Biomarkers for the diagnosis of sepsis-associated acute kidney injury: systematic review and meta-analysis

Yun Xie*, Peijie Huang*, Jiaxiang Zhang*, Rui Tian, Wei Jin, Hui Xie, Jiang Du, Zhigang Zhou, Rulian Wang

Department of Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: Y Xie, P Huang, J Zhang; (II) Administrative support: R Wang, Z Zhou; (III) Provision of study materials or patients: R Tian, W Jin, H Xie, J Du; (IV) Collection and assembly of data: Y Xie, P Huang, J Zhang; (V) Data analysis and interpretation: Y Xie; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

These authors contributed equally to this work.

Correspondence to: Rulian Wang, Zhigang Zhou. Department of Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No. 650 New Songjiang Road, Songjiang, Shanghai 201600, China. Email: wangyusun@hotmail.com; pollyerik2004@163.com.

Background: With the development of new techniques, blood and other humoral biomarkers have become increasingly important in the diagnosis of sepsis-associated acute kidney injury (AKI). We aimed to review and summarize the biomarkers associated with the diagnosis of sepsis-associated AKI.

Methods: We performed a systematic review in PubMed, Embase, Web of Science, Cochrane and CNKI literature databases. Chinese and English articles published before January 30, 2021. We extracted information on the sensitivity and specificity of biomarkers to diagnose sepsis-associated AKI, the sample size of individuals with sepsis-associated AKI, the demographic variables, the diagnostic criteria and the sample acquisition protocol. Revman 5.3 software was used to analyze data. The sources of heterogeneity of included studies main were different diagnostic criteria for sepsis and AKI, time of sample collection and Patients came from different departments. We defined the inclusion of related studies by using PICOs (Patient, Intervention, Comparison and Outcome) criteria, in particular the design of studies to be included. P: Patients of sepsis. I: Patients of sepsis-associated AKI. C: Patients without sepsis-associated AKI. O: Diagnosis of sepsis associated kidney injury.

Results: A total of 1,227 articles, including 42 studies, were identified. Increases in urine and serum neutrophil gelatinase-related lipid carrier protein (NGAL), urinary interleukin-18, urinary Kim-1, urinary Nefrin-1, urinary sCD163, serum estradiol levels, and serum soluble thrombolytic regulatory protein were most strongly correlated with the diagnosis of sepsis-associated AKI. The SROC of urinary KIM-1 ranked first, followed by the other biomarkers: urinary KIM-1 > urinary NGAL > blood NGAL > urinary IL-18. According to the sample size, the SROC values of urinary NGAL, blood NGAL, urinary IL-18 and urinary KIM-1 were 0.907, 0.857, 0.861 and 0.931, respectively. The sequence was still urinary KIM-1 > urinary NGAL > blood NGAL > urinary IL-18.

Conclusions: According to the SROC curve area, the diagnostic sequence of sepsis-associated AKI biomarkers was urinary Kim-1 > urinary NGAL > blood NGAL > urinary IL-18. This meta-analysis provided diagnostic features of blood and urine biomarkers based on their association with the diagnosis of sepsis-associated AKI.

Keywords: Sepsis; acute kidney injury (AKI); biomarkers; diagnosis

Submitted Sep 15, 2020. Accepted for publication Feb 24, 2021.
doi: 10.21037/apm-20-1855

View this article at: http://dx.doi.org/10.21037/apm-20-1855
Introduction

Sepsis is defined as organ dysfunction caused by the host's adverse response to infection. One of the most common organs affected is the kidney, leading to acute kidney injury associated with sepsis (SA-AKI). In recent years, the incidence of sepsis has been increasing annually. A comprehensive assessment of 750 million people admitted to the hospital in the United States from 1979 to 2000 found that sepsis increased from 82.7 to 240.4 per 100,000 individuals, with an annual growth rate of 8.7% (1), and the inpatient mortality rate was as high as 17.9% (2). Secondary AKI significantly increased sepsis mortality. Sepsis is associated with up to 50% of AKI cases, and up to 60% of sepsis patients have AKI (3,4). Patients with sepsis combined with AKI had significantly higher mortality than those without AKI (5-7). In addition, sepsis-related patients with AKI have significantly increased mortality compared with patients with AKI of another etiology (6). Independent risk factors for the occurrence of AKI in sepsis include insufficient blood volume and exposure to toxic renal therapy, among others. Although the pathophysiological mechanism of AKI in sepsis is still not fully understood, the relationship between the two is close (8); some studies have shown that the inflammatory cascade reaction of sepsis is the cause of AKI (9).

To date, sepsis and acute kidney injury (AKI) have been diagnosed primarily based on urine volume and serum creatinine measurements. The commonly used diagnostic criteria are the RIFLE, AKIN and KDIGO standards (10-12). Since the late diagnosis of AKI based solely on urine volume and serum creatinine has been questioned, early diagnosis is of great clinical concern, so we need to provide more insights on this. Numerous studies have focused on the early identification of AKI biomarkers. Zhang et al. conducted a meta-analysis in 2016 (13), focusing on neutrophil gelatinase-associated lipocalin (NGAL), a plasma biomarker of human AKI, also known as lipid carrier protein-2. However, these researchers summarized only a partial biomarker of AKI in plasma; other biomarkers, such as urinary interleukin-18 and kim-1, have not been evaluated (14). There also were inconsistent findings regarding the research topic of biomarkers of sepsis-associated AKI.

Therefore, the following steps need to be taken: provide a ranking system for distinguishing disease in high-risk patients and determining prognosis. The purpose of this study was to compare biomarker levels in patients with AKI with samples from at-risk controls. This study intends to compare the predictive value of and differences in various indicators of AKI in patients with sepsis through literature data analysis and to explore the correlation between the biomarkers of patients with sepsis-associated AKI.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1855).

Methods

Data sources and research choices

We manually searched the PubMed, Embase, Web of Science, Cochrane libraries and CNKI for articles on biomarkers of AKI in blood and urine samples released before January 30, 2021. We also searched the references of these articles for relevant papers to include in the study. Two researchers screened and evaluated all studies independently, and a third reviewer intervened when differences arose. For literature search, the terms used were “sepsis”, “acute kidney injury”, “biomarkers”, “diagnosis”.

Inclusion criteria

(I) the article is an original research paper on adult patients with sepsis, (II) the research concerns the association of clinical outcomes and biomarkers measured in blood or urine in an accurate value report (diagnosis of AKI in patients with risk and/or AKI mortality), (III) the paper describes the demographic variables of the study participants, and (IV) the paper is written in Chinese or English. We defined the inclusion of related studies by using PICOs (Patient, Intervention, Comparison and Outcome) criteria, in particular the design of studies to be included.


Exclusion criteria

(I) Articles written in languages other than Chinese or English, (II) articles unrelated to AKI, (III) articles that were not original studies, (IV) in vivo/in vitro studies, (V) pediatric studies, (VI) articles that analyzed biomarkers not measured in blood or urine, and (VII) articles that analyzed biomarkers for therapeutic monitoring.

Data extraction and quality assessment

We created Excel spreadsheets (Microsoft Corp., Redmond, WA, USA) to extract data from the included studies,
and two researchers independently completed the data extraction. The average or median levels and standard deviation (SD) of AKI etiology and biomarkers in blood or urine were obtained. When the biomarkers were measured multiple times, only the measurements of the first day were extracted.

Research groups
First, the patients with sepsis were divided into two groups, namely, the AKI group and the non-AKI group, according to whether they had AKI status after admission.

We extracted the average blood and urine biomarker concentrations from the different subgroups. The sensitivity, specificity, true positives, false positives, false negatives, true negatives, area under the ROC curve and other indicators were collected. In addition, the data on demographic variables (age, gender and number of participants in each subgroup), diagnostic criteria for sepsis, diagnostic criteria for AKI, AKI mortality rate, time of sample collection and patients came from different departments. Then, the weighted sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio and 95% CI of each study were calculated by using Revman 5.3 software, and the SROC curve was calculated and summarized to indicate the accuracy of the diagnostic test and reflect the SROC.

The closer the curve is to the upper left corner, the higher the value is, and thus the higher the accuracy of the diagnostic test is; the results are represented by a forest chart.

Results

Literature retrieval

Literature retrieval produced a total of 1,227 articles from the database: PubMed, 444 articles; Web of Science, 512 articles; Embase, 259 articles; Cochrane library, 9 articles; and 3 articles from the reference lists of the articles included in the study. Studies were primarily excluded by reviewing titles and abstracts for the following factors: in vitro/animal studies (n=434), duplications (n=423), articles other than original studies (comments, editorials or case reports, n=90), and articles (n=30) that were not related to the incidence or mortality of AKI. After initial screening, 95 articles remained for full-text review. Of these, six articles contained insufficient data. For four of these articles, we attempted to contact the author; however, copies of the full text were not available. The remaining 42 articles were used for the meta-analysis (Figure 1).

Research characteristics and quality assessment

Demographic variables included in the study are summarized in Table 1. A total of 42 articles involving 4,189 patients were included in this meta-analysis. In 25% of the studies, AKI was diagnosed based on the AKIN criteria.
<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Diagnostic criteria for AKI</th>
<th>Sepsis</th>
<th>Study size</th>
<th>Male (%)</th>
<th>Age</th>
<th>Mortality (%)</th>
<th>Sample retrieved time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary NGAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albeladi 2017</td>
<td>RIFLE</td>
<td>Sepsis2.0</td>
<td>75</td>
<td>50.7</td>
<td>51.6</td>
<td>53.3</td>
<td>Over the first and second 24 h of an ICU admission</td>
</tr>
<tr>
<td>Aydogdu 2013</td>
<td>RIFLE</td>
<td>Sepsis2.0</td>
<td>129</td>
<td>64.3</td>
<td>68.5</td>
<td>45.0</td>
<td>Within first 24 hours of ICU admission</td>
</tr>
<tr>
<td>Fan 2014</td>
<td>RIFLE</td>
<td>Sepsis2.0</td>
<td>126</td>
<td>68.2</td>
<td>57.0</td>
<td>54.8</td>
<td>Admission</td>
</tr>
<tr>
<td>Hjortrup 2015</td>
<td>KDIGO</td>
<td>Sepsis1.0</td>
<td>100</td>
<td>57.0</td>
<td>66.0</td>
<td>39.0</td>
<td>At enrolment</td>
</tr>
<tr>
<td>Li 2010</td>
<td>Aakin</td>
<td>Sepsis1.0</td>
<td>74</td>
<td>68.9</td>
<td>52.0</td>
<td>21.6</td>
<td>Within first 2 hours of Sepsis</td>
</tr>
<tr>
<td>Martensson 2010</td>
<td>RIFLE or AKIN</td>
<td>Sepsis1.0</td>
<td>45</td>
<td>66.0</td>
<td>52.6</td>
<td>11.0</td>
<td>Analyzed twice daily</td>
</tr>
<tr>
<td>Niu 2015</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>60</td>
<td>81.7</td>
<td>65.4</td>
<td>NA</td>
<td>Admission, 12, 24, 48, 72 h</td>
</tr>
<tr>
<td>Park 2019</td>
<td>KDIGO</td>
<td>Sepsis3.0</td>
<td>140</td>
<td>48.0</td>
<td>75.0</td>
<td>NA</td>
<td>On presentation at the emergency department</td>
</tr>
<tr>
<td>Rocha 2018</td>
<td>KDIGO</td>
<td>Sepsis2.0</td>
<td>75</td>
<td>52.0</td>
<td>71.4</td>
<td>53.3</td>
<td>Within the first 48 hours of the diagnosis of sepsis</td>
</tr>
<tr>
<td>Si 2015</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>168</td>
<td>57.7</td>
<td>68.0</td>
<td>44.2</td>
<td>On day 1 of admission</td>
</tr>
<tr>
<td>Xing 2013</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>73</td>
<td>56.2</td>
<td>50.0</td>
<td>46.6</td>
<td>0, 1, 6, 24, 48, 72 h after admission</td>
</tr>
<tr>
<td>Yan 2011</td>
<td>AKIN</td>
<td>Sepsis1.0</td>
<td>112</td>
<td>56.3</td>
<td>64.7</td>
<td>27.7</td>
<td>2, 8 h after Sepsis diagnosis</td>
</tr>
<tr>
<td>Yan 2013</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>141</td>
<td>55.3</td>
<td>68.0</td>
<td>17.0</td>
<td>8 h after Sepsis diagnosis</td>
</tr>
<tr>
<td>Zhou 2014</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>148</td>
<td>56.7</td>
<td>67.2</td>
<td>14.9</td>
<td>0, 4, 8, 12, 24, 48 h after sepsis diagnosis</td>
</tr>
<tr>
<td><strong>Blood NGAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camou 2013</td>
<td>RIFLE or AKIN</td>
<td>Sepsis2.0</td>
<td>50</td>
<td>76.0</td>
<td>60.3</td>
<td>66.0</td>
<td>At admission (D0), at 24 hours (D1) and at 48 hours (D2)</td>
</tr>
<tr>
<td>de Geus 2013</td>
<td>AKIN</td>
<td>Sepsis1.0</td>
<td>75</td>
<td>50.7</td>
<td>57.6</td>
<td>45.0</td>
<td>Within the first 24 hours at admission</td>
</tr>
<tr>
<td>Hjortrup 2015</td>
<td>KDIGO</td>
<td>Sepsis1.0</td>
<td>124</td>
<td>57.0</td>
<td>66.0</td>
<td>39.0</td>
<td>At enrolment</td>
</tr>
<tr>
<td>Khawaja 2019</td>
<td>RIFLE</td>
<td>Sepsis2.0</td>
<td>46</td>
<td>69.0</td>
<td>46.5</td>
<td>32.6</td>
<td>Within 12 h of ICU admission</td>
</tr>
<tr>
<td>Martensson 2010</td>
<td>RIFLE or AKIN</td>
<td>Sepsis1.0</td>
<td>45</td>
<td>65.7</td>
<td>52.6</td>
<td>11.4</td>
<td>Analyzed twice daily</td>
</tr>
<tr>
<td>Ralib 2017</td>
<td>KDIGO</td>
<td>Sepsis1.0</td>
<td>129</td>
<td>65.9</td>
<td>48.6</td>
<td>41.1</td>
<td>Within the first 24 hours at admission</td>
</tr>
<tr>
<td>Shapiro 2010</td>
<td>RIFLE</td>
<td>Sepsis1.0</td>
<td>661</td>
<td>52.0</td>
<td>59.0</td>
<td>NA</td>
<td>At enrolment</td>
</tr>
<tr>
<td>Wang 2014</td>
<td>KDIGO</td>
<td>Sepsis1.0</td>
<td>87</td>
<td>61.0</td>
<td>71.0</td>
<td>17.3</td>
<td>Within 24 hours after admission</td>
</tr>
<tr>
<td>Xing 2013</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>73</td>
<td>56.2</td>
<td>50.0</td>
<td>46.6</td>
<td>0, 1, 6, 24, 48, 72 h in ICU</td>
</tr>
<tr>
<td><strong>Urinary IL-18</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nian 2018</td>
<td>KDIGO</td>
<td>Sepsis2.0</td>
<td>60</td>
<td>60.0</td>
<td>51.6</td>
<td>NA</td>
<td>0, 4, 8, 24, 48 h after sepsis diagnosis</td>
</tr>
<tr>
<td>Parikh 2005</td>
<td>KDIGO</td>
<td>Sepsis2.0</td>
<td>138</td>
<td>52.0</td>
<td>50.2</td>
<td>34.0</td>
<td>At 24 and 48 h after sepsis diagnosis</td>
</tr>
<tr>
<td>Zhou 2016</td>
<td>KDIGO</td>
<td>Sepsis2.0</td>
<td>64</td>
<td>59.4</td>
<td>40.9</td>
<td>NA</td>
<td>0, 6, 10, 24, 48, 72 h after sepsis diagnosis</td>
</tr>
<tr>
<td>Zhu 2016</td>
<td>KDIGO</td>
<td>Sepsis2.0</td>
<td>56</td>
<td>51.8</td>
<td>66.2</td>
<td>28.6</td>
<td>6 h after Sepsis diagnosis</td>
</tr>
<tr>
<td><strong>Urinary KIM-1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fan 2016</td>
<td>RIFLE</td>
<td>Sepsis2.0</td>
<td>135</td>
<td>52.6</td>
<td>50.8</td>
<td>8.9</td>
<td>&lt;12 h after admission</td>
</tr>
</tbody>
</table>

Table 1 (continued)
Table 1 (continued)

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Diagnostic criteria for AKI</th>
<th>Sepsis</th>
<th>Study size</th>
<th>Male (%)</th>
<th>Age</th>
<th>Mortality (%)</th>
<th>Sample retrieved time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee 2018</td>
<td>RIFLE</td>
<td>Sepsis3.0</td>
<td>33</td>
<td>60.6</td>
<td>66.3</td>
<td>45.4</td>
<td>Admitted to the ICU</td>
</tr>
<tr>
<td>Tu 2014</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>150</td>
<td>67.3</td>
<td>58.0</td>
<td>32.7</td>
<td>0, 1, 3, 6, 24, and 48 h of ICU admission</td>
</tr>
<tr>
<td>Urinary Netrin-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nian 2018</td>
<td>KDIGO</td>
<td>Sepsis2.0</td>
<td>60</td>
<td>60.0</td>
<td>51.6</td>
<td>NA</td>
<td>0, 4, 8, 24, 48 h after admission</td>
</tr>
<tr>
<td>Tu 2014</td>
<td>AKIN</td>
<td>Sepsis2.0</td>
<td>150</td>
<td>67.3</td>
<td>58.0</td>
<td>32.7</td>
<td>0, 1, 3, 6, 24, and 48 h of ICU admission</td>
</tr>
</tbody>
</table>

ACCP/SCCM, American College of Chest Physicians/Society of Critical Care Medicine; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ELISA, enzyme-linked immunosorbent assay; ER, emergency room; KDIGO, Kidney Disease: Improving Global Outcomes; NGAL, neutrophil gelatinase-associated lipocalin; NR, not reported; PC, prospective cohort; PETIA, particle-enhanced turbidimetric immunoassay; RIA, radioimmunoassay; RIFLE, Risk, Injury, Failure, Loss, End-Stage Kidney Disease; SSC, Survival Sepsis Campaign; SCCM/ESICM/ACCP/ATS/SIS, Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society.

Other standards, such as RIFLE and KDIGO, are used with the AKIN standard. The mean age was 55 to 79 years, and the mortality rate was 30% to 66%. Blood and urine were collected 30 minutes after admission and 72 hours after AKI diagnosis. In terms of sample type, 50% of the studies used biomarkers in urine. Fifty percent used biomarkers in the blood. Blood and urine were used in 3 articles.

Biomarker characteristics associated with AKI diagnosis

We conducted a meta-analysis of 22 blood biomarkers related to the diagnosis of AKI in sepsis (Table 1). Biomarkers such as NGAL, KIM-1, and IL-18, were collected, among which NGAL (16-38) had the highest levels, and among the biomarkers with significant diagnostic value among subgroups, sensitivity and specificity were also high (Table 2). However, general heterogeneity was shown. We conducted an impact analysis to check the sensitivity of the results. The impact analysis suggested that the heterogeneity may be caused by the limited number of studies. By removing the outliers studies, we observed a strong effect of the biomarkers. The biomarkers NGAL, KIM1 and IL-18 were analyzed by subgroup. Since most of the included studies were case-control studies, we excluded other study design types. Markers of endothelial dysfunction, including sTM, C protein, E selectin, and PAI-1, showed diagnostic significance (39,40). Among them, C protein, E selectin and PAI-1 have been found to have lower predictive value for AKI than sTM (41-43); therefore, they were not included in the table. The coagulation function marker ATIII also showed diagnostic significance, as did markers of inflammatory response, including KIM-1 (44), IL-18 (38,45-48), and OPG (49), and estradiol as a marker of hormone response level (50).

Systematic assessment of biomarkers associated with AKI diagnosis

For urinary NGAL, a total of 1,470 patients with sepsis were included in 14 studies. True positive AKI was diagnosed in 496 cases, false positive in 180 cases, false negative in 119 cases and true negative in 675 cases (Figure 2A). For blood NGAL, a total of 1,358 patients with sepsis were included in 9 studies. True positive AKI was diagnosed in 283 cases, false positive in 381 cases, false negative in 86 cases and true negative in 608 cases (Figure 2B). For urinary interleukin-18, a total of 4 studies were searched and included, there were 84 cases of true positive, 41 cases of false positive, 32 cases of false negative and 99 cases of true negative (Figure 2C). For urinary KIM-1, a total of 3 studies were included in the search, there were 124 cases of true positive, 37 cases of false positive, 21 cases of false negative and 194 cases of true negative (Figure 2D). For urinary Netrin-1, a total of 2 studies were searched and included, there were 73 cases of true positive, 59 cases of false positive, 25 cases of false negative and 137 cases of true negative (Figure 2E). The sensitivity of urinary NGAL was 0.81 [0.77, 0.84], and the specificity was 0.79 [0.76, 0.82] (Figure 3A). The sensitivity of blood NGAL was 0.77 [0.72, 0.81], and the specificity was 0.61 [0.58, 0.65] (Figure 3B). The sensitivity of urinary interleukin-18 was 0.80 [0.77, 0.82], with a specificity of 0.70 [0.67, 0.72]
Table 2 Diagnostic value of biomarkers to predict AKI in septic patients in individual studies

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>AUROC</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (include Urine and blood)</td>
<td>0.72–0.92</td>
<td>803</td>
<td>570</td>
<td>207</td>
<td>1305</td>
<td>0.80 [0.77, 0.82]</td>
<td>0.70 [0.67, 0.72]</td>
</tr>
<tr>
<td>Urinary KiM-1</td>
<td>0.73–0.752</td>
<td>75</td>
<td>9</td>
<td>16</td>
<td>93</td>
<td>0.86 [0.79, 0.91]</td>
<td>0.84 [0.79, 0.88]</td>
</tr>
<tr>
<td>Urinary IL-18</td>
<td>0.62–0.973</td>
<td>84</td>
<td>41</td>
<td>32</td>
<td>99</td>
<td>0.80 [0.77, 0.82]</td>
<td>0.70 [0.67, 0.72]</td>
</tr>
<tr>
<td>Urinary Netrin-1</td>
<td>0.778–0.853</td>
<td>73</td>
<td>59</td>
<td>25</td>
<td>137</td>
<td>0.74 [0.65, 0.83]</td>
<td>0.70 [0.63, 0.76]</td>
</tr>
<tr>
<td>Urinary sCD163</td>
<td>0.69</td>
<td>15</td>
<td>20</td>
<td>4</td>
<td>25</td>
<td>0.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Circulating osteoprotegerin (OPG)</td>
<td>0.827</td>
<td>40</td>
<td>7</td>
<td>8</td>
<td>40</td>
<td>0.84</td>
<td>0.85</td>
</tr>
<tr>
<td>Soluble thrombomodulin (sTM)</td>
<td>0.735–0.77</td>
<td>51</td>
<td>1</td>
<td>42</td>
<td>63</td>
<td>0.55</td>
<td>0.98</td>
</tr>
<tr>
<td>Serum estradiol</td>
<td>0.788</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
<td>49</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Antithrombin III (ATIII)</td>
<td>0.618</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>N-acetyl-β-D-glucosaminidase (NAG)</td>
<td>0.84 (0.72–0.91)</td>
<td>42</td>
<td>NR</td>
<td>NR</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tissue inhibitor of metalloproteinase-2 (TIMP-2)</td>
<td>0.8</td>
<td>42</td>
<td>NR</td>
<td>NR</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reported.

Figure 2 Forest plot. (A) Forest plot of urinary NGAL. (B) Forest plot of blood NGAL. (C) Forest plot of urinary interleukin-18. (D) Forest plot of urinary KIM-1. (E) Forest plot of urinary Netrin-1.

(Figure 3C). The sensitivity of urinary KIM-1 was 0.86 [0.79, 0.91], with a specificity of 0.84 [0.79, 0.88] (Figure 3D). The sensitivity of urinary Netrin-1 was 0.74 [0.65, 0.83], with specificity of 0.70 [0.63, 0.76] (Figure 3E).

Risk of bias

The risk of bias and the adjustment factors among the studies are summarized in Figure 4. Patent selection, flow and timing of most articles had low risk of bias.

Sensitivity and false positive rate

According to the sensitivity and false positive rate, the sequence was urinary KIM-1 > urinary NGAL > urinary IL-18 > blood NGAL (Figure 5).
Figure 3 Sensitivity and specificity. (A) Sensitivity and specificity of urinary NGAL. (B) Sensitivity and specificity of blood NGAL. (C) Sensitivity and specificity of urinary IL-18. (D) Sensitivity and specificity of KIM-1. (E) Sensitivity and specificity of urinary Netrin-1.

Figure 4 Quality assessment of included eligible studies using QUADAS-2.
Figure 5 Weighted cross diagram. (A) Urinary NGAL; (B) blood NGAL; (C) urinary interleukin-18; (D) urinary KIM-1.

**SROC and the diagnostic ratio (DOR) of urinary NGAL, blood NGAL, IL-18 and KIM-1**

According to the sample size, the SROC values of urinary NGAL, blood NGAL, urinary IL-18 and urinary KIM-1 were 0.907, 0.857, 0.861 and 0.931, respectively (Figure 6). The sequence was urinary KIM-1 > urinary NGAL > blood NGAL > urinary IL-18. Without sample weights, the SROCs of urinary NGAL, blood NGAL, urinary IL-18 and urinary KIM-1 were 0.874, 0.853, 0.839 and 0.911, respectively (Figure 7). The SROC of urinary KIM-1 ranked first, followed by the other biomarkers: urinary KIM-1 > urinary NGAL > blood NGAL > urinary IL-18. The diagnostic odds ratios of urinary NGAL, blood NGAL, urinary IL-18 and urinary KIM-1 were 3.01 (2.26, 3.76), 2.70 (2.06, 3.35), 2.55 (0.83, 4.28) and 3.54 (2.15, 4.93), respectively (Figure 8). Due to the small number of urinary Netrin-1 studies, an SROC calculation could not be completed.

**Discussion**

In this meta-analysis, we summarized novel biomarkers associated with AKI diagnosis in high-risk groups (previously creatinine, urea nitrogen, cystatin C, etc.) and biomarkers associated with AKI mortality. Forty-nine studies involving 4,189 patients were identified by searching several databases and screening articles. We found significant increases in NGAL, urinary interleukin-18, KIM-1, and urinary Netrin-1 in the blood of patients with AKI. Although urinary sCD163, serum sex hormone levels and soluble thromboregulatory proteins are also significantly different between AKI patients and high-risk patients, the number of studies on these biomarkers is small, so the results cannot be meta-analyzed.

Neutrophil gelatinase-related lipid carrier protein (NGAL) is a member of the lipid carrier protein superfamily and is expressed by neutrophils and various epithelial cells (51). As a proximal tubular injury-related
protein, NGAL is expressed in injured renal tubular epithelial cells and has a high effect size for the diagnosis of AKI (assessed by a combination odds ratio). NGAL in blood and urine samples is the most widely studied biomarker for the early prediction of AKI, and Zhang et al. (13) reported the value of the blood and urinary NGAL biomarker in the diagnosis and prognosis of sepsis-associated AKI. They report that NGAL not only is an effective predictor of AKI during sepsis but also has potential predictive value for RRT and mortality. However, this study did not distinguish the different diagnostic characteristics of urinary NGAL and blood NGAL. In our meta-study, it was found that the diagnostic value of urinary NGAL was slightly higher than that of blood NGAL. Haase-Fielitz et al. (52) also conducted a systematic evaluation, identifying 58 articles and including >16,500 patients with AKI, and found that both plasma and urinary NGAL could predict AKI and its severity, and the total AUC in different clinical environments was 0.79–0.87. However, this study involved a wide range of AKI patients, and a separate study is still needed for patients with sepsis, a special condition. Therefore, a summary of the results of our study shows that plasma and urinary NGAL have good diagnostic accuracy for sepsis-associated AKI (AUC is 0.86 and 0.90, respectively).

Kidney damage molecule-1 (KIM-1) is a type I transmembrane glycoprotein that has an immunoglobulin and mucin domain structure; KIM-1 is also a kind of proximal renal tubular injury-related protein that is expressed in renal tubular epithelial cells; it is not expressed in normal renal tissues or urine tests but is expressed at very high levels after ischemic or toxic damage in rodents and in the dedifferentiation of renal proximal tubule epithelial cells. AKI can be diagnosed early because urine excretion increases significantly 2 to 8 h after injury. It has been reported in the literature that urinary KIM-1 elevation has the highest specificity for the recognition of renal injury and can distinguish...
prerenal AKI from acute tubular necrosis (38). In addition, hyperuricosa and KIM-1 expression were prospectively assessed in a cohort of 201 hospitalized AKI patients and were associated with adverse clinical outcomes (death and need for dialysis) in AKI patients (53). In our study, 124 cases of true positive, 37 cases of false positive, 21 cases of false negative and 194 cases of true negative after Kim-1 diagnosis of AKI were found, with a sensitivity of 0.86 [0.79, 0.91] and a specificity of 0.84 [0.79, 0.88]. Our study found a ranking of urinary Kim-1 > urinary NGAL > blood NGAL > urinary IL-18 according to the SROC curve area. This indicates that urinary Kim-1 has high diagnostic value. However, as the sample size is still too small, further studies with a large sample size are needed in clinical practice.

IL-18 is a pro-inflammatory cytokine expressed conditionally in late inserted cells in the distal convoluted tubule, connecting tubules to collecting tubules in healthy human kidneys. In addition, these cells contain the three main components needed to release the active pro-inflammatory cytokine IL-18, namely, pro-IL-18, P2X7 and intracellular protease caspase-1 (54), which are converted to IL-18 in its active form and then leave the cell and enter the urine, for example, in AKI (55). In the first cross-sectional study of people with a variety of kidney diseases, urine levels of IL-18 were significantly higher and the diagnosis of ATN was highly sensitive and specific for groups with PA, UTI, chronic kidney disease, and normal kidney function compared with the healthy control group. IL-18 can be used as a marker of proximal renal tubular injury in ATN (44). Furthermore, urinary IL-18 was significantly upregulated and predicted mortality during mechanical ventilation before serum creatinine increased in patients with AKI acute respiratory distress syndrome (56). Early urine measurements of IL-18 were associated with AKI severity and mortality; however, in prospective analyses, IL-18 showed no ability to predict the subsequent development of AKI. Our study showed that the diagnosis of sepsis-associated AKI with urinary IL-18 was a true negative in 84 cases, false positive in 41 cases, false negative in 32 cases, and true negative in 99 cases, with a sensitivity of 0.72 [0.63, 0.80] and a specificity 0.71 [0.62, 0.78]. Considering that IL-18 is a pro-inflammatory cytokine that plays an important role in sepsis, IL-18 measurement may also be affected by many coexisting variables, such as endotoxemia, inflammation and autoimmune diseases; therefore, its sensitivity and specificity are affected.

Netrin-1 is a laminin-related neuronal guidance molecule that is not expressed or is barely expressed in the tubular epithelial cells of normal kidneys. At present,
a large number of studies have shown that Netrin-1 is highly expressed in renal tubular epithelial cells under various pathological conditions of the kidney and plays an important role in protecting the kidney by inhibiting the inflammatory response, among other mechanisms. In addition, Netrin-1 can be detected in urine within a short period of time; therefore, it may play an early role in the prediction and diagnosis of acute renal injury. Through a urine test in patients with AKI, the level of Netrin-1 was found to change in 38 of the studies analyzed (9); compared with that in healthy people, the urinary Netrin-1 level in patients with AKI increased significantly, and the increase was most obvious in the sepsis group, showing that the early identification of urinary Netrin-1 levels had a certain clinical significance in AKI and may become a new diagnostic index of early AKI. In our study, the sensitivity and specificity of Netrin-1 after aggregation were shown to be 0.74 [0.65, 0.83] and 0.70 [0.63, 0.76], respectively. There were 73

Figure 8 Diagnostic odds ratio. (A) Urinary NGAL; (B) blood NGAL; (C) urinary interleukin-18; (D) urinary KIM-1.
cases of true positive, 59 cases of false positive, 25 cases of false negative and 137 cases of true negative. Due to the small amount of literature, the diagnostic value of Netrin-1 still needs to be further studied.

This systematic evaluation and meta-analysis may facilitate the further study of sepsis-associated AKI diagnosis in a variety of different ways. First, it established the diagnostic sequence of sepsis-associated AKI biomarkers, ranked as urinary KIM-1 > urinary NGAL > blood NGAL > urinary IL-18, according to the SROC curve area. Second, the diagnostic characteristics of a variety of biomarkers were demonstrated. The same biomarker has different manifestations in blood and urine, among which the diagnostic value of urinary NGAL is slightly higher than that of blood NGAL. Third, these biomarkers represent the pathophysiological process of sepsis-associated AKI. In our meta-analysis, the diagnosis of sepsis-associated AKI was associated with inflammation, endothelial dysfunction, coagulation and even hormones. Although some nonquantitative methods were not included in this meta-analysis, they are still worth exploring.

There are limitations to this meta-analysis. First, although subgroup analyses of different biomarkers diagnosed with AKI were performed, heterogeneity could not be explained for each biomarker. Various types of controls were used in the study, and study inclusion was associated with biomarker measures and different treatments of AKI. Due to the limited information, we cannot carry out further analysis. Second, each biomarker included a limited number of studies, which hinders the reproducibility of the results. The number of studies for each biomarker should be considered when evaluating the effectiveness of the ranking system. Third, only studies involving two or more biomarkers were included in this meta-analysis. Therefore, not considering promising biomarkers assessed in a single study may limit the study of whole-blood or urine biomarkers.

Conclusions

This systematic evaluation and meta-analysis outlined the diagnostic characteristics of sepsis-associated AKI blood and urine biomarkers. According to the SROC curve area, the diagnostic sequence of sepsis-associated AKI biomarkers was urinary KIM-1 > urinary NGAL > blood NGAL > urinary IL-18. This sequence, provided by evaluating the effect size of sepsis-associated biomarkers in AKI diagnosis, can be used as a reference for the further study of AKI biomarkers and clinical diagnosis.

Acknowledgments

We thank all the staff for their valuable contribution to the study.

Funding: This project was supported by grants from the Songjiang District Science and Technology Project (No. 19SJKJGG92), the 3rd Sansheng TCP Young and Middle-aged Scientific Research Funding, Shanghai science and technology committee scientific and technological support project (No. 18411950600 and No. 18411950602), Clinical Research Innovation Plan of Shanghai General Hospital (CTCCR-2016B01) and Wu jieping medical foundation (No. 320.6750.18546).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1855

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1855). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

2. Gotts JE, Matthay MA. Sepsis: pathophysiology and


