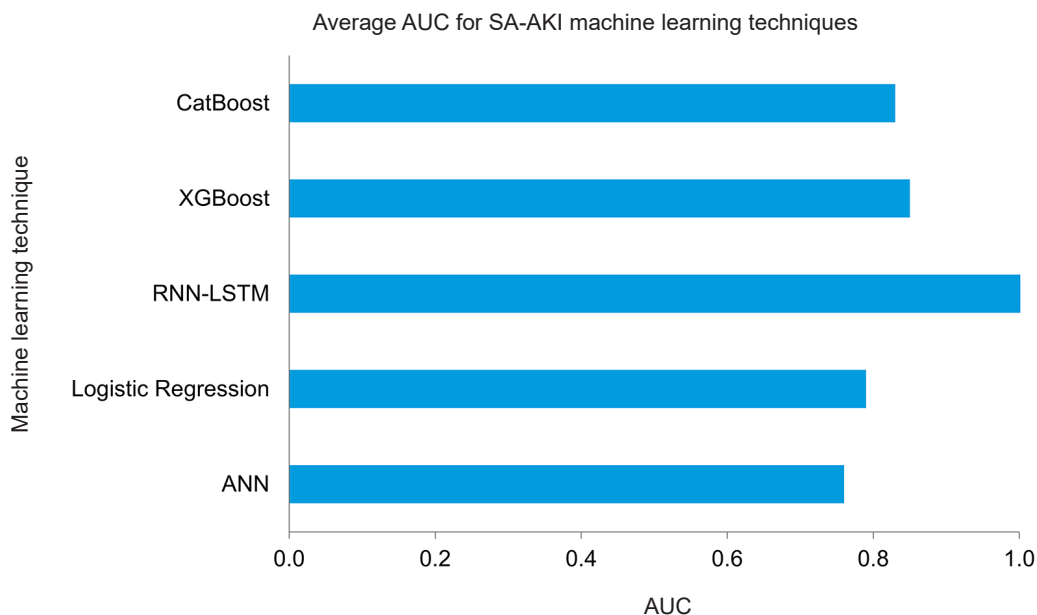


Figure 5. Performance of various machine learning techniques for SA-AKI prediction. ANN, artificial neural network; AUC, area under the curve; CatBoost, Categorical Boosting; Logistic Regression, a statistical method for analyzing datasets in which there are one or more independent variables that determine an outcome; RNN-LSTM, recurrent neural network-long short-term memory; SA-AKI, sepsis-associated acute kidney injury; XGBoost, Extreme Gradient Boosting.

to predict AKI development within a short timeframe post-ICU admission. Here, the XGBoost model once again stood out, indicating its versatility across related medical conditions. A review study by Yu et al. [16] further underlined the importance of ML by summarizing various models tailored for predicting AKI across diverse patient groups and environments. The compiled results suggested that while ML

models displayed a range from moderate to superb discrimination for AKI events, there remains room for further refinement and evaluation in real-world clinical settings [16,23-31].

In reflecting upon the strengths of these ML-centered studies, it becomes evident that such methodologies offer several advantages over traditional statistical analysis ap-

proaches. ML models, given their ability to handle large data sets and complex interactions, tend to produce more accurate, robust, and generalizable findings [54]. These models are especially skilled at uncovering nonlinear relationships, thereby providing a more sophisticated understanding of the data's underlying patterns. Moreover, the ability of ML models to surpass traditional risk scores highlights their transformative potential in patient care. This is particularly relevant for early detection and intervention strategies, which can significantly improve patient outcomes.

Unsupervised learning

Unsupervised learning involves training ML algorithms on unlabeled data to discover patterns, structures, or relationships within the data [56,57]. Clustering is a notable technique in unsupervised learning, where algorithms categorize similar data points into groups. In the specialized context of SA-AKI, unsupervised learning provides invaluable insights by delineating distinct subgroups of

sepsis patients, each characterized by unique clinical profiles and outcomes. For instance, an unsupervised learning algorithm like k-means clustering can be employed to analyze clinical data from sepsis patients, including vital signs, laboratory results, and comorbidity information. This can reveal different clusters of patients with similar clinical characteristics. Clinicians can then evaluate whether these specific patient clusters have different risks of developing AKI, thereby facilitating the formulation of more personalized treatment plans.

Recently, Lai et al. [32] conducted a prospective observational cohort study of 999 critically ill patients with dialysis-requiring SA-AKI admitted to surgical ICUs in Taiwan between 2009 and 2018. The mean age was 63.9 years, and 71.5% were male. The authors performed unsupervised consensus clustering based on 23 clinical variables upon initializing renal replacement therapy to identify distinct sub-phenotypes (Fig. 6). Three sub-phenotypes that were identified included 1) cluster 1 (n = 352) with favorable baseline conditions but greatest acute illness severity, 2) cluster 2 (n = 396) with intermediate features, and 3) clus-

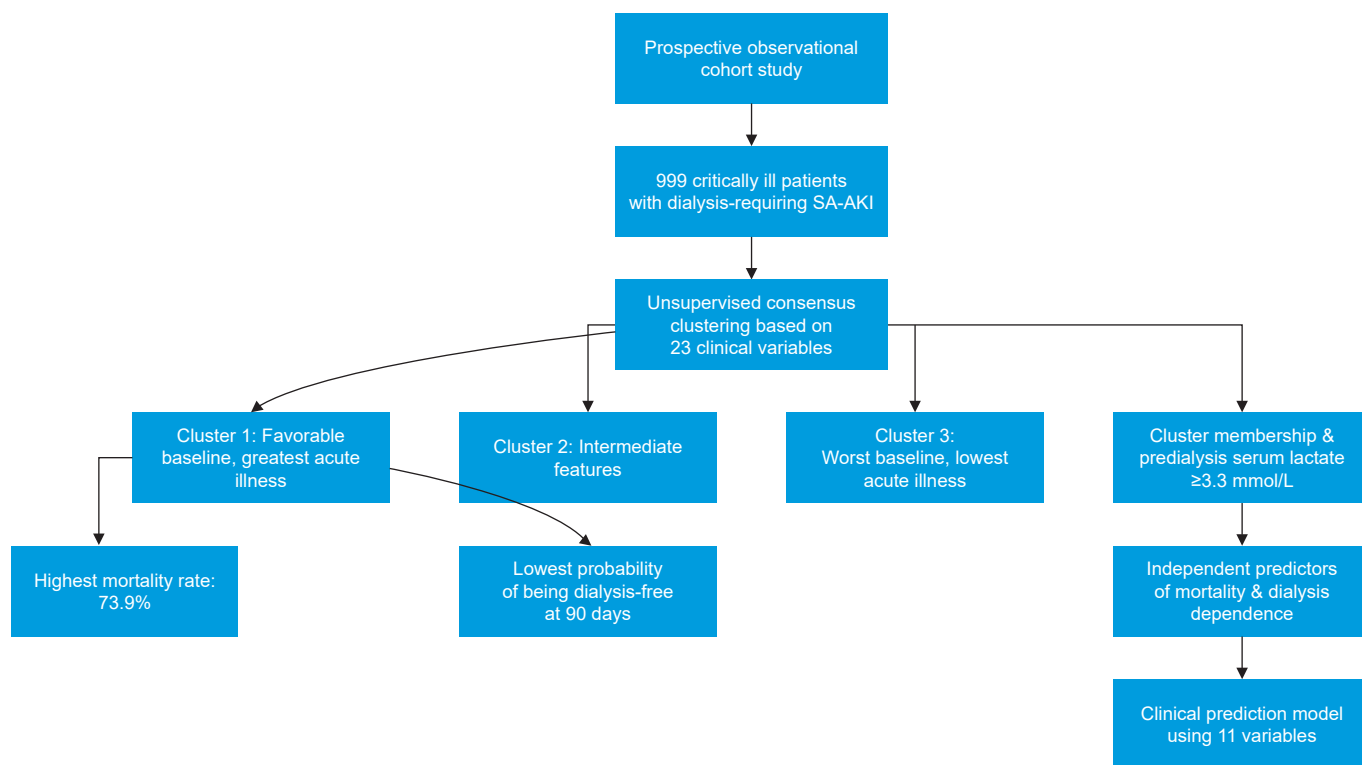


Figure 6. Flow diagram illustrating the study on SA-AKI sub-phenotypes.

SA-AKI, sepsis-associated acute kidney injury.

ter 3 (n = 251) with worst baseline conditions but lowest acute illness severity. Cluster 1 had the highest mortality rate (73.9%) and lowest probability of being dialysis-free at 90 days. Cluster membership and predialysis serum lactate ≥ 3.3 mmol/L were independent predictors of mortality and dialysis dependence. A clinical prediction model using 11 variables accurately identified cluster 1 as a high-risk sub-phenotype (AUC, 0.99). When applied to an external validation cohort of 898 SA-AKI patients, the model identified a high-risk subgroup with increased mortality. This study demonstrates that ML approaches can identify clinically relevant sub-phenotypes and predictors in heterogeneous syndromes like SA-AKI.

Reinforcement learning

Reinforcement learning is a type of ML where an agent learns to make decisions by interacting with an environment. The agent receives feedback in the form of rewards or penalties based on its actions, and its objective is to maximize cumulative rewards over time. In the context of SA-AKI, reinforcement learning can be used to optimize treatment strategies for sepsis patients to minimize the risk

of AKI. An example application of reinforcement learning in SA-AKI is developing a treatment recommendation system for sepsis patients in the ICU (Fig. 7). The reinforcement learning agent can learn from historical patient data and clinical guidelines to recommend actions such as fluid administration, antibiotic choices, and vasopressor usage. The agent continually adapts its recommendations based on patient responses and outcomes, aiming to optimize patient care and reduce the incidence of AKI.

Reinforcement learning has been studied with promising findings for potential utilization among critically ill patients with sepsis [58–64]. From optimizing fluid resuscitation strategies to determining when and which antibiotics should be administered, RL agents have showcased their capability to refine treatment strategies based on patient feedback and outcomes continuously. Moreover, the technology presents the appealing possibility of integrating extensive datasets, facilitating a more comprehensive patient management approach that considers a multitude of variables [58–64]. Notwithstanding these advancements, there remains a notable deficiency in data concerning the specific employment of reinforcement learning for SA-AKI, underscoring the need for dedicated future investigations.

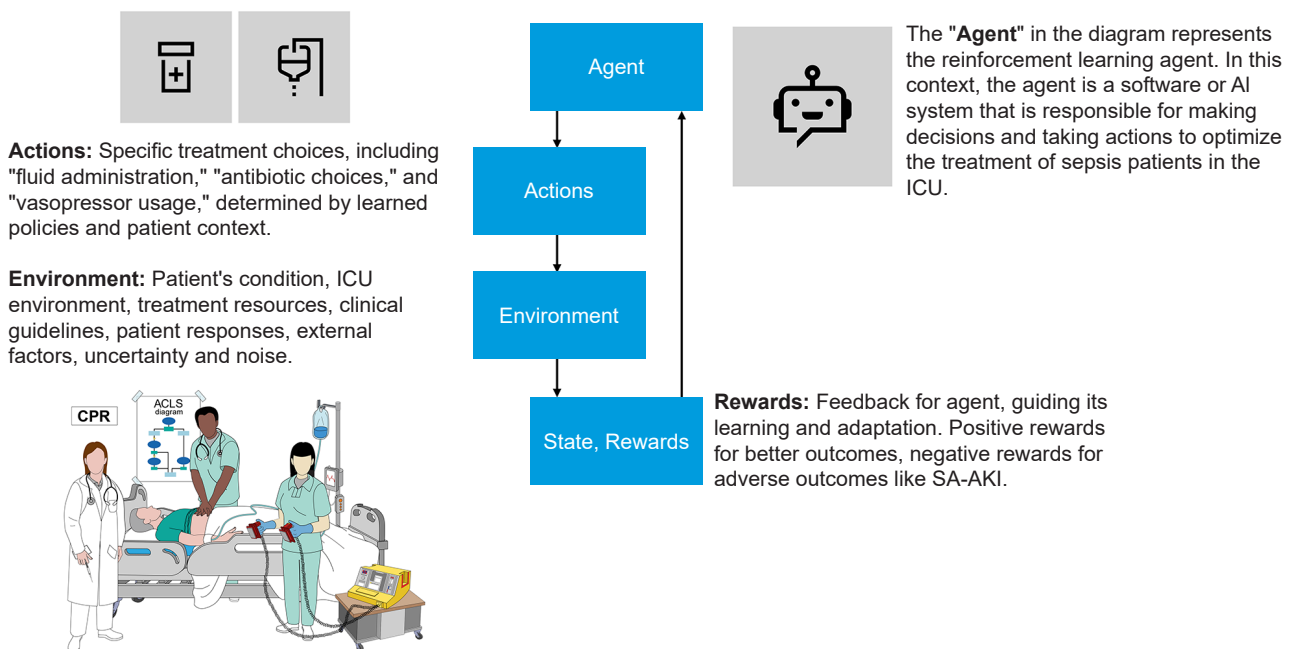


Figure 7. Reinforcement learning for sepsis treatment optimization to prevent acute kidney injury.

ACLS, advanced cardiac life support; AI, artificial intelligence; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; SA-AKI, sepsis-associated acute kidney injury.

Constraints and ethical considerations

AI and ML have shown tremendous potential in the medical field, including in identifying and managing SA-AKI. However, utilizing these tools is not without challenges and ethical considerations [54,65–67].

Data privacy and security concerns

In medical research using ML models, protecting patient data is critical. This encompasses the challenges of ensuring that AI tools neither inadvertently expose nor misuse this confidential information. Additionally, the secure transfer of such data, which frequently traverses between various databases, servers, and institutions, demands the implementation of robust and encrypted protocols to thwart potential breaches. Concurrently, the ethical imperative of obtaining informed consent cannot be understated, emphasizing the necessity for patients to be comprehensively apprised of the utilization and repercussions associated with their data in AI-driven systems. ML models need to be broadly applicable and independently validated. The challenge is making them effective across various healthcare settings. Federated learning is a new approach that improves these models by learning from spread-out data without compromising privacy. This strategy tackles data silos and fosters the development of robust models delivering consistent results across diverse settings. Promoting federated learning and the standardization of ML models is crucial for achieving trustworthy, universal AI healthcare solutions.

Bias and fairness in artificial intelligence algorithms

Bias can emerge in AI models if the training data lacks representation from the broader population. For example, an algorithm predominately informed by data from a single ethnic group may not be as productive for another, possibly resulting in erroneous predictions or misdiagnoses of SA-AKI risk. Moreover, the opaque nature of “black-box” algorithms, which obscure their decision-making processes, raises ethical quandaries. Healthcare practitioners must discern mechanisms by which these AI models derive their outcomes, especially when these outcomes influence critical medical decisions. Nevertheless, techniques such

as SHAP (Shapley Additive exPlanations), Gradient-based Class Activation Mapping (Grad-CAM), and LIME (Local Interpretable Model-agnostic Explanations) can enhance the model’s explainability [20]. These methods highlight the features significantly influencing model predictions, offering more profound insights into its decision-making process. Incorporating these techniques not only improves the interpretability of deep learning models but also bolsters trust and reliability in their application to SA-AKI research and clinical practices.

Regulatory and legal aspects

Integrating AI and ML tools in SA-AKI research and therapeutic interventions necessitates the establishment of standardized protocols and guidelines. Alongside standardization, a complex challenge emerges of ascertaining accountability in AI-induced misdiagnoses or mistreatments, raising questions about whether the onus lies with the software developers, the healthcare establishment, or the treating physician. Furthermore, akin to pharmacological agents or medical apparatuses, AI instruments might be subject to rigorous clinical evaluations and requisite regulatory endorsements before widespread adoption.

Future directions

The advancement of AI technologies holds promise in transforming the landscape of SA-AKI research. Notably, the integration of AI facilitates real-time monitoring of susceptible patients, potentially paving the way for instantaneous therapeutic interventions. Reinforcement learning, a specialized subset of ML, can elucidate optimal therapeutic strategies through simulation and iterative learning from diverse clinical scenarios. Furthermore, generative AI models emerge as instrumental tools in generating simulated patient data [68,69], thereby enriching our comprehension of SA-AKI’s pathophysiology and enabling accurate prognostications of its progression. Foundation models and large language models (LLMs) have demonstrated significant progress in healthcare [68,70], notably in analyzing complex data to enhance patient care. They learn from extensive datasets, adapting to specific tasks with minimal manual input, which can lower the costs of AI development and maintenance in hospitals. A recent

study highlighted the effectiveness of LLMs in interpreting continuous renal replacement therapy machine alarms in intensive care [71], suggesting they could be integrated into critical care. Yet, this area is still developing and needs more research to reach its full potential.

As AI continues its innovation trajectory, personalized medicine stands at the forefront of its transformative potential. Through AI's analytical prowess, treatment regimens can be meticulously tailored, considering an individual's genetic composition, historical medical data, and myriad other determinants. Additionally, AI-powered predictive modalities are poised to give healthcare practitioners invaluable foresight, facilitating the early identification of patients at high risk of SA-AKI, thus ensuring timely medical interventions. Further amplifying its potential, integrating AI systems across medical establishments might catalyze collaborative learning, refining and enhancing predictive algorithms.

Conclusion

In SA-AKI research and therapeutic interventions, AI emerges as a transformative catalyst, poised to redefine diagnostics, risk stratification, and treatment modalities. The potential of AI to revolutionize early detection through advanced algorithms and real-time monitoring is juxtaposed with multifaceted challenges encompassing data security, biases in algorithmic outcomes, and intricate regulatory frameworks. As we venture further into the AI-driven era of medicine, the confluence of these technologies promises a paradigm shift towards more personalized, predictive, and collaborative healthcare. Therefore, it mandates rigorous ethical, technical, and legal safeguards to utilize its beneficial potential without causing harm.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Investigation: All authors

Supervision: KBK

Visualization: WC, KBK

Writing—original draft: WC, CT, KBK

Writing—review & editing: WC, CT, KBK

All authors read and approved the final manuscript.

ORCID

Wisit Cheungpasitporn, <https://orcid.org/0000-0001-9954-9711>

Charat Thongprayoon, <https://orcid.org/0000-0002-8313-3604>

Kianoush B. Kashani, <https://orcid.org/0000-0003-2184-3683>

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