Rates, predictors and mortality of sepsis-associated acute kidney injury: systematic review and meta-analysis

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Research article

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Abstract

Objective: The incidence and mortality of sepsis-induced acute kidney injury is high. Many studies have explored the causes of sepsis-induced acute kidney injury (AKI). However, its predictors are still uncertain; additionally, a complete overview is missing. A systematic review and a meta-analysis were performed to determine the predisposing factors for sepsis-induced AKI.

Method: A systematic literature search was performed in the Medline, Embase, Cochrane Library, PubMed and Web of Science databases, with an end date parameter of May 25, 2019. Valid data were retrieved in compliance with the inclusion and exclusion criteria.

Result: Forty-seven observational studies were included for analysis. A cumulative number of 55911 sepsis patients were evaluated. The incidence of AKI caused by septic shock is the highest. 30 possible risk factors were included in the meta-analysis. The results showed that 20 factors were found to be significant. The odds ratio (OR), 95% confidence interval (CI) and Prevalence of the most prevalent predisposing factors for sepsis-induced AKI were as the following: Septic shock \([2.88(2.36-3.52), 60.47\%]\), Hypertension \([1.43(1.20-1.70), 38.39\%]\), Diabetes mellitus \([1.59(1.47-1.71), 27.57\%]\), Abdominal infection \([1.44(1.32-1.58), 30.87\%]\), Vasopressors use \([2.95(1.67-5.22), 64.61\%]\), Vasoactive drugs use \([3.85(1.89-7.87), 63.22\%]\), Mechanical ventilation \([1.64(1.24-2.16), 68.00\%]\), Positive blood culture \([1.60(1.35-1.89), 41.19\%]\), Smoke history \([1.60(1.09-2.36), 43.09\%]\). Other risk factors include cardiovascular, coronary artery disease, liver disease, unknown infection, diuretics use, ACEI or ARB, gram-negative bacteria and organ transplant.

Conclusion: A large number of factors are associated with AKI development in sepsis patients. Our review can guide risk-reducing interventions, clinical prediction rules, and patient-specific treatment and management strategies for sepsis-induced acute kidney injury.

Background

Sepsis-associated acute kidney injury (S-AKI) is a major public health condition with great disease burden. S-AKI is a syndrome of acute functional impairment and organ damage that could be associated with long-term adverse outcomes. Sepsis is the most common cause of acute kidney injury (AKI) in critically-ill patients, which can be observed in 40-50% of AKI patients. Importantly, S-AKI is closely associated with poor clinical outcomes. For instance, the mortality rate of sepsis patients with AKI complication is significantly higher than that of the non-AKI patients. Among critically-ill patients with AKI, S-AKI is correlated with a higher risk of in-hospital death and longer hospital stay than AKI caused by any other reasons. Despite multiple advances have been achieved in medicine and surgery treatment, the morbidity remains rather high. Mounting evidence suggested that AKI incidence has been increasing. A 10-year cohort study that included more than 90,000 patients from more than 20 ICUs indicated that AKI incidence increased by 2.8% per year. Moreover, along with the global aging trend, majority of the sepsis patients were elderly, and the number of patients with sepsis-associated AKI may continue to increase.
Sepsis-associated AKI portends a high burden of morbidity and mortality in both children and adults with critical illness. Unfortunately, the pathogenesis of S-AKI is still not completely understood. There are also difficulties in the early diagnosis and treatment of S-AKI awaiting to be solved. Therefore, early identification of risk factors and prevention of S-AKI is extremely important. Although a number of studies have explored the risk factors for AKI development in sepsis patients, the opinions remain inconclusive due to regional differences and the inconsistency of the diagnostic criteria of sepsis and AKI. Our study aimed to systematically review previous observational studies (cohort/case-control studies) and to perform meta-analyses with the eligible evidence to investigate the association between sepsis and AKI.

**Methods**

**Inclusion Criteria**

Studies that met the following criteria were included for data extraction: (1) Patients were older than 16 years with a hospitalization stay of greater than 24 hours; (2) Studies contained information on 2×2 contingency table; (3) Sepsis and septic shock were diagnosed based on internationally-recognized standards, such as sepsis 1.0, sepsis 2.0, sepsis 3.0; (4) Acute kidney injury was diagnosed based on internationally-recognized standards, such as KDIGO, AKIN and RIFLE; (5) Cohort or case-control studies in which the patients were grouped into sepsis AKI and sepsis non-AKI.

**Data Sources and Search Strategy**

A systematic review and meta-analysis of scientific peer-reviewed literature were performed by following the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline (see Additional files 1).

The systematic literature search was performed in the Medline, Embase, Cochrane Library, PubMed and Web of Science databases from inception to June 2019 with no restrictions to retrieve studies that assessed the risk of AKI development in sepsis patients. The following search terms were used: (septic OR sepsis OR severe sepsis OR Septicemia OR septic shock OR sepsis-associated OR sepsis-associated) AND (Acute Kidney Injury OR Acute Renal Injury OR Acute Renal Insufficiency OR AKI OR acute renal failure OR ARF). The reference list of the included articles was also manually retrieved. Gray literature (generally refers to literature that was not published) and conference abstracts were not included.

**Data Extraction**

Two independent reviewers participated in the entire process of literature retrieval. The first-round screening was performed based on the title and abstract to exclude studies on irrelevant topics. Next, the included articles were screened based on full text and ineligible articles that did not meet the inclusion criteria were excluded. Data extraction was performed using a standardized data collection form, including:
1. study characteristics: publication year, study design, country of origin, sepsis and acute kidney injury diagnostic criteria, sepsis type, period of data report;

2. number of the 2×2 contingency table and unadjusted crude odds ratios with regard to demographic data (gender) and investigated independent variables/predictors (comorbidities, source of infection, medication, invasive treatment, sepsis types and blood culture);

3. outcome: the primary endpoint was S-AKI, and the secondary outcome was prevalence of influence factors and mortality in patients with S-AKI.

Quality Assessment

Study selection, data extraction, and quality assessment were independently performed by two authors. Any disagreements would be resolved through discussions until a consensus was reached. If disagreements persisted, another reviewer would be invited to the discussion to achieve a final consent. Quality assessment of the observational studies that were included in the meta-analysis was performed using the Newcastle-Ottawa scale (available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Statistical Analysis

The core characteristics of the study and patients were sorted out and summarized. The frequency distribution was expressed as a percentage. For the meta-analysis, we only used unadjusted crude odds ratios (OR) from no less than 3 studies to standardize the results due to the great variability of multivariable models across studies. Stata/SE version 11 was used for statistical analyses and a two-sided \( P \) value of 0.05 or less was considered statistical significant. Heterogeneity among studies was evaluated by calculating the \( I^2 \) statistic (significance level at \( I^2 > 50\% \)) and chi-square test (significance level at \( P < 0.10 \)). \( I^2 \) values of 25\% and 75\% were used as the criteria for classifying the degree of intertrial heterogeneity (\( I^2 < 25\% \) low heterogeneity, \( I^2 > 25\% \) while \( < 75\% \) moderate heterogeneity, \( I^2 > 75\% \) high heterogeneity). If severe heterogeneity was present at \( I^2 > 50\% \), the random effect models were chosen, otherwise the fixed effect models were used. For results with a heterogeneity of less than 50\% and a fixed-effect model, the stability would be explored by transforming into a random effects model. Meta regression and subgroup analyses (≥ 6 studies) were conducted according to publication year, study design, country of origin, sepsis type and diagnostic criteria of acute kidney injury and sepsis, on the condition of high intertrial heterogeneity presented (\( I^2 > 50\% \) and \( P < 0.10 \)). A sensitivities analysis of the overall risk (≥ 3 studies) was conducted by omitting 1 study in each turn, to estimate the impact of individual study. The publication bias was visually examined by using funnel plots, and the Egger test was used to carry out asymmetric test on the pooled data of ≥ 7 studies.

Results

1. Literature search (Figure 1)
8033 records from the Medline, Embase, Cochrane Library, PubMed and Web of Science databases were initially identified. After filtering by title and abstract, duplicate articles, review studies, and those on unrelated topics were excluded, and 626 studies were reviewed in full text. After excluding the comment papers, studies with inconsistent control settings, articles with unspecified AKI or sepsis diagnostic criteria, studies performed in special population, and those with limited data, 47 articles met the inclusion criteria and were included in the systematic review and meta-analysis.

2. Characteristics of the Included Studies (Table 1)

The characteristics of the included articles were shown in Table 1. Studies were published between 2008 and 2019, and were from eighteen countries (Spain, Greece, United Kingdom, France, Netherlands, Sweden, Canada, United States, Brazil, China, Japan, Saudi Arabia, Turkey, Finland, Portugal, South Korea and Australia) on four continents (Europe, America, Asia and Oceania). Overall 12 retrospective cohort studies, 25 prospective cohort studies and 12 case-control studies were included, with a total of 55,911 sepsis patients. Document quality assessment showed that the methodological quality of all studies was high, achieving a quality score of 8 ($\geq 6$).

3. Summary data from the included studies (Table 2)

This study summarized the characteristics of sepsis patients who developed AKI. ICU mortality, hospital mortality, 28-day mortality and 90-day mortality of S-AKI were respectively reported at 45.99% (1899/4325) in 15 studies, 49.84% (2732/5481) in 10 studies, 36.67% (161/439) in 4 studies, 64.66% (2406/3721) in 5 studies. In S-AKI patients, all mortality rates of AKI caused by septic shock were the highest, while that caused by severe sepsis was the lowest.

The most prevalent comorbidity was ARDS (47.02%, 489/1040, from 3 studies), followed by hypertension (38.39%, 3263/8500, from 32 studies), diabetes (27.57%, 2248/8155, from 32 studies) and stroke (22.79%, 67/294, from 4 studies), while cirrhosis and liver disease accounted for only 4.71% (99/2104, from 6 studies) and 3.74% (554/14081, from 7 studies) respectively. Hepatic failure was more common in sepsis patients compared with those with septic shock and severe sepsis. Hypertension in septic shock was less common than sepsis and severe sepsis (26.16% VS 42.28% and 58.07%), while chronic kidney disease was more prevalent (45.13% VS 15.52% and 11.02%). Hypertension and diabetes were more prevalent in severe sepsis than in sepsis and septic shock (58.7% VS 42.28% and 26.16%, 30.20% VS 20.53% and 26.75%).

On admission, patient source mainly included emergency admission (50.88%, 9235/18149, from 8 studies) and medical admission (47.02%, 8701/18506, from 7 studies), followed by operative admission and surgical ward. Vasoactive drugs were the most commonly used drugs, accounting for 64.61% (1293/2001, from 5 studies), among which vasopressors was the most frequently used, accounting for 63.22% (911/1441, from 7 studies), followed by steroids, diuretics, ACEI or ARB, stains and NSAIDS. Vasoactive drugs and vasopressors were more prevalent in septic shock and severe sepsis than in sepsis.
Six sources of infection were reported in this study, including pulmonary infection (46.05%, 1480/3214, from 19 studies), respiratory infection (32.08%, 85/273, from 7 studies), abdominal infection (30.87%, 2152/6971, from 25 studies), urinary tract infection (11.14%, 630/5653, from 19 studies), skin or soft tissue infection (6.03%, 335/5554, from 13 studies), and unknown infection (6.02%, 100/1662, from 4 studies).

Community acquired infection was reported in 3 studies with a prevalence of 57.36% (2041/3558), which was higher than nosocomial acquired infection reported in 2 studies (39.81%, 2474/6215). Twenty-four studies reported mechanical ventilation in 68.00% of the patients (7167/10539, from 24 studies), and mechanical ventilation was more frequently used in septic shock and severe sepsis cases compared with sepsis cases. Other prevalent factors included positive blood culture (41.38%, 3259/7876, from 8 studies) and smoking history (43.09%, 642/1490, from 5 studies).

4. Risk factors for AKI (Figure 2)

Comorbidities

The pooled data on hypertension from 32 studies indicated that it was a significant predictor (OR 1.43, 95%CI 1.20-1.70), with a moderate heterogeneity ($I^2 = 74.00\%$). Source of heterogeneity was not identified through subgroup analysis. The results of the sensitivity analysis were consistent. After excluding 3 studies with rather high heterogeneity, the heterogeneity decreased and the result remained stable (see Additional files 2).

The pooled data on diabetes mellitus from 32 studies indicated that it was a significant predictor (OR 1.59, 95%CI 1.47-1.71), with a moderate heterogeneity ($I^2 = 37.1\%$). The results remained stable even with random effect model (see Additional files 3).

The pooled data on chronic kidney disease from 14 studies indicated that it was a significant predictor (OR 3.49, 95%CI 2.36-5.15), with a moderate heterogeneity ($I^2 = 71.70\%$). Source of heterogeneity was not identified through subgroup analysis. The results of the sensitivity analysis were consistent. After excluding the study with high heterogeneity, the $I^2$ was reduced to 25.6% (low heterogeneity) and the result remained stable (see Additional files 4).

Cardiovascular disease (from 14 studies, OR 1.31, 95%CI 1.24-1.40) and liver disease (from 17 studies, OR 1.68, 95%CI 1.47-1.90) were identified as risk factors with low heterogeneity, and the results remained stable even with random effect model (see Additional files 5 and 6).

The pooled data on coronary artery disease from 8 studies indicated that it was a significant predictor (OR 1.27, 95%CI 1.08-1.49), with a moderate heterogeneity ($I^2 = 37.1\%$). The results remained stable with the random effect model (see Additional files 7).

Source of infection
The pooled data on pulmonary infection from 8 studies indicated that it was a significant predictor (OR 0.77, 95% CI 0.60-0.99), with a moderate heterogeneity ($I^2 = 77.60\%$). Source of heterogeneity was not identified through subgroup analysis. The results of the sensitivity analysis were consistent (see Additional files 8).

The pooled data on abdominal infection from 25 studies indicated that it was a significant predictor (OR 1.44, 95% CI 1.32-1.58), with a moderate heterogeneity ($I^2 = 40.20\%$). The results of the sensitivity analysis were consistent. After excluding a study with high heterogeneity, the result remained stable, and the results were also stable with the fixed effect model (see Additional files 9).

The pooled data on unknown infection from 25 studies indicated that it was a significant predictor (OR 2.01, 95% CI 1.35-2.98), with a low heterogeneity ($I^2 = 0\%$). The results were still stable with the random effect model (see Additional files 10).

**Medications**

Vasopressors (from 7 studies, OR 3.15, 95% CI 2.00-4.96) and ACEI or ARB (from 8 studies, OR 1.61, 95% CI 1.10-2.36) were all identified as risk factors with high heterogeneity ($I^2 \geq 75\%$). Source of heterogeneity was not identified through subgroup analysis and the sensitivity analysis results were stable (see Additional files 11).

The pooled data on diuretics from 5 studies indicated that it was a significant predictor (OR 1.40, 95% CI 1.13-1.72), with a low heterogeneity ($I^2 = 0\%$). The results remained stable with the random effect model (see Additional files 12).

Figure 3. Forest plot for meta-analysis of the association between male sex and AKI

**Other factors**

The pooled data on male sex from 43 studies indicated that it was a significant predictor (OR 1.22, 95% CI 1.06-1.40), with a moderate heterogeneity ($I^2 = 69.80\%$). Source of heterogeneity was not identified through subgroup analysis. The sensitivity analysis results were consistent (see Additional files 13).

The pooled data on positive blood culture from 9 studies indicated that it was a significant predictor (OR 1.60, 95% CI 1.35-1.89), with a moderate heterogeneity ($I^2 = 50.20\%$). Source of heterogeneity was not identified through subgroup analysis. The sensitivity analysis results were consistent (see Additional files 14).

The pooled data on smoking history from 5 studies indicated that it was a significant predictor (OR 1.60, 95% CI 1.09-2.36), with a high heterogeneity ($I^2 = 78.30\%$). The sensitivity analysis results were consistent. After excluding a study with high heterogeneity, the result remained stable (see Additional files 15).
The pooled data on septic shock from 7 studies indicated that it was a significant predictor (OR 1.40, 95% CI 1.13-1.72), with a low heterogeneity ($I^2 = 8.2\%$). The results were still stable with the random effect model (see Additional files 16).

Gram-negative bacteria (from 3 studies, OR 2.19, 95% CI 1.52-3.15) and organ transplant (from 3 studies, OR 1.96, 95% CI 1.48-2.61) were all identified as risk factors with low heterogeneity ($I^2 = 0\%$), and the results remained stable with the random effect model (see Additional files 17 and 18).

The pooled data on mechanical ventilation from 24 studies indicated that it was a significant predictor (OR 1.64, 95% CI 1.24-2.16), with a high heterogeneity ($I^2 = 88.70\%$). Source of heterogeneity was not identified through subgroup analysis. The sensitivity analysis results were consistent (see Additional files 19).

5. Tests for Publication Bias (Figure 2)

The Egger's rank correlation test and the Egger linear regression test indicated no publication bias of all risk factors ($\geq$ 7 studies) except for cardiovascular disease ($P = 0.015$). Due to the limited study number ($\leq$ 7 studies), publication bias was not evaluated with the predictors of smoking history, cirrhosis, multiorgan dysfunction ($\geq$ 3); unknown infection, vasoactive drug administration, use of diuretics and organ transplant.

Discussion

Major Findings

To the best of our knowledge, this is the first meta-analysis providing comprehensive insights into the risk factors for AKI in sepsis patients. In total, 47 studies including 55,911 sepsis patients were included, and 46 risk factors were examined in the systematic review. The results showed that 19 factors were found to be significant, including comorbidities, sources of infection, medications and invasive treatments. Risk factors of S-AKI come from a wide range of sources, making it difficult to prediction and prevention. We found that AKI caused by septic shock had the highest incidence and mortality among sepsis patients from included studies. At the same time, we also found great intertrial heterogeneity in the studies exploring the association between sepsis and AKI, which therefore results in reduced evidence power, leading to controversial opinion regarding the risk factors for AKI in sepsis patients. So we hope that more homogeneous research can be carried out in the future and more reliable conclusions can be obtained.

Analysis of Risk Factors

Risk factors for sepsis-associated AKI can be categorized as pre-sepsis risk factors, sepsis disease related factors and sepsis-related treatment factors. The pre-sepsis risk factors (e.g., concurrent chronic diseases, sex, age, smoking history) and sepsis disease itself (e.g., sepsis type, source of infection,
bacterial infection) cannot be altered since they have been existing at the time of diagnosis. However, these factors can be used to identify the patients that are at high risk of AKI, so that timely precautions shall be applied accordingly to reduce the potential risks in the future. On the other hand, the risk factors associated with sepsis-related treatment can be manually controlled by using efficient strategies (e.g., medication, mechanical ventilation).

- **Pre-sepsis risk factors**

Our study showed multiple chronic comorbidities could be associated with AKI development in sepsis patients. Hypertension and diabetes mellitus were the most common risk factors for AKI among all comorbidities, and other factors included chronic kidney diseases, cardiovascular diseases, coronary artery diseases and liver diseases. This may be due to the fact that majority of the sepsis patients were older adults aged 65 years and older.\(^{59-60}\) We found diabetes mellitus and hypertension were associated with higher risks of AKI, which is consistent with other studies.\(^{61-63,66}\) Chronic kidney disease has been recognized as a significant risk factor for AKI.\(^{64-65}\) Moreover, when AKI occurs in CKD patients, it is more severe and difficult to recover. There is increasing recognition that AKI and chronic kidney disease (CKD) are closely linked and are likely to promote one another. However, the association between severity of CKD (e.g., as measured by levels of estimated GFR) and risk of AKI has not been quantified until a recent meta-analysis showing that CKD may increase the risk of AKI in patients with diabetes or hypertension. Therefore, in addition to directly increasing the risk of AKI, diabetes mellitus, hypertension and CKD could also interact to promote the development of AKI.\(^{66}\) Besides, these three factors are also prevalent risk factors for AKI, so more attention should be paid to the patients with the above three risk factors to avoid potential risks of AKI.

Opinions regarding the association between gender and AKI remains controversial, while our study found that male patients may be at a slightly higher risks of AKI compared with female counterparts. A study found lower glomerular filtration rate (eGFR) and higher albumin-creatinine ratio (ACR) were associated with higher AKI risks in both men and women, and male sex was associated with higher risk of AKI, a slight attenuation in lower eGFR but not in higher ACR.\(^{67}\)

- **Sepsis-disease-related risk factors**

In our study, among sepsis patients, AKI caused by septic shock had the highest incidence and mortality, and septic shock was also a significant risk factor for AKI, so more attention should be paid to the prevention of AKI in patients with septic shock.

The data summary indicated that pulmonary and abdominal infections were the most common source of infection among sepsis patients who developed AKI, and our study also found that both were associated with AKI development. Abdominal infections could increase risk of AKI development, but our study found that lung infection was a protective factor for AKI. At present, there is no research investigating relevant field. Considering the high heterogeneity (\(I^2 = 77.6\%\)), a sensitivity analysis was performed and showed
stable results. The subgroup analysis showed different results among Chinese population and other population. The pulmonary infection was a risk factor among Chinese population (OR 1.62, 95%CI 1.06-2.49), but a protective factor in other populations (OR 0.61, 95%CI 0.50-0.74). We were cautious about the overall results and the results of subgroup analysis since there is lack of reasonable interpretation for the results as well as the heterogeneity among different population. Further research may be needed to investigate relevant issue in the further.

The relationship between the occurrence of AKI and the bacterial infection has rarely been reported. Our study found that gram-negative bacteria could be a risk factor for AKI. However, it remains unclear which gram-negative bacteria could be involved. Only one study showed that Escherichia coli may be associated with the development of AKI\(^\text{67}\). More research on this topic may be needed in the future.

- **Sepsis-related treatment risk factors**

Our study found that diuretics, vasopressors and ACEI or ARB could be associated with the occurrence of AKI. Vasoactive drugs are commonly used in patients with sepsis, especially septic shock. Our research found that vasopressors increased the risk of AKI, while the association between ALI and other medications remain uncertain. A large cohort study\(^\text{68}\) showed ACEI/ARB could be associated with a small increase in AKI risk while individual patient characteristics were much more closely correlated with the rate of AKI. Among patients with CKD, there was no increased risk of developing AKI compared with those who are not exposed to ACEI/ARB, while exposure to ACEI/ARB in people without CKD increases the risk of AKI. A multi-center prospective study in Shanghai showed that diuretics accounted for 22.2% of all drug-induced AKI, ranked only after antibiotics.\(^\text{69}\) The reasons for the association between diuretics use and increased AKI risks could be as follows. First, loop diuretics block sodium chloride uptake in the macula densa, independent of any effect on sodium and water balance, thereby stimulating the RAAS (renin-angiotensin-aldosterone system), and leading to AKI. Sometimes, AKI is caused by the combined action of diuretics and other drugs, which may include antibiotics, contrast media, ACEI/ARB and NSAIDs.\(^\text{70}\) Another study showed a triple therapy combination consisting of diuretics with ACEI or ARB and NSAIDs was associated with an increased risk of AKI.\(^\text{71}\) However, the high heterogeneity of the above factors cannot be ignored, and we have not found the source through subgroup analysis. Therefore, the results should be interpreted with caution. This part of heterogeneity may come from the specific types, duration and dosage of drugs and the interaction with other drugs. More homogeneous clinical randomized trials in sepsis patients should be conducted to confirm the role of these drugs and their interactions in inducing AKI.

At present, many studies have confirmed that mechanical ventilation was a risk factor for AKI, which is consistent with our results.\(^\text{72,73}\) A Study has shown that in patients in the intensive care unit, mechanical ventilation is used among up to 75% of the patients.\(^\text{74}\) Our summary data showed that 68% of sepsis patients who developed AKI used mechanical ventilation, which is even higher in patients with septic shock and severe sepsis. Therefore, we have to pay special attention to prevent the development of AKI in patients with mechanical ventilation. Hypoxemia, hypercapnia, and excessive PEEP values during
mechanical ventilation are all risk factors for AKI. If there are other risk factors at the same time, AKI is more likely to occur. Now, there is no good measure to prevent or reduce the AKI caused by mechanical ventilation. Some studies have shown that the development of AKI can be reduced by adjusting ventilator parameters, improving hypoxia status as soon as possible, avoiding persistent hypercapnia, and using too little PEEP (positive end-expiratory pressure) value. However, a meta-analysis showed that invasive MV could be associated with a threefold increase in odds of AKI in critically ill patients, as well as tidal volume (Vt) and PEEP settings. Therefore, future research should focus on the strategy that can reduce the AKI risks induced by mechanical ventilation.

**Limitations**

However, our study also has limitations. First of all, our results were based on unadjusted estimates due to the great variability of multivariable models across studies. Therefore, we may fail to identify the independent predictors of AKI in the presence of confounding factors. Secondly, significant heterogeneity was observed for certain risk factors due to the varied geographic locations, demographic data and inconsistent diagnostic criteria of AKI and sepsis, and we did not identify the source through subgroup analysis, which may have impacts on our research results. In addition, due to the small number of studies, heterogeneity and publication bias of certain risk factors were not evaluated.

**Conclusion**

The most common risk factors for S-AKI were as follows: septic shock, hypertension, diabetes mellitus, abdominal infection, smoke history, positive blood culture, vasopressors use, mechanical ventilation. Other risk factors included cardiovascular, coronary artery disease, liver disease, unknow infection, diuretics use, use of ACEI or ARB, gram-negative bacteria infection and organ transplant. Despite of our rigorous methodology, the inherent limitations of the included studies prevented us from reaching definitive conclusions. However, this article is the first systematic review and meta-analysis investigating the risk factors for AKI development in sepsis patients, which can be used to assist clinical targeted care strategies for AKI prevention, detection, and management among sepsis patients.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent to publish**

Not applicable.

**Availability of data and materials**
All data generated or analysed during this study are included in this published article [and its seen Additional files and Supplementary materials].

**Competing interests**

There is no conflict of interest in relation to this study.

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**Author contributions**

LJF: study design, data collection, data analysis, writing; XHB: data collection, data analysis, writing; YZW: data collection, data analysis; WLS: study design, writing. all authors have read and approved the final manuscript.

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**Abbreviations**

AKI Acute kidney injury

S-AKI Sepsis-associated acute kidney injury

ARF Acute renal failure

OR Odds ratio
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Tables
| Author      | Publication year | Country | AKI diagnostic criteria | Sepsis types             | Study period       | Research design     | Numble | AKI | Quality score |
|------------|------------------|---------|-------------------------|--------------------------|-------------------|---------------------|--------|-----|---------------|
| Bu et al.  | 2019             | China   | KDIGO                   | Sepsis and Septic shock  | 2015-2017          | Retrospective case-control study | 132/90 | 7   |               |
| Hsu et al. | 2019             | China   | AKIN                    | Sepsis                   | 2012-2016          | Retrospective case-control study | 99/597 | 6   |               |
| Vilander et al. | 2019       | Finland | KDIGO                   | Sepsis                   | 2011-2012          | Prospective cohort study | 300/353 | 7   |               |
| Xing et al. | 2019             | China   | KDIGO                   | Septic shock             | 2018.8-2018.11     | Prospective cohort study | 29/43  | 8   |               |
| Moman et al. | 2018            | USA     | KDIGO                   | Septic shock             | 2007-2009          | Retrospective cohort study | 160/73  | 8   |               |
| Zhi et al.  | 2018             | China   | AKIN                    | Sepsis                   | 2009-2015          | Retrospective case-control study | 315/267 | 5   |               |
| Zhou et al. | 2018             | China   | AKIN                    | Sepsis                   | 2010-2017          | Retrospective case-control study | 405/348 | 6   |               |
| Costa et al. | 2018            | Brazil  | KDIGO                   | Septic shock             | 2014-2015          | Prospective cohort study | 66/63  | 7   |               |
| Song et al. | 2018             | China   | KDIGO                   | Sepsis                   | 2015-2016          | Prospective cohort study | 52/72  | 7   |               |
| Hu et al.   | 2018             | China   | RIFLE                   | Sepsis                   | 2016-2017          | Prospective cohort study | 52/53  | 8   |               |
| Authors          | Year | Country     | Classification | System | Disease(s)                                      | Study Period  | Study Type     | N Cases |
|------------------|------|-------------|----------------|--------|------------------------------------------------|---------------|----------------|---------|
| Fatani et al.    | 2018 | Saudi Arabia| RIFLE          |        | Severe sepsis and Septic shock                  | 2016-2017     | Prospective    | 127/73  |
| Gameiro et al.   | 2017 | Portugal    | KDIGO          |        | Sepsis and Septic shock                         | 2008-2014     | Retrospective  | 399/57  |
| Katayama et al.  | 2017 | Japan       | KDIGO          |        | Sepsis                                         | 2011-2016     | Retrospective  | 163/351 |
| Vilander et al.  | 2017 | Finland     | KDIGO          |        | Septic shock                                   | 2011-2012     | Prospective    | 252/226 |
| Suberviola et al.| 2017 | Spain       | KDIGO          |        | Septic shock                                   | 2005-2010     | Prospective    | 312/74  |
| Fisher et al.    | 2017 | Sweden      | KDIGO          |        | Septic shock                                   | -             | Prospective    | 225/71  |
| Pérez-Fernández et al. | 2017 | USA        | KDIGO          |        | Severe sepsis and Septic shock                  | 2005-2007     | Prospective    | 82/178  |
| Pereira et al.   | 2017 | Portugal    | REFILE         |        | Severe sepsis and Septic shock                  | 2008-2014     | Retrospective  | 384/72  |
| Panich et al.    | 2017 | Thailand    | AKIN           |        | Sepsis                                         | 2014-2014     | Prospective    | 79/60   |
| Su et al.        | 2016 | China       | KDIGO          |        | Severe sepsis                                  | -             | Prospective    | 45/27   |
| Yilmaz et al.    | 2015 | Turkey      | AKIN           |        | Severe sepsis                                  | 2011-2013     | Retrospective  | 68/50   |
| Authors          | Year | Country | AKIN/KDIGO | Event          | Time Period   | Study Design     | Participants |
|------------------|------|---------|------------|----------------|---------------|-----------------|--------------|
| Medeiros et al.  | 2015 | Japanese | AKIN       | Sepsis         | 2013-2014     | Retrospective   | 144/56       |
| Dai et al.       | 2015 | China   | KDIGO      | Sepsis         | 2012-2014     | Prospective     | 55/57        |
| Sood et al.      | 2014 | Canada  | RIFLE      | Septic shock   | 1996-2008     | Prospective     | 3298/1195    |
| Peng et al.      | 2014 | China   | KDIGO      | Sepsis         | 2008-2011     | Prospective     | 101/110      |
| Patschan et al.  | 2014 | Germany | AKIN       | Sepsis         | -             | Retrospective   | 22/11        |
| Tu et al.        | 2014 | China   | AKIN       | Sepsis         | 2011-2013     | Prospective     | 49/101       |
| Fan et al.       | 2014 | China   | RIFLE      | Sepsis         | 2012-2014     | Prospective     | 58/67        |
| CHO et al.       | 2014 | Korea   | RIFLE      | Sepsis         | 2010-2011     | Prospective     | 44/18        |
| Terzi et al.     | 2014 | Greece  | RIFLE      | Sepsis         | -             | Prospective     | 16/29        |
| Poukkonen et al. | 2013 | Finland | KDIGO      | Severe sepsis  | 2011-2012     | Retrospective   | 153/270      |
| Legrand et al.   | 2013 | France  | AKIN       | Severe sepsis  | 2006-2010     | Prospective     | 69/68        |
| Cardinali        | 2013 | Spain   | RIFLE      | Severe sepsis  | 2005-2008     | Prospective     | 65/74        |
| Authors                  | Year | Country    | Scale | Type                           | Study Details       | Cases/Controls |
|--------------------------|------|------------|-------|--------------------------------|--------------------|----------------|
| Fernandez et al.         | 2013 | Netherlands| AKIN  | Sepsis                         | 2007-2008          | 49/432         |
| de Geus et al.           | 2013 | Netherlands| AKIN  | Sepsis                         | Prospective        | 49/432         |
| Katagiri et al.          | 2013 | Japan      | RIFLE | Sepsis                         | 2010-2011          | 24/10          |
| Aydogdu et al.           | 2013 | Turkey     | RIFLE | Sepsis                         | 2008-2010          | 63/66          |
| Suh et al.               | 2013 | South Korea| RIFLE | Sepsis and Septic shock        | 2010 Retrospective | 573/419        |
| Poukkonen et al.         | 2013 | Finland    | KDIGO | Severe sepsis                  | 2011-2012          | 437/393        |
| Zhao et al.              | 2013 | China      | AKIN  | Sepsis                         | 2011-2013          | 90/58          |
| Payen et al.             | 2012 | Brazil     | AKIN  | Severe sepsis and Septic shock | 2004-2005          | 129/47         |
| Frank et al.             | 2012 | USA        | AKIN  | Septic shock                   | 1999-2009          | 627/637        |
| Plataki et al.           | 2011 | USA        | RIFLE | Septic shock                   | 2005-2007          | 237/153        |
| Martensson et al.        | 2010 | Sweden     | RIFLE or AKIN| Septic shock               | Prospective        | 18/7           |
| YANG et al.              | 2009 | China      | AKIN  | Septic shock                   | 2001-2008          | 126/32         |

Page 23/36
| Authors          | Year | Country                | AKIN/Sepsis Code | Time Period     | Study Design | Cases/Controls | Score |
|------------------|------|------------------------|------------------|-----------------|--------------|----------------|-------|
| Lopes et al. 56  | 2009 | Portugal               | AKIN             | 2004-2007       | Retrospective| 99/216         | 7     |
| Bagshaw et al. 57| 2009 | Canada, the United States and Saudi Arabia | RIFLE            | 1989-2005       | Retrospective| 2917/1615      | 7     |
| Bagshaw et al. 58| 2008 | Australia              | RIFLE            | 2000-2005       | Retrospective| 14039/19336    | 8     |
Table 2. Summary data of all sepsis patients who developed AKI from included studies.

| Characteristics | No. Studies | Prevalence sepsis |  | Prevalence septic shock |  | Prevalence severe sepsis |  |
|-----------------|-------------|-------------------|---|-------------------------|---|--------------------------|---|
|                 |             | No. Studies       | Prevalence | No. Studies          | Prevalence | No. Studies          | Prevalence |
| Septic AKI      | 47          | 48.73%            | 22       | 41.98%                | 12         | 60.47%                 | 5          |
|                 | (27248/5591)| (16399/3906)      | (12678/2096)| (768/1570)         |
|                 | 1           | 7)                | 5)       |                        |            |                         |            |
| Sex (male)      | 44          | 59.70%            | 22       | 63.68%                | 11         | 59.64%                 | 5          |
|                 | (5913/9904)| (1380/2167)       | (3191/5350)| (495/768)           |
| Comorbidities   |             |                   |          |                        |            |                         |            |
| Hypertension    | 32          | 38.39%            | 14       | 42.28%                | 6          | 26.16%                 | 5          |
|                 | (3263/8500)| (859/1817)        | (1073/4102)| (446/768)         |
| Diabetes mellitus | 32        | 27.57%            | 13       | 20.53%                | 7          | 26.75%                 | 5          |
|                 | (2248/8155)| (373/1817)        | (1897/7091)| (232/768)         |
| Stroke          | 4           | 22.79%            | 1        | 22.33%                | -          | -                      | 1          |
|                 | (67/294)   | (67/300)          | -        | -                     | -          |                        | (8/45)     |
| Cancer          | 6           | 18.23%            | -        | -                     | 2          | 18.80%                 | 1          |
|                 | (705/3745)|                       | -        |                        | (650/3458)| (8/49)                 |
| Chronic kidney  | 14          | 16.46%            | 7        | 15.52%                | 2          | 45.13%                 | 2          |
|                 | (449/2795)| (178/1147)        | (102/226)| (65/590)           |
| Cardiovascular  |             |                   |          |                        |            |                         |            |
| disease         | 11          | 16.30%            | 4        | 19.47%                | -          | -                      | 1          |
|                 | (2522/15477)| (169/868)        | -        |                        | -          |                        | (3/45)     |
| Congestive heart failure | 7 | 12.69% | 2 | 17.26% | 4 | 12.64% | 1 |
|                 | (491/3869)| (39/226)        | (446/3529)| (8/68)            |
| COPD            | 17          | 12.41%            | 6        | 12.69%                | 5          | 12.99%                 | 1          |
|                 | (1114/8976)| (90/709)        | (873/6721)| (25/437)          |
| Condition                  | 4 | 2 | 1 | 3 | 2                  |
|---------------------------|---|---|---|---|--------------------|
| Hepatic failure           | 12.16% | 39.76% | 9.90% | 12.61% |
| Coronary artery disease   | 11.58% | 10.14% | 9.30% | 6.15% |
| Systolic heart failure    | 11.25% | 8.00% | 14.32% | 11.90% |
| Immunosuppression         | 4.71% | 1.73% | 7.50% | - |
| Cirrhosis                 | 3.74% | 3.57% | 8.73% | 8.59% |
| Liver disease             | 50.88% | 50.90% | 41.46% | 97.12% |
| Emergency admission       | 47.02% | 49.16% | 36.99% | - |
| Operative admission       | 30.91% | 22.33% | 23.02% | 28.81% |
| Surgical ward             | 17.73% | 16.51% | 21.29% | - |
| Pulmonary infection       | 46.05% | 57.96% | 41.10% | 48.02% |
| Section           | Count | Percentage | Count | Percentage | Count | Percentage |
|-------------------|-------|------------|-------|------------|-------|------------|
| Respiratory       | 7     | 32.08%     | 2     | 41.22%     | 2     | 32.74%     | 2     | 26.36%     |
|                   | (273/85) | (54/131) | (74/226) | (29/110) |
| Abdominal         | 25    | 30.87%     | 7     | 32.12%     | 7     | 28.16%     | 5     | 28.65%     |
|                   | (2152/6971) | (177/551) | (1253/4450) | (220/768) |
| Urinary tract     | 19    | 11.14%     | 6     | 12.01%     | 6     | 11.34%     | 5     | 11.38%     |
|                   | (630/5653) | (58/483) | (483/4259) | (80/703) |
| Skin or soft tissue | 13    | 6.03%      | 3     | 2.15%      | 4     | 5.40%      | 3     | 10.71%     |
|                   | (335/5554) | (5/232) | (218/4033) | (68/635) |
| Unknown           | 4     | 6.02%      | -     | -          | 2     | 8.30%      | -     | -          |
|                   | (100/1662) | -     | (73/879) |
| Community acquired | 3     | 57.36%     | -     | -          | 1     | 56.80%     | 2     | 65.08%     |
|                   | (2041/3558) | -     | (1657/2917) | (384/590) |
| Nosocomial acquired | 2     | 39.81%     | -     | -          | 2     | 39.81%     | -     | -          |
|                   | (2474/6215) | -     | (2474/6215) |

**Medications**

| Section           | Count | Percentage | Count | Percentage | Count | Percentage | Count | Percentage |
|-------------------|-------|------------|-------|------------|-------|------------|-------|------------|
| Vasopressors      | 7     | 64.61%     | 3     | 45.04%     | 2     | 59.38%     | -     | -          |
|                   | (1293/2001) | (100/222) | (513/864) |
| Vasoactive drugs  | 5     | 63.22%     | 2     | 35.69%     | 1     | 67.50%     | 2     | 96.44%     |
|                   | (911/1441) | (131/367) | (108/160) | (569/590) |
| Steroids          | 3     | 30.80%     | 2     | 38.16%     | -     | -          | -     | -          |
|                   | (85/276) | (79/207) |
| Diuretics         | 4     | 30.77%     | -     | -          | 1     | 39.40%     | 2     | 30.85%     |
|                   | (296/962) | -     | (97/252) | (182/590) |
| ACEI or ARB       | 8     | 25.62%     | 1     | 18.41%     | 3     | 24.97%     | 3     | 33.59%     |
|                   | (619/2416) | (58/315) | (200/801) | (220/655) |
| Stains            | 5     | 21.77%     | -     | -          | 2     | 24.13%     | 1     | 15.79%     |
|                   | (296/962) | -     | (97/252) | (182/590) |
|                          | (357/1640) | (118/489) | (69/437) |
|--------------------------|-----------|-----------|----------|
| Nsaids                   | 9.63%     | 11.45%    | 12.54%   |
|                          | (203/2108)| (56/489)  | (74/590) |

**Bacteria**

| Gram- negative bacteria  |          |          |
|--------------------------|----------|----------|
|                         | 3        | 1        |
|                         | 17.26%   | 22.3%    |
|                         | (160/927)| (49/225) |

| Gram- positive bacteria  |          |          |
|--------------------------|----------|----------|
|                         | 4        | 1        |
|                         | 10.43%   | 28.6%    |
|                         | (99/949) | (63/225) |

**Invasive treatment**

| Mechanical ventilation  | 23       | 6          |
|--------------------------|----------|-----------|
|                         | 68.00%   | 71.21%    |
|                         | (7167/10539)| (5481/7643)|

| Renal replacement therapy | 6        | 1         |
|---------------------------|----------|-----------|
|                           | 39.51%   | 18.18%    |
|                           | (320/810)| (12/66)   |

| Dialysis                  | 3        | 2         |
|----------------------------|----------|-----------|
|                           | 28.92%   | 27.39%    |
|                           | (59/204) | (3/303)   |

| Blood transfusion         | 3        | 2         |
|----------------------------|----------|-----------|
|                           | 19.46%   | 7.64%     |
|                           | (94/483) | (11/144)  |

| Organ transplant          | 3        | 2         |
|----------------------------|----------|-----------|
|                           | 3.76%    | 3.94%     |
|                           | (252/6703)| (245/6215)|

| Positive blood culture    | 8        | 4         |
|----------------------------|----------|-----------|
|                           | 41.38%   | 42.89%    |
|                           | (3259/7876)| (2836/6612)|

| Bloodstream infection     | 4        | 1         |
|----------------------------|----------|-----------|
|                           | 6.61%    | 7.40%     |
|                           | (237/3586)| (216/2917)|

| Smoke                     | 5        | 1         |
|----------------------------|----------|-----------|
|                           | 43.09%   | 32.35%    |
|                           | (203/2108)| (74/590)  |
| History                  | (642/1490) | (291/720) | (22/68) |
|-------------------------|------------|-----------|---------|
| ARDS                    | 3 47.02%   | 1 81.19%  | 2 43.34%|
|                         | (489/1040) | (82/101)  | (407/939)|
| Multiorgan dysfunction  | 3 50.11%   | 1 70.48%  |        |
|                         | (436/870)  | (222/315) |        |

| Mortality               |            |           |         |
|-------------------------|------------|-----------|---------|
| ICU mortality           | 10 45.99%  | 2 50.00%  | 4 50.47%|
|                         | (1989/4325)| (46/92)   | (1672/3313)|
| Hospital mortality      | 15 49.84%  | 7 42.17%  | 3 55.83%|
|                         | (2732/5481)| (245/581) | (1935/3466)|
| 28-day mortality        | 4 36.67%   | 1 30.61%  | 1 71.42%|
|                         | (161/439)  | (15/49)   | (90/126) |
| 90-day mortality        | 5 64.66%   | -         | 1 58.42%|
|                         | (2406/3721)|           | (1704/2917)|
| COPD: chronic obstructive pulmonary disease
| ACEI or ARB: angiotensin converting enzyme inhibitors or Angiotensin Receptor Blocker
| ARDS: acute respiratory distress syndrome

**Supplemental Information Note**

Additional files 1 Checklist. PRISMA Checklist.

Additional files 2 Fig. Hypertension-Forest plot, Funnel plot, Sensitivity and Subgroup analysis.

Additional files 3 Fig. Diabetes mellitus-Forest plot and Funnel plot.

Additional files 4 Fig. Chronic kidney disease-Forest plot, Funnel plot, Sensitivity and Subgroup analysis.
Additional files 5 Fig. Cardiovascular Diseases - Forest plot, Funnel plot.

Additional files 6 Fig. Liver disease - Forest plot and Sensitivity analysis.

Additional files 7 Fig. Coronary artery disease - Forest plot and Funnel plot.

Additional files 8 Fig. Pulmonary infection - Forest plot, Funnel plot, Sensitivity and subgroup analysis.

Additional files 9 Fig. Abdominal infection - Forest plot, Funnel plot and Sensitivity analysis.

Additional files 10 Fig. Unknown source of infection - Forest plot.

Additional files 11 Fig. Vasoactive drugs - Forest plot and Sensitivity analysis.

Additional files 12 Fig. Vasopressors - Forest plot, Funnel plot, Sensitivity and Subgroup analysis.

Additional files 13 Fig. Diuretic - Forest plot.

Additional files 14 Fig. Sex (male) - Forest plot, Funnel plot, Sensitivity and Subgroup analysis.

Additional files 15 Fig. Positive blood culture - Forest plot, Funnel plot and Sensitivity analysis.

Additional files 16 Fig. Smoke history - Forest plot, Sensitivity analysis.

Additional files 17 Fig. Septic shock - Forest plot and Funnel plot.

Additional files 18 Fig. Gram-negative bacteria - Forest plot.

Additional files 19 Fig. Organ transplant - Forest plot and Sensitivity analysis.

Additional files 20 Fig. Mechanical ventilation - Forest plot, Funnel plot, Sensitivity and Subgroup analysis.

**Figures**
Figure 1

Flow diagram of study selection process
Figure 2

Meta-analysis of risk factors for AKI
Figure 3

Forest plot for meta-analysis of the association of male sex and AKI.
Figure 4

Funnel plot to detect publication bias for male sex, Egger test, $P=0.32$. 
Figure 5

Subgroup analyzes for meta-analysis of the association of pulmonary infection and AKI.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAChecklist.doc
- AdditionalFiles20Fig.MechanicalVentilation.doc
• Additionalfiles10Fig.Unknownsourceofinfection.doc
• Additionalfiles5Fig.CardiovascularDiseases.doc
• Additionalfiles4Fig.Chronickidneydisease.doc
• Additionalfiles9Fig.Abdominalinfection.doc
• Additionalfiles7Fig.Coronaryarterydisease.doc
• Additionalfiles6Fig.Liverdisease.doc
• Additionalfiles8Fig.Pulmonaryinfection.doc
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• Additionalfiles1Fig.Hypertension.doc
• Additionalfiles2Fig.Hypertension.doc
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• Additionalfiles12Fig.Diuretic.doc
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• Additionalfiles19Fig.Mechanicalventilation.doc