Research Square

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

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Research article

Keywords: acute kidney injury, sepsis, risk factor, meta-analysis, systematic review

Posted Date: March 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-18145/v1

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Version of Record: A version of this preprint was published on July 31st, 2020. See the published version at https://doi.org/10.1186/s12882-020-01974-8.

Abstract

Background 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 55911sepsis 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, unknow 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.

Highlights

Highlights of this article

1.this the first systematic review and meta-analysis of risk factors for AKI development in sepsis patients.

2.Forty-seven observational studies were included for analysis. A cumulative number of 55911sepsis patients were evaluated.

3.Thirty-one possible risk factors were included in the meta-analysis. The results showed that twenty factors were found to be significant. In addition, we have summarized the prevalence of these factors in sepsis who developed acute kidney injury.

Background

Sepsis-associated acute kidney injury (S-AKI) is a major public health problem. S-AKI is a syndrome of acute impairment of function and organ damage linked with long-term adverse outcomes depending on the extent of acute injury superimposed on underlying organ reserve. Sepsis is the most common cause of acute kidney injury (AKI) in critically ill patients and is associated with 40–50% of AKI patients.[1–4] Importantly, S-AKI is strongly associated with poor clinical outcomes. Mortality in patients with sepsis complicated by AKI is significantly higher than in non-AKI patients.[5] Among critically ill patients with AKI, S-AKI have a higher risk of in-hospital death and longer hospital stay than AKI caused by any other cause.[3] Despite recent advances in medicine and surgery, Its morbidity have not declined. Mounting evidence suggests that AKI incidence is increasing. In a large 10-year cohort that included more than 90,000 patients from more than 20 ICUs, AKI incidence increased by 2.8% per year.[1] Moreover, With the global aging trend, and the majority of sepsis patients are mainly elderly, the number of patients with sepsis-induced AKI may continue to increase.[6–7] 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 clear. There are also many difficulties in the early diagnosis and treatment of S-AKI. Therefore, the early identification of risk factors and prevention of S-AKI is extremely important. Unfortunately, a number of studies have explored the risk factors for AKI development in sepsis patients, but few studies have yielded relatively consistent results. Because of the inconsistency of diagnostic criteria of sepsis and AKI and regional differences, the application of the research results obtained is controversial and limited. However, there still has not been a study published for systematic review and meta-analysis on this topic. The aim of this work was to systematically review and meta-analyses the evidence on the association between sepsis and AKI in cohort and case-control studies.

Methods

Inclusion Criteria

We selected all studies that met the following criteria:(1) Patients older than 16 years with a hospitalization stay of greater than 24 hours (2) studies were able to extract data from the 2×2 contingency table (3)sepsis and septic shock was diagnosed by the Internationally recognized standards in the original study, such as sepsis 1.0[9],sepsis2.0[10],sepsis3.0[11].(4) acute kidney injury was diagnosed by the Internationally recognized standards, such as KDIGO, AKIN and RIFLE. (5) studies had a cohort or case-control design and 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 was performed; the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline were followed for this report.[8]

The systematic literature search was performed in the Medline, Embase, Cochrane Library, PubMed and Web of Science databases from inception to the June 2019 with no restrictions, for studies that assessed

the risk of AKI development in sepsis patients. following search terms were used and combined: (septic OR sepsis OR severe sepsis OR Septicemia OR septic shock OR sepsis-induced OR sepsis-associated) AND (Acute Kidney Injury OR Acute Renal Injury OR Acute Renal Insufficiency OR AKI OR acute renal failure OR ARF). A manual search on the reference lists of included articles was also carried out. Gray literature (generally refers to nonpublicly published literature) and conference abstracts were not searched.

Data Extraction

Two independent reviewers participated in the entire process of literature retrieval. First, the titles and abstracts of the retrieved literature are analyzed to exclude irrelevant studies. After that, full-text analysis is performed by the inclusion/exclusion criteria. Data extraction was performed using a standardized data collection form. Data collected included:

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 will be S-AKI, the Secondary outcome was prevalence of influence factors and mortality in patients of S-AKI.

Quality Assessment

Study selection, data extraction, and quality assessment were independently performed by two authors. Any disagreements are resolved through discussions between authors until a consensus is reached. if disagreements persisted, they were solved by a third reviewer. Quality assessment for the observational studies included in the meta-analysis was performed using the Newcastle-Ottawa scale (available at http://www.ohri.ca/programs/clinical_epidemiology/oxf ord.asp).

Statistical Analysis

The core characteristics of the study and patients were sorted out and summarized through Microsoft Office Excel 2010. The frequency distribution is expressed as a percentage. For the meta-analysis, we only used unadjusted crude odds ratios from ≥3 studies (OR) to standardize the results because of the wide variability of multivariable models across studies. We used Stata/SE version11 for statistical analyses and a two-sided *P* value of 0.05 or less to indicate statistical significance. 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). We categorized I^2 of <25%, 25% to 75%, and >75% as corresponding to low, moderate, and high between trial heterogeneity, respectively. 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-effects model, we will explore its stability by transforming into a random effects model. Meta regression and subgroup analyses (≥6 studies) would were conducted according to publication year, study design, country of origin, sepsis type and diagnostic criteria of acute kidney injury and sepsis, if heterogeneity among studies was high (I^2>50% and P□0.10). We conducted a sensitivities analysis (≥3 studies) on the overall risk estimate by omitting 1 study in each turn, to estimate whether the results could have been affected markedly by a single study. We explored publication bias by examining funnel plots visually, and using the Egger test for asymmetry for those risk factors with pooled data from≥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, most of them are excluded due to the duplicate, review, or unrelated topic. After 626 studies were reviewed in full text, 579 articles were excluded according to review and comments papers, inconsistent control settings, unknown AKI or sepsis diagnostic criteria, special population, duplicate and limited data. Finally, 47 articles including 22 sepsis,12 septic shock,5 severe sepsis and 8 others met the inclusion criteria and were conducted systematic review and meta-analysis.

2.Characteristics of Included Studies (table 1)

The characteristics of the included articles are 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). All studies were observational including 12 retrospective cohorts, 25 prospective cohorts and 12 case-control studies. A total of 55911 sepsis patients were included in the analysis. Document quality assessment shows that the methodological quality of all studies is high, achieving a quality score of ≥6 of 8.

3.Summary data from 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% (1989/4325) in 15 studies,49.84% (2732/5481) in 10 studies, 36.67% (161/439) in 4 studies, 64.66% (2406/3721) in 5 studies. The 90-day mortality is the highest. In S-AKI patients, all mortality rates of AKI caused by septic shock are the highest, while that caused by severe sepsis was the lowest.

Regarding comorbidities, the most common one is 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). Cirrhosis and Liver disease were the least common and account

for only (4.71% ,99/2104, from 6 studies) and (3.74%,554/14081, from 7 studies). Hepatic failure in sepsis were more common in sepsis than in septic shock and severe sepsis. Hypertension in septic shock is 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 mainly comes from 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. In the use of Medications, vasoactive drugs are the most commonly used drugs, accounting for 64.61% (1293/2001, from 5studies), and vasopressors among vasoactive drugs is 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, with the order of occurrence rate from high to low being the following: pulmonary(46.05%,1480/3214, from 19 studies), respiratory(32.08%,85/273, from 7 studies), abdominal(30.87%,2152/6971, from 25 studies), Urinary tract (11.14%, 630/5653, from 19 studies), skin or soft tissue (6.03%, 335/5554, from 13 studies), unknow (6.02%, 100/1662,from 4 studies).

Community acquired infection was reported in 3 studies at 57.36% (2041/3558), which was higher than nosocomial acquired infection reported in 2 studies at 39.81% (2474/6215). Twenty-four studies reported mechanical ventilation in 68.00% (7167/10539, from 24 studies), and mechanical ventilation in septic shock and severe sepsis was more prevalent than in sepsis. Other prevalent factors include positive blood culture (41.38%,3259/7876, from 8 studies), Smoke history (43.09%,642/1490, from 5 studies).

4.Risk Factor Analysis of AKI

Comorbidities

Hypertension was pooled from 32 studies with a significant (OR,1.43;95%CI:1.20-1.70), moderate heterogeneity(I^2=74.00%). Sources of heterogeneity were not identified using subgroup analysis. The results of the sensitivity analysis are consistent. After 3 studies with heterogeneity is excluded, the heterogeneity decrease and the result remains stable.

Diabetes mellitus was pooled from 32 studies with a significant (OR 1.59;95%CI:1.47-1.71), moderate heterogeneity(I^2=37.1%). The results are still stable after using the random effects model.

Chronic kidney disease was pooled from 14 studies with a significant (OR,3.49;95%CI:2.36-5.15), moderate heterogeneity(I2=71.70%). Sources of heterogeneity were not identified using subgroup analysis. The results of the sensitivity analysis are consistent. After a study with heterogeneity is

excluded, the heterogeneity among studies was reduced to low heterogeneity (25.6%) and the result remains stable.

Cardiovascular disease (from 14 studies, OR,1.31;95%CI:1.24-1.40), liver disease (from 17 studies, OR, 1.68;95%CI: 1.47-1.90) were all low heterogeneity and identified as risk factors. Their results are still stable after using the random effects model.

Coronary artery disease was pooled from 8 studies with a significant (OR,1.27;95%CI:1.08-1.49), moderate heterogeneity(I^2=37.1%). The results are still stable after using the random effects model.

Source of infection

Pulmonary infection was pooled from 8 studies with a significant (OR,0.77;95CI:0.60-0.99), moderate heterogeneity (I^2= 77.60%). Sources of heterogeneity were not identified using subgroup analysis. The results of the sensitivity analysis are consistent.

Abdominal infection was pooled from 25 studies with a significant (OR,1.44; 95%CI:1.32-1.58), moderate heterogeneity (I^2= 40.20%). The results of the sensitivity analysis are consistent. After a study with heterogeneity is excluded, the heterogeneity disappears and the result remains stable. The results are still stable after using the fixed effects model.

Unknow infection was pooled from 25 studies with a significant (OR,2.01;95CI:1.35-2.98), low heterogeneity(I^2=0%). The results are still stable after using the random effects model.

Medications

Vasoactive drugs were pooled from 5 studies with a significant (OR,3.85;95%CI:1.89-7.87), high heterogeneity (I^2=86.40%). After a study with heterogeneity is excluded, the heterogeneity disappears and the result remains stable. The results of the sensitivity analysis are consistent.

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 high heterogeneity($I^2 \geq 75\%$) and identified as risk factors. Sources of heterogeneity were not identified using subgroup analysis and their results of the sensitivity analysis are stable

Diuretics was pooled from 5 studies with a significant (OR,1.40;95%CI:1.13-1.72), low heterogeneity(I^2=0%). The results are still stable after using the random effects model.

Other factors

Male sex was pooled from 43 studies with a significant (OR,1.22;95%CI:1.06-1.40), moderate heterogeneity(I^2=69.80%). Sources of heterogeneity were not identified using subgroup analysis. The results of the sensitivity analysis are consistent.

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 low heterogeneity(I^2=0%) and identified as risk factors. Their results are still stable after using the random effects model.

Mechanical ventilation was pooled from 24 studies with a significant (OR,1.64;95%CI:1.24-2.16), high heterogeneity (I^2=88.70%). Sources of heterogeneity were not identified using subgroup analysis. he results of the sensitivity analysis are consistent.

Positive blood culture was pooled from 9 studies with a significant (OR,1.60;95%CI:1.35-1.89), moderate heterogeneity(I^2=50.20%). Sources of heterogeneity were not identified using subgroup analysis. The results of the sensitivity analysis are consistent.

Smoke history was pooled from 5 studies with a significant (OR,1.60;95%CI:1.09-2.36), high heterogeneity(I^2=78.30%). The results of the sensitivity analysis are consistent. After a study with heterogeneity is excluded, the heterogeneity disappears and the result remains stable.

Organ transplant was pooled from 3 studies with a significant (OR,1.96; 95%CI: 1.48-2.61), low heterogeneity(I^2=0%). The results are still stable after using the random effects model.

5.Tests for Publication Bias

All risk factors (≥7 studies) of the egger's rank correlation test and the Egger linear regression test indicated no evidence of publication bias except cardiovascular disease (P=0.015) (table3). Smoke history, cirrhosis, multiorgan dysfunction (≥3)，unknow site of infection, vasoactive drugs, diuretics and organ transplant were not performed test of public bias because of less number of studies(＜7 studies)

Discussion

Major Findings

To the best of our knowledge, this is the first meta-analysis providing comprehensive insights into the risk factors of AKI in sepsis patients. In total, 47 studies including 55911 sepsis patients were included.46 factors were examined in systematic review and summarized. Among comorbidities present, the top three in terms of prevalence are ARDS, hypertension and diabetes mellitus; On admission, patient mainly comes from emergency admission and medical admission; Regarding sources of infection, the top three in terms of prevalence are pulmonary, respiratory and abdominal. vasopressors and vasoactive drugs were the most frequently used drugs in present S-AKI patients. Other prevalent factors include mechanical ventilation, community acquired infection, positive blood culture, and Smoke history. 31 factors were assessed with 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%]. We also found that AKI caused by septic shock had the highest incidence and mortality among sepsis patients from included studies.

Analysis of Risk Factor

Risk factors for sepsis-associated AKI can be categorized as pre-sepsis, sepsis disease itself and sepsis-related treatment. As for the risk factors of pre-sepsis (eg, concurrent chronic diseases, sex, age, smoke history) and sepsis disease itself (eg, sepsis type, source of infection, infected bacteria), these existed before or when the sepsis was diagnosed, and are almost impossible to change. However, these factors can remind us that people with these factors are at high risk for AKI, so that we can take timely precautions such as reducing the occurrence of more risk factors in the future. The risk factors associated with sepsis-related treatment are things we can control and change (eg, medication, mechanical ventilation).

(1) Risk factors of pre-sepsis

Our study showed many chronic diseases among comorbidities were associated with AKI development in sepsis patients. Hypertension and diabetes mellitus among comorbidities were the most common risk factor of AKI, other factors include Chronic kidney disease, cardiovascular, coronary artery disease and liver disease. This may be due to the fact that Sepsis patients include a large proportion of older adults aged 65 years and older.[59-60] We found diabetes mellitus and hypertension increased the risk 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 acute kidney injury (AKI) and chronic kidney disease (CKD) are closely linked and likely 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 relatively recently. A meta-analysis showing that CKD increased risk of developing 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 occurrence of AKI.[66] In addition, these three factors are also prevalent risk factors of AKI, so we should pay more attention to patients with these three factors to reduce the incidence of AKI.

Whether gender is a risk factor for AKI is controversial, but our study found a slight association between AKI and male sex. A studyfound lower glomerular filtration rate (eGFR) and higher albuminuria (albumin-creatinine ratio [ACR]) were associated with higher AKI risk in both men and women, and male sex was associated with higher risk of AKI, with a slight attenuation in lower eGFR but not in higher ACR.[67]

(2) Risk factors of sepsis disease itself

In our study, AKI caused by septic shock among sepsis patients 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 summarized indicate that Pulmonary and abdominal infections are the most common source of infection for sepsis who developed AKI, both of them are also the most common risk factors for patients with sepsis. And our study also found that both are also associated with AKI development. Abdominal infections could increase risk of AKI development, but our study found that lung infection is a protective factor for AKI. At present, there is no research report on such results. Because of its high heterogeneity(I^2=77.6%), we conducted sensitivity analysis and subgroup analysis. The result of sensitivity analysis on the overall risk estimate were stable by recommending 1 study in each turn. The results of subgroup analysis showed that after grouping according to Chinese population and non-Chinese population, the heterogeneity of the two groups decreased, and pulmonary infection was a risk factor in 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 are cautious about the overall results and the results of subgroup analysis, because there is no reasonable explanation for this result and there is a great deal of heterogeneity. Further research on this phenomenon may be needed in the future.

The relationship between the occurrence of AKI and the infected bacteria has rarely been reported. Our study found that gram-negative bacteria are a risk factor for AKI. It is unclear which bacteria in Gram-negative bacteria are involved in AKI. Only one study showed that Escherichia coli may be associated with the development of AKI. More research may be needed to verify in the future.[49]

(3) Risk factors of sepsis-related treatment

In medication, our study found that vasoactive drugs, diuretics, vasopressors and ACEI or ARB are 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, whether other vasoactive drugs can cause this result is uncertain. A large cohort study (Mansfield et al., 2016) shows ACEI/ARB is associated with only a small increase in AKI risk while individual patient characteristics are much more strongly associated with the rate of AKI. Among patients with CKD, there is 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.[68] Another study showed a triple therapy combination consisting of diuretics with ACEI or ARB and NSAIDs was associated with an increased risk of acute kidney injury.[69] But it cannot be ignored that these factors have high heterogeneity, and we have not found the source of it, so we are cautious about these results. 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 acute kidney injury.

At present, many studies have confirmed that mechanical ventilation was a risk factor for AKI , which were consistent with our result.[70,71] A Study have shown that in patients in the intensive care unit, mechanical ventilation is used up to 75%.[72] Our summary data shows 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 shows that invasive MV is associated with a threefold increase in ods of AKI in critically ill patients, and tidal volume (Vt) and PEEP settings do not see to modify the risk.[71] Therefore, future research should focus on how to reduce AKI caused by mechanical ventilation.

Limitations

However, some limitations in our meta-analysis should be mentioned: (1) Our results were based on unadjusted estimates due to the wide variability of multivariable models across studies, which did not allow us to determine which factors are independent predictors of AKI because of the existence of confounding factors.(2) Significant heterogeneity was present for some risk factors because population-based studies encompassed different geographic locations, demographic data and inconsistent the diagnostic criteria of AKI and sepsis, but we have not found its source by using subgroup analysis, which may have an impact on our research results. In addition, part of the risk factors, due to the small number of studies, did not explore heterogeneity and publication bias.

Conclusion

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

Abbreviations

AKI acute kidney injury

S-AKI Sepsis-associated acute kidney injury

ARF Acute Renal failure

OR Odds ratio

CI Confidence interval

CKD Chronic kidney disease

KDIGO Kidney Disease Improving Global Outcomes

AKIN Acute kidney injury network classification

RIFLE Risk, injury, failure,end stage kidney disease

NSAIDs Non-steroidal anti-inflammatory drugs

COPD Chronic obstructive pulmonary disease

ACEI or ARB angiotensin converting enzyme inhibitors or Angiotensin Receptor Blocker

PEEP positive end-expiratory pressure

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 Additional files and Supplementary materials].

Competing interests

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

Funding

This work was supported by Regular funded projects awarded to XHB from the Health Committee of Hunan Province.

The funders had no role in any stage of the design and conduct of the study, collection, management, analysis, and interpretation of data in the study, or the preparation, review, or approval of the manuscript.

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.

Acknowledgment

Not applicable.

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Tables

Table 1.Characteristics of included studies in systematic review and meta-analysis

Author	Plublication year	Country	AKI diagnostic criteria	Sepsis types	Study period	Research design	NO.aki/no aki	Quality score
Bu et al.[12]	2019	China	KDIGO	Sepsis and Septic shock	2015-2017	Retrospective case-control study	132/90	7
Hsu et al.[13]	2019	China	AKIN	Sepsis	2012-2016	Retrospective case-control study	99/597	6
Vilander et al.[14]	2019	Finland	KDIGO	Sepsis	2011-2012	Prospective cohort study	300/353	7
Xing et al.[15]	2019	China	KDIGO	Septic shock	2018.8-2018.11	Prospective cohort study	29/43	8
Moman et al.[16]	2018	USA	KDIGO	Septic shock	2007-2009	Retrospective cohort study	160/73	8
Zhi et al.[17]	2018	China	AKIN	Sepsis	2009-2015	Retrospective case-control study	315/267	5
Zhou et al.[18]	2018	China	AKIN	Sepsis	2010-2017	Retrospective case-control study	405/348	6
Costa et al.[19]	2018	Brazil	KDIGO	Septic shock	2014-2015	Prospective cohort study	66/63	7
Song et al.[20]	2018	China	KDIGO	Sepsis	2015-2016	Prospective cohort study	52/72	7
Hu et al.[21]	2018	China	RIFLE	Sepsis	2016-2017	Prospective cohort study	52/53	8
Fatani et al.[22]	2018	Saudi Arabia	RIFLE	Severe sepsis and Septic shock	2016-2017	Prospective cohort study	127/73	7
Gameiro et al.[23]	2017	Portugal	KDIGO	Sepsis and Septic shock	2008-2014	Retrospective case-control study	399/57	6
Katayama et al.[24]	2017	Japan	KDIGO	Sepsis	2011-2016	Retrospective case-control study	163/351	7

Vilander et al.[25]	2017	Finland	KDIGO	Septic shock	2011–2012	Prospective cohort study	252/226	7
Suberviola et al.[26]	2017	spain	KDIGO	Septic shock	2005-2010	Prospective cohort study	312/74	7
Fisher et al.[27]	2017	Sweden	KDIGO	Septic shock	-	Prospective cohort study	225/71	6
Pérez-Fernández et al.[28]	2017	USA	KDIGO	Severe sepsis and Septic shock	2005-2007	Prospective cohort study	82/178	7
Pereira et al.[29]	2017	Portugal	REFILE	Severe sepsis and Septic shock	2008-2014	Retrospective case-control study	384/72	7
Panich et al.[30]	2017	Thailand	AKIN	Sepsis	2014-2014	Prospective cohort study	79/60	7
Su et al.[31]	2016	China	KDIGO	Severe sepsis	-	Prospective cohort study	45/27	6
Yilmaz et al.[32]	2015	Turkey	AKIN	Severe sepsis	2011-2013	Retrospective cohort study	68/50	7
Medeiros et al.[33]	2015	Japanese	AKIN	Sepsis	2013-2014	Retrospective cohort study	144/56	8
Dai et al.[34]	2015	China	KDIGO	Sepsis	2012-2014	Prospective cohort study	55/57	7
Sood et al.[35]	2014	Canada	RIFLE	Septic shock	1996-2008	Prospective cohort study	3298/1195	7
Peng et al.[36]	2014	China	KDIGO	Sepsis	2008-2011	Prospective cohort study	101/110	8
Patschan et al.[37]	2014	Germany	AKIN	Sepsis	-	Retrospective case-control study	22/11	7
Tu et al.[38]	2014	China	AKIN	Sepsis	2011-2013	Prospective cohort study	49/101	6
Fan et al.[39]	2014	China	RIFLE	Sepsis	2012-	Prospective cohort	58/67	7

					2014	study		
CHO et al.[40]	2014	Korea	RIFLE	Sepsis	2010-2011	Prospective cohort study	44/18	7
Terzi et al.[41]	2014	Greece	RIFLE	Sepsis	-	Prospective cohort study	16/29	6
Poukkanen et al.[42]	2013	Finland	KDIGO	Severe sepsis	2011-2012	Retrospective case-control study	153/270	7
Legrand et al.[43]	2013	France	AKIN	Severe sepsis and Septic shock	2006-2010	Prospective cohort study	69/68	8
Cardinal-Fernández et al.[44]	2013	Spain	RIFLE	Severe sepsis	2005-2008	Prospective cohort study	65/74	7
de Geus et al.[45]	2013	Netherlands	AKIN	Sepsis	2007-2008	Prospective cohort study	49/432	7
Katagiri et al.[46]	2013	Japan	RIFLE	Sepsis	2010-2011	Prospective cohort study	24/10	6
Aydogdu et al.[47]	2013	Turkey	RIFLE	Sepsis	2008-2010	Prospective cohort study	63/66	7
Suh et al.[48]	2013	South Korean	RIFLE	Sepsis and Septic shock	2010	Retrospective case-control study	573/419	8
Poukkanen et al.[49]	2013	Finland	KDIGO	Severe sepsis	2011-2012	Retrospective case-control study	437/393	7
Zhao et al.[50]	2013	China	AKIN	Sepsis	2011-2013	Retrospective case-control study	90/58	6
Payen et al.[51]	2012	Brazil	AKIN	Severe sepsis and Septic shock	2004-2005	Retrospective cohort study	129/47	6
Frank et al.[52]	2012	USA	AKIN	Septic shock	1999-2009	Retrospective cohort study	627/637	7
Plataki et al.[53]	2011	USA	RIFLE	Septic shock	2005-2007	Retrospective cohort	237/153	7

						study		
Ma˚rtensson et al.[54]	2010	Sweden	RIFLE OR AKIN	Septic shock		Prospective cohort study	18/7	6
YANG et al.[55]	2009	China	AKIN	Septic shock	2001-2008	Retrospective cohort study	126/32	7
Lopes et al.[56]	2009	Portugal	AKIN	Sepsis	2004-2007	Retrospective cohort study	99/216	7
Bagshaw et al.[57]	2009	Canada, the United States and Saudi Arabia	RIFLE	Septic shock	1989-2005	Retrospective cohort study	2917/1615	7
Bagshaw et al.[58]	2008	Australia	RIFLE	Sepsis	2000-2005	Retrospective cohort study	14039/19336	8

Table 2.Summary data of all sepsis patients who developed AKI from included studies.

Characteristic	No.Studies	Prevalence	sepsis		septic shock		severe sepsis	
			No.Studies	Prevalence	No.Studies	Prevalence	No.Studies	Prevalence
Septic AKI	47	48.73% (27248/55911)	22	41.98% (16399/39067)	12	60.47% (12678/20965)	5	38.92% (768/1570)
Sex(male)	44	59.70% (5913/9904)	22	63.68% (1380/2167)	11	59.64% (3191/5350)	5	64.45% (495/768)
Comorbidities								
ARDS	3	47.02% (489/1040)	1	81.19% (82/101)	2	43.34% (407/939)	-	-
Hypertension	32	38.39% (3263/8500)	14	42.28% (859/1817)	6	26.16% (1073/4102)	5	58.07% (446/768)
Diabetes mellitus	32	27.57% (2248/8155)	13	20.53% (373/1817)	7	26.75% (1897/7091)	5	30.20% (232/768)
Stroke	4	22.79% (67/294)	1	22.33% (67/300)	-	-	1	17.78% (8/45)
Cancer	6	18.23% (705/3745)	-	-	2	18.80% (650/3458)	1	16.33% (8/49)
Chronic kidney disease	14	16.46% (449/2795	7	15.52% (178/1147	2	45.13% (102/226	2	11.02% (65/590)
Cardiovascula disease	11	16.30% (2522/15477)	4	19.47% (169/868)	-	-	1	7.00% (3/45)
Congestive heart failure	7	12.69% (491/3869	2	17.26% (39/226)	4	12.64% (446/3529	1	8.80% (6/68)
COPD	17	12.41% (1114/8976)	6	12.69% (90/709)	5	12.99% (873/6721)	1	5.20% (25/437)
Hepatic failure	4	12.16% (449/3691)	2	39.76% (134/337)	1	9.90% (290/2917)	3	12.61% (83/658)
Coronary artery disease	8	11.58% (457/3948	4	10.14% (88/868)	2	9.30% (274/2946)	1	6.15% (4/65)
Systolic heart failure	4	11.25% (135/1200	1	8.00% (24/300)	2	14.32% (59/412)	1	11.90% (52/437)
Immnosuppression	7	10.35% (1888/18249)	2	12.74% (1300/14204)	3	15.80% (550/3481)	1	7.20% (35/437)
Cirrhosis	6	4.71% (99/2104)	1	1.73% (7/405)	2	7.50% (59/787)	-	-

Liver disease	7	3.74% (554/14081)	3	3.57% (509/14282)	1	8.73% (22/252)	2	8.59% (17/198)
Admission category								
Emergency admission	7	50.88% (9235/18149)	2	50.90% (7298/14339)	2	41.46% (1314/3169)	2	97.12% (573/590
Medical admission	8	47.02% (8701/18506)	3	49.16% (6938/14112)	2	36.99% (1311/3544	-	-
Operative admission	5	30.91% (353/1142)	1	22.33% (67/300)	1	23.02% (58/252	2	28.81% (170/590)
Surgical ward	7	17.73% (3787/21359	3	16.51% (2375/14388)	3	21.29% (1380/6482	-	-
Source of infection								
Pulmonary	19	46.05% (1480/3214	8	57.96% (448/773)	5	41.10% (603/1467)	3	48.02% (316/658)
Respiratory	7	32.08% (273/85	2	41.22% (54/131)	2	32.74% (74/226)	2	26.36% (29/110)
Abdominal	25	30.87% (2152/6971)	7	32.12% (177/551)	7	28.16% (1253/4450)	5	28.65% (220/768)
Urinary tract	19	11.14% (630/5653)	6	12.01% (58/483)	6	11.34% (483/4259)	5	11.38% (80/703)
Skin or soft tissue	13	6.03% (335/5554)	3	2.15% (5/232)	4	5.40% (218/4033	3	10.71% (68/635)
Unknow	4	6.02% (100/1662)	-	-	2	8.30% (73/879)	-	-
Community acquired	3	57.36% (2041/3558)	-	-	1	56.80% (1657/2917)	2	65.08% (384/590)
Nosocomial acquired	2	39.81% (2474/6215)	-	-	2	39.81% (2474/6215)	-	-
Medications								
Vasopressors	7	64.61% (1293/2001)	3	45.04% (100/222)	2	59.38% (513/864)	-	-
vasoactive drugs	5	63.22% (911/1441)	2	35.69% (131/367)	1	67.50% (108/160)	2	96.44% (569/590)
Steroids	3	30.80% (85/276)	2	38.16% (79/207)	-	-	-	-

Diuretics	4	30.77% (296/962)	-	-	1	39.40% (97/252)	2	30.85% (182/590)
ACEI or ARB	8	25.62% (619/2416)	1	18.41% (58/315)	3	24.97% (200/801)	3	33.59% (220/655)
Stains	5	21.77% (357/1640)	-	-	2	24.13% (118/489)	1	15.79% (69/437)
Nsaids		9.63% (203/2108)	1	16.19% (51/315)	2	11.45% (56/489)	2	12.54% (74/590)
Bacteria								
Gram-negative bacteria	3	17.26% (160/927)	-	-	1	22.3% (49/225)	-	-
Gram-positive bacteria	4	10.43% (99/949)	1	18.20% (4/22)	1	28.6% (63/225)	-	-
Invasive treatment								
Mechanical ventilation	23	68.00% (7167/10539)	7	49.17% (415/844)	6	71.21% (5481/7643)	4	75.25% (529/703)
renal replacement therapy	6	39.51% (320/810)	1	36.53% (19/52)	1	18.18% (12/66)	-	-
Dialysis	3	28.92% (59/204)	2	35.04% (48/137)	-	-	-	-
Blood transfusion	3	19.46% (94/483)	1	7.64% (11/144)	2	27.39% (3/303)	-	-
Organ transplant	3	3.76% (252/6703)	-	-	2	3.94% (245/6215)	1	1.60% (7/437)
Positive blood culture	8	41.38% (3259/7876)	-	-	4	42.89% (2836/6612)	2	30.29% (146/482)
Bloodstream infection	4	6.61% (237/3586)	1	17.31% (9/52)	1	7.40% (216/2917)	1	4.70% (6/437)
Smoke history	5	43.09% (642/1490)	2	40.42% (291/720)	-	-	1	32.35% (22/68)
Multiorgan dysfunction (≥3)	3	50.11% (436/870)	1	70.48% (222/315)	-	-	-	-
Mortality								
ICU mortality	10	45.99% (1989/4325)	2	50.00% (46/92)	4	50.47% (1672/3313)	1	35.38% (23/65)
Hospital mortality	15	49.84% (2732/5481)	7	42.17% (245/581)	3	55.83% (1935/3466)	1	29.29% (128/437)

28-day mortality	4	36.67% (161/439)	1	30.61% (15/49)	1	71.42% (90/126)	-	-
90-day morality	5	64.66% (2406/3721)	-	-	1	58.42% (1704/2917)	2	40.0% (236/590)

COPD:chronic obstructive pulmonary disease

ACEI or ARB :angiotensin converting enzyme inhibitors or Angiotensin Receptor Blocker

Supplemental Information Note

Additional files:Results of meta-analysis of all factors

Additional files1 Checklist.PRISMA Checklist. (This file was omitted by the authors in this version of the paper)

Additional files2 Fig.Sex(male)-Forest plot,Funnel plot,Sensitivity and Subgroup analysis.

Additional files3 Fig.Septic shock-Forest plot and Funnel plot.

Additional files4 Fig.Positive blood culture-Forest plot,Funnel plot and Sensitivity analysis.

Additional files5 Fig.Smoke history-Forest plot,Sensitivity analysis.

Additional files6 Fig.Bloodstream infection-Forest plot.

Additional files7 Fig.Hypertension-Forest plot,Funnel plot,Sensitivity and Subgroup analysis.

Additional files8 Fig.Diabetes mellitus-Forest plot and Funnel plot.

Additional files9 Fig.Stroke-Forest plot.

Additional files10 Fig.Cancer-Forest plot.

Additional files11 Fig.Chronic kidney disease-Forest plot,Funnel plot,Sensitivity and Subgroup analysis.

Additional files12 Fig.Cardiovascular Diseases -Forest plot,Funnel plot.

Additional files13 Fig.Congestive heart failure-Forest plot,Funnel plot and Sensitivity.

Additional files14 Fig.COPD-Forest map,Funnel plot,Sensitivity and Subgroup analysis.

Additional files15 Fig.Coronary artery disease-Forest plot and Funnel plot.

Additional files16 Fig.Systolic heart failure-Forest plot,Sensitivity analysis.

Additional files17 Fig.Immnosuppression-Forest plot,Funnel plot and Sensitivity analysis.

Additional files18 Fig.Liver disease-Forest plot and Sensitivity analysis.

Additional files19 Fig.Pulmonary infection-Forest plot,Funnel plot,Sensitivity and subgroup ananlysis.

Additional files20 Fig.Abdominal infection-Forest plot,Funnel plot and Sensitivity analysis.

Additional files21 Fig.Urinary tract infection-Frest plot,and Funnel plot,Sensitivity and Subgroup analysis.

Additional files22 Fig.Unknown source of infection-Forest plot.

Additional files23 Fig.Vasopressors-Forest plot,Funnel plot,Sensitivity and Subgroup analysis.

Additional files24 Fig.Vasoactive drugs-Forest plot and Sensitivity analysis.

Additional files25 Fig.Diuretic-Forest plot.

Additional files26 Fig.ACEI or ARB-Forest plot,Funnel plot ,Sensitivity and Subgroup analysis.

Additional files27 Fig.Stains-Forest plot.

Additional files28 Fig.Gram-negative bacteria-Forest plot.

Additional files29 Fig.Gram-positive bacteria-Forest plot and Sensitivity analysis.

Additional files30 Fig.Mechanical ventilation-forest plot,Funnel plot,Sensitivity and Subgroup analysis.

Additional files31 Fig.Organ transplant-Forest plot and Sensitivity analysis.

Additional files32 Fig.Blood transfusion-Forest plot,Sensitivity analysis.

Figures

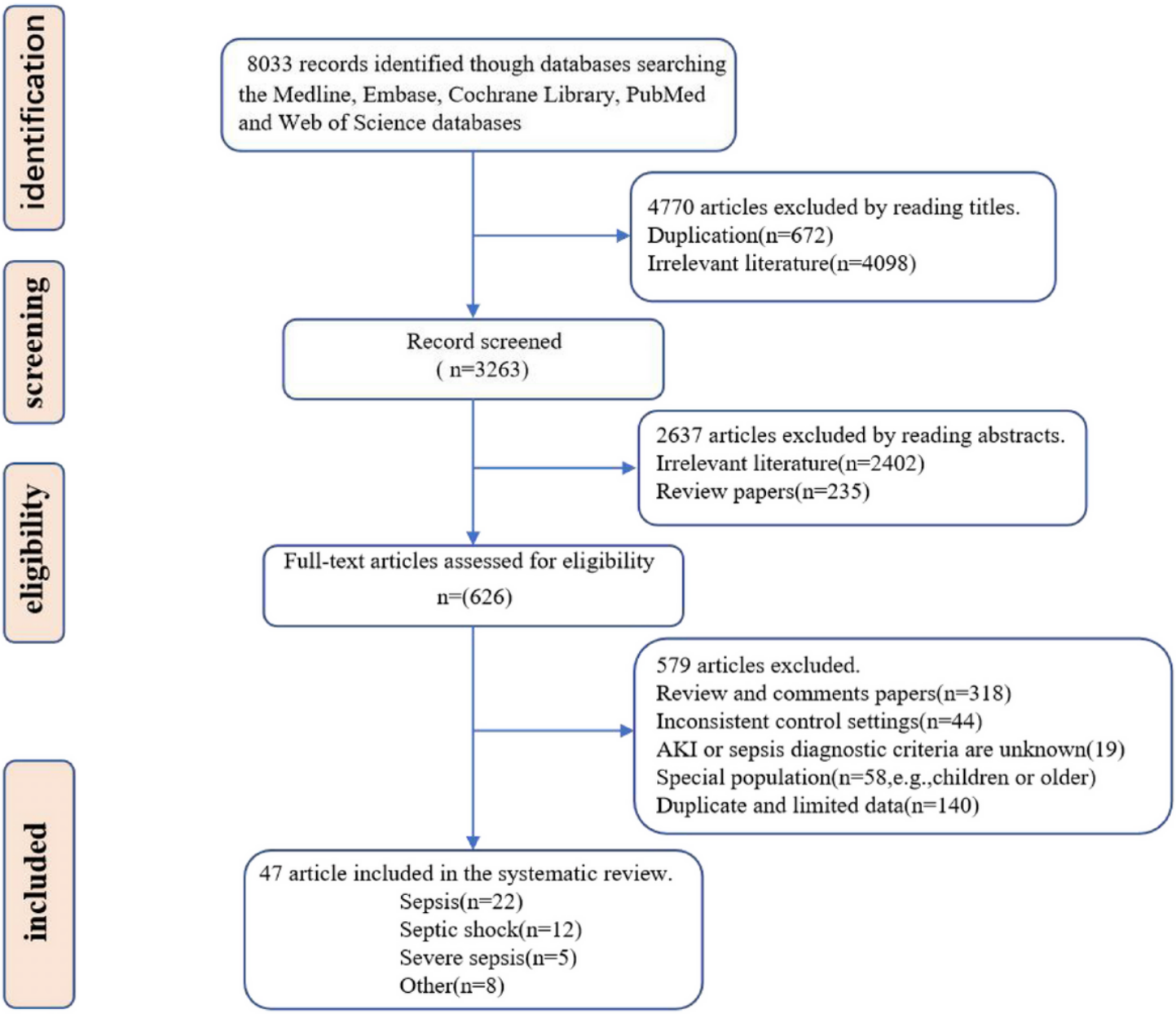

Figure 1

Flow diagram showing search strategy and study selection. The diagram shows the numbers of titles and studies reviewed in preparation of this meta-analysis of development of acute kidney injury in sepsis patients. n represents the number of studies included in data syntheses. 8 included ‘other’ article represent that the study subjects included at least two of three sepsis (sepsis, septic shock and severe sepsis)

Risk factor	Pooled OR (95% CI)	Forest plot	No.Studies	Univariable			Prevalence	Measure of Heterogeneity			egger'test
				Negative	Null	Positive		c^2	P -Value	I^2	
Sex(male)	1.22 (1.06-1.40)		43		33	10	60.40%	138.92	0	69.80%	0.521
Septic shock	2.88 (2.36-3.52)		7		0	7	66.37%	6.53	0.366	8.20%	0.167
Positive blood culture	1.60 (1.35-1.89)		9		5	4	41.19%	16.08	0.041	50.20%	0.847
Smoke history	1.60 (1.09-2.36)		5		3	2	43.09%	18.42	0.001	78.30%	-
Bloodstream infection	0.99 (0.80-1.24)		4		4	0	6.61%	2.78	0.427	0.00%	-
Comorbidities											
Hypertension	1.43 (1.20-1.70)		32		10	22	38.39%	119.09	0	74.00%	0.374
Diabetes mellitus	1.59 (1.47-1.71)		32		11	21	27.57%	50.93	0.013	37.10%	0.736
Stroke	1.16 (0.81-1.66)		4		3	1	22.79%	5.98	0.112	49.90%	-
Cancer	0.94 (0.80-1.09)		6		3	3	18.23%	7.87	0.163	36.50%	-
Chronic kidney disease	3.49 (2.36-5.15)		14		4	10	18.10%	46.01	0	71.70%	0.105
Cardiovascula CVD	1.31 (1.24-1.40)		11		10	1	16.30%	7.2	0.707	0.00%	0.015
Congestive heart failure	1.43 (0.85-2.41)		7		3	4	12.69%	28.15	0	78.70%	0.679
COPD	0.83 (0.66-1.03)		17	3	13	1	10.35%	39.82	0.001	59.80%	0.545
Coronary artery disease	1.27 (1.08-1.49)		8		6	2	11.58%	10.32	0.171	32.10%	0.334
Systolic heart failure	1.02 (0.66-1.57)		4		3	1	12.16%	6.69	0.083	55.10%	-
Immnosuppression	1.16 (0.90-1.50)		7		6	1	10.35%	25.3	0	76.30%	0.545
Liver disease	1.68 (1.47-1.90)		17		11	6	3.74%	19.28	0.313	11.80%	0.481
Source of infection											
Pulmonary	0.77 (0.60-0.99)		19	7	10	2	46.05%	80.38	0	77.60%	0.712
Abdominal	1.44 (1.32-1.48)		25		19	6	30.87%	40.16	0.021	40.20%	0.353
urinary tract	1.17 (0.86-1.59)		17		14	3	11.14%	40.96	0.001	60.90%	-
Unknow	2.01 (1.35-2.98)		4		2	2	6.02%	0.38	0.945	0.00%	-
Medications											
Vasopressors	3.15 (2.00-4.96)		7		1	6	64.61%	69.93	0	80.60%	0.144
Vasoactive drugs	3.85 (1.89-7.87)		5		1	4	63.22%	29.46	0	86.40%	-
Diuretics	1.40 (1.13-1.72)		4		3	1	30.77%	2.29	0.515	0.00%	-
ACEI or ARB	1.71 (1.16-2.52)		8		4	4	25.62%	27.15	0	74.20%	0.437
Stains	1.11 (0.69-1.76)		5	1	3	1	21.77%	21.19	0	81.10%	-
Bacteria											
Gram-negative bacteria	2.19 (1.52-3.15)		3		1	2	17.26%	0.99	0.61	0.00%	-
Gram-positive bacteria	1.24 (0.86-1.24)		4		4	0	10.43%	4.71	0.194	36.30%	-
Invasive treatment											
Mechanical ventilation	1.78 (1.33-2.39)		23	2	11	10	68.00%	185.92	0	90.05%	0.082
Organ transplant	1.96 (1.48-2.61)		3		1	2	3.76%	0.77	0.681	0.00%	-
Blood transfusion	1.96 (0.81-4.73)		3		2	1	19.46%	5.41	0.067	63.10%	-

COPD:chronic obstructive pulmonary disease; ACEI OR ARB:Angiotensin converting enzyme inhibitor OR Arbitration

Figure 2

Meta-analysis of risk factors of AKI.

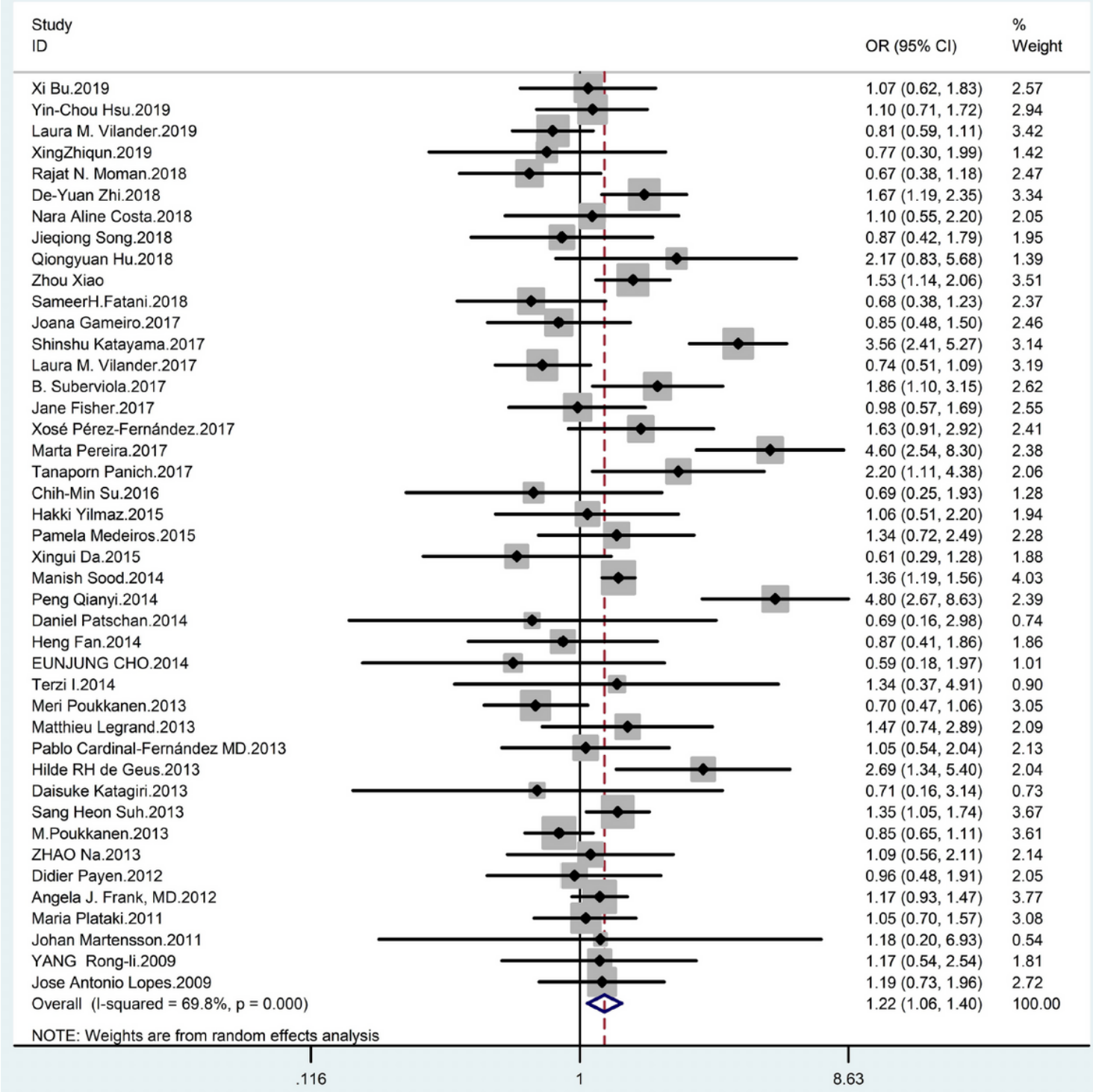

Figure 3

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

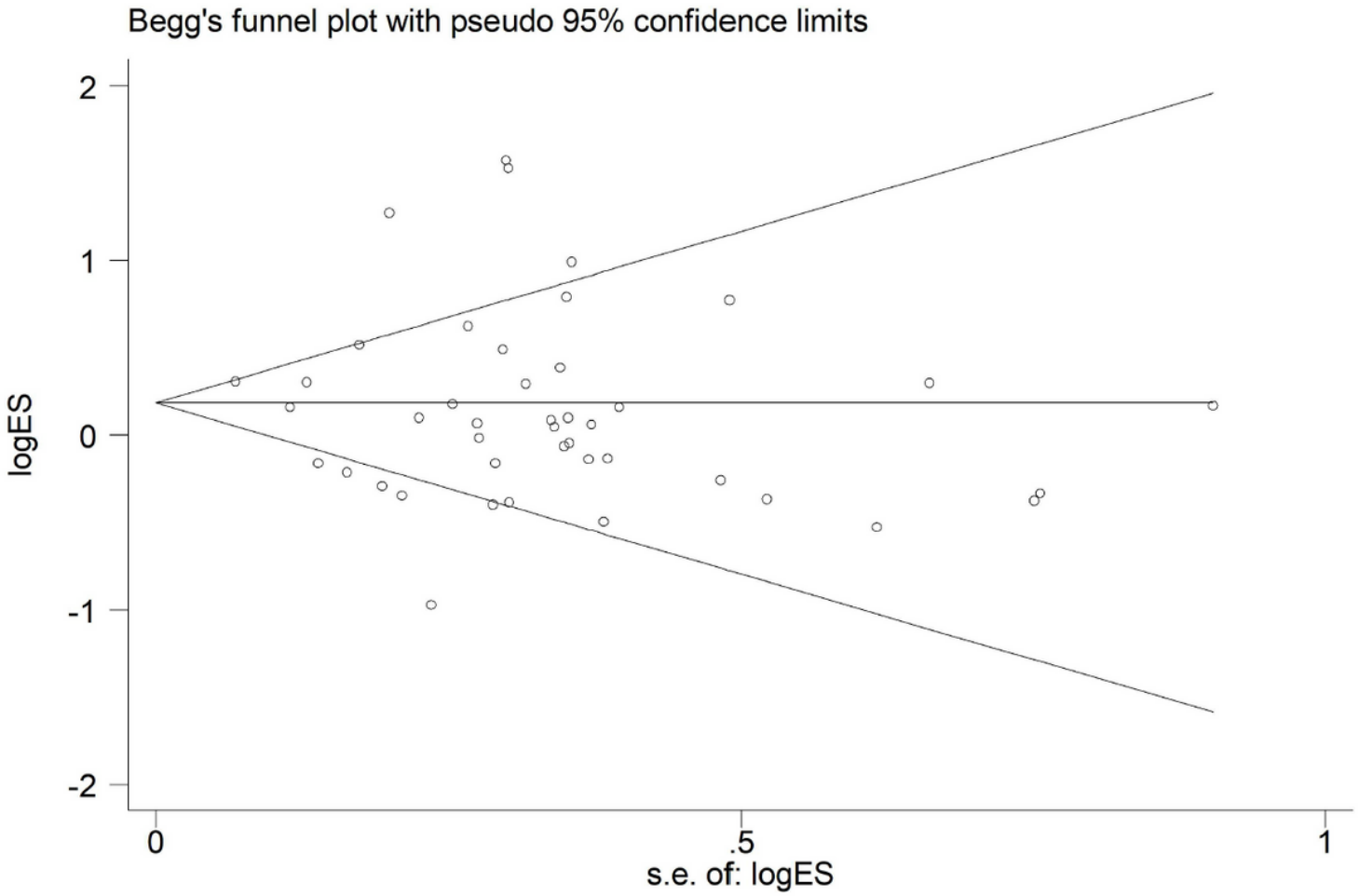

Figure 4

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

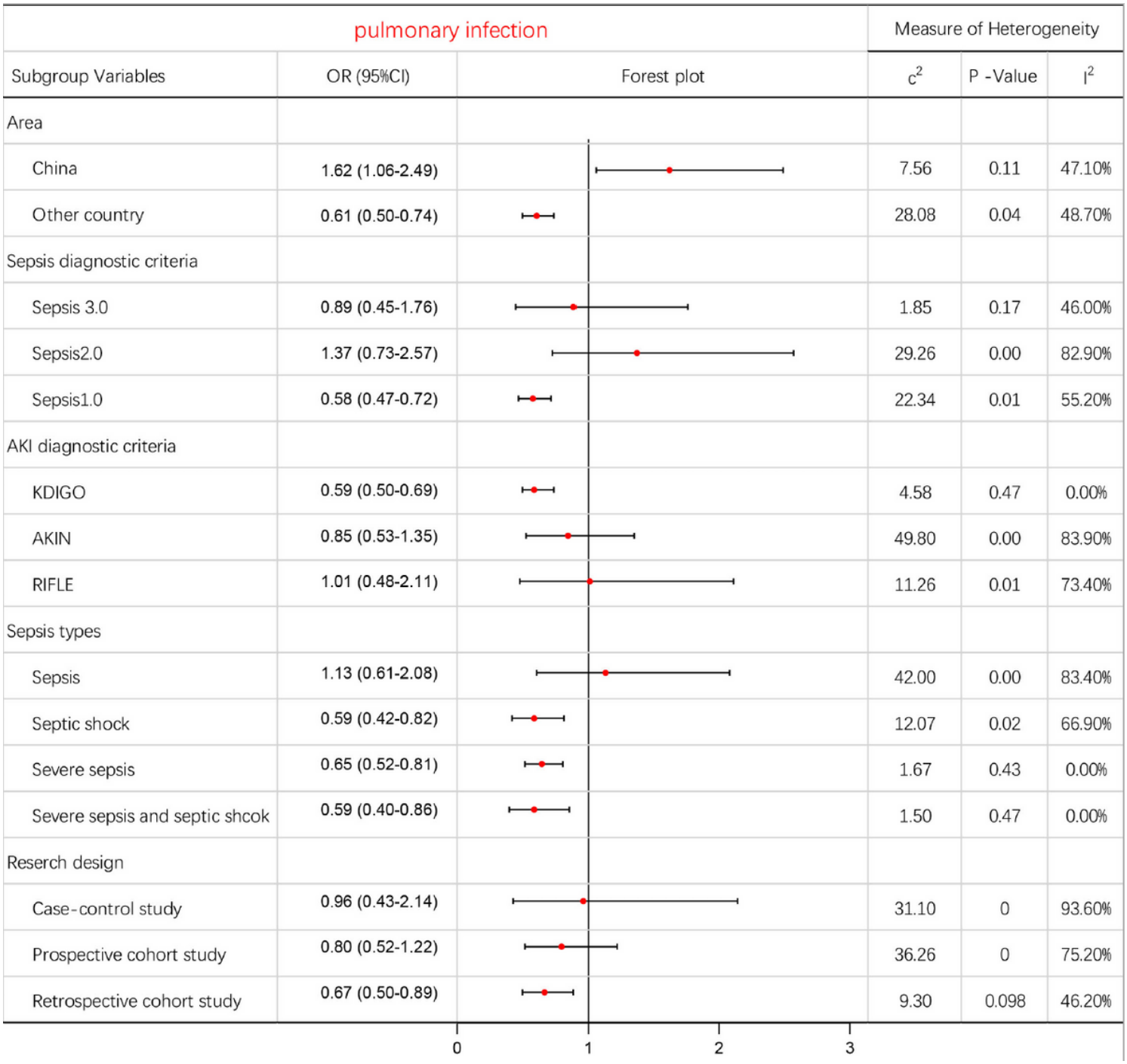

Figure 5

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

Supplementary Files

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