Comparative accuracy of biomarkers for the prediction of hospital-acquired acute kidney injury: a systematic review and meta-analysis

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Abstract
Background: Several biomarkers have been proposed to predict the occurrence of acute kidney injury (AKI); however, their efficacy varies between different trials. The aim of this study was to compare the predictive performance of different candidate biomarkers for AKI.

Methods: In this systematic review, we searched PubMed, Medline, Embase, and the Cochrane Library for papers published up to August 15, 2022. We selected all studies of adults (> 18 years) that reported the predictive performance of damage biomarkers (neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP)), inflammatory biomarker (interleukin-18 (IL-18)), and stress biomarker (tissue inhibitor of metalloproteinases-2 × insulin-like growth factor-binding protein-7 (TIMP-2 × IGFBP-7)) for the occurrence of AKI. We performed pairwise meta-analyses to calculate odds ratios (ORs) and 95% confidence intervals (CIs) individually. Hierarchical summary receiver operating characteristic curves (HSROCs) were used to summarize the pooled test performance, and the Grading of Recommendations, Assessment, Development and Evaluations criteria were used to appraise the quality of evidence.

Results: We identified 242 published relevant studies from 1,803 screened abstracts, of which 110 studies with 38,725 patients were included in this meta-analysis. Urinary NGAL/creatinine (diagnostic odds ratio [DOR] 16.2, 95% CI 10.1–25.9), urinary NGAL (DOR 13.8, 95% CI 10.2–18.8), and serum NGAL (DOR 12.6, 95% CI 9.3–17.3) had the best diagnostic accuracy for the risk of AKI. In subgroup analyses, urinary NGAL, urinary NGAL/creatinine, and serum NGAL had better diagnostic accuracy for AKI than urinary IL-18 in non-critically ill patients. However, all of the biomarkers had similar diagnostic accuracy in critically ill patients. In the setting of medical and non-sepsis patients, urinary NGAL had better predictive performance than urinary IL-18, urinary L-FABP, and urinary TIMP-2 × IGFBP-7: 0.3. In the surgical

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Background
Acute kidney injury (AKI) is associated with a higher risk of chronic kidney disease (CKD), end-stage renal disease (ESRD), and long-term adverse cardiovascular effects [1, 2]. Due to the lack of effective treatment for impaired kidney function, the best strategy in clinical practice is to identify AKI as early as possible, reverse its cause, and even improve the sequelae. In the past decades, several serum creatinine (SCr)-based classification systems have been proposed to define AKI [3]. Serum creatinine has traditionally served as a surrogate of kidney function, despite its limitations as a diagnostic surrogate of AKI [4]. The limitations of SCr include a lack of steady-state conditions in critically ill patients, and that the determinants of SCr (rate of production, apparent volume of distribution, and rate of elimination) are variable. Therefore, there is an unmet need for other objective measures to help detect AKI in a timely manner. The role of several biomarkers in the early prediction or risk assessment of AKI has been proposed, including kidney tubular damage markers (e.g., neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP)) [5–9], inflammation markers (e.g., interleukin-18 (IL-18)) [6, 10, 11], and stress markers (e.g., tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7 (TIMP-2 × IGFBP-7)). The ADQI expert group suggests that routine clinical assessments should be combined with stress, damage, and functional biomarkers to stratify risk, discriminate etiologies, assess severity, plan management, and predict the duration and recovery of AKI [12]. In addition, previous meta-analyses including patients with various clinical scenarios have suggested that these biomarkers hold promise as practical tools in the early prediction of AKI [5, 13–17]. However, few studies have compared the diagnostic accuracy of these AKI biomarkers, and systematic assessments of the quality of evidence, which can provide updated information for clinical guidelines, are lacking. Therefore, the aim of this study was to compare the reported predictive accuracy of AKI biomarkers in various clinical settings and appraise the quality of evidence using a pairwise meta-analysis. The findings of this study may be used to update guidelines and recommendations.

Methods
Search strategy and selection criteria
We conducted this pairwise meta-analysis according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement [18] and used Cochrane methods [19]. We prospectively submitted the systematic review protocol for registration on PROSPERO [CRD42020207883].

Data sources and search strategy
The primary outcome was incident AKI. Electronic searches were performed on PubMed (Ovid), Medline, Embase, and Cochrane library from inception to August 15, 2022 (Additional file 1: Appendix). We screened references by titles and abstracts and included related studies for further analysis. Reference lists of related studies, systematic reviews, and meta-analyses were manually examined to identify any possible publications relevant to our analysis. Both abstracts and full papers were selected for quality assessment and data synthesis.

Inclusion and exclusion criteria
The inclusion criteria were as follows: (1) clinical studies that included participants over 18 years of age and of any ethnic origin or sex; (2) studies that reported candidate AKI biomarkers including NGAL, KIM-1, L-FABP, IL-18, and TIMP-2 × IGFBP-7; and (3) studies that assessed the occurrence of incident AKI. The exclusion criteria were as follows: (1) studies including patients who had previously received dialysis; (2) studies including pregnant or lactating patients; (3) letters, conference or case reports; and (4) studies that lacked data on sensitivity or specificity of biomarkers to predict the occurrence of AKI. Only regular full papers were selected for quality assessment and data synthesis. We contacted the authors of abstracts for further detailed information, if available.
Study selection and data extraction
Six investigators (Heng-Chih Pan, Terry Ting-Yu Chiou, Chih-Chung Shiao, Che-Hsiung Wu, Hugo You-Hsien Lin, and Ming-Jen Chan) independently reviewed the search results and identified eligible studies. Any resulting discrepancies were resolved by discussion with a seventh investigator (Vin-Cent Wu). All relevant data were independently extracted from the included studies by eight investigators (Heng-Chih Pan, Chih-Chung Shiao, Terry Ting-Yu Chiou, Yih-Ting Chen, Chun-Te Huang, Ya-Fei Yang, Shu-Chen Yu, and Zi-Ming Chen) according to a standardized form. Extracted data included study characteristics (lead author, publication year, population setting, biomarkers, study endpoint, sample size, events, timing of measurements) and participants’ baseline data (mean age (years), gender (%), comorbidities, severity of illness). When available, odds ratios and 95% confidence intervals (CIs) from cohort or case-controlled studies were extracted. Other a priori determined parameters included the type of intensive care unit (ICU) setting (surgical/mixed or medical), criteria used to diagnose AKI and severe AKI, cohort size, and the presence of sepsis. Any disagreements were resolved by discussion with the investigators (Heng-Chih Pan and Vin-Cent Wu).

Quality assessment
The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used to assess the quality of each included study [20, 21]. The following 4 domains were assessed: patient selection, index test, reference standard, and flow and timing. Any disagreements in the quality assessment were resolved by discussion and consensus [15].

Pre-specified subgroup analysis
We hypothesized that the following factors could have high impacts on patient outcomes observed among different studies: clinical setting (ICU/non-ICU), patient population (surgical versus mixed/medical), whether the studies only included patients with sepsis or not and different AKI criteria (risk, injury, failure, loss, ESRD (RIFLE); Acute Kidney Injury Network (AKIN); Kidney Disease: Improving Global Outcomes (KDIGO)).

Data synthesis and statistical analysis
A 2 by 2 table reporting the patient number of true positive, false positive, true negative, and false negative findings for the cutoff point given by the included studies was used to generate sensitivity, specificity, and diagnostic odds ratio (DOR) for each study. The sensitivity, specificity, and DOR for all of the included studies were combined using a bivariate model. DOR was defined as the endpoint of primary interest in this study because it combines the strengths of sensitivity and specificity with the advantage of accuracy as a single indicator [22]. The sensitivity and specificity were defined as the endpoints of secondary interest in the study. The diagnostic performance for AKI among the 12 different biomarkers was compared using a bivariate model in which the type of biomarker was treated as a categorical covariate. Hierarchical summary receiver operating characteristic curves (HSROCs), which consider the threshold effect [23], were used to illustrate the overall diagnostic performance for each biomarker. The analysis was further stratified by the following pre-specified subgroups: surgical versus mixed/medical patients, ICU/non-ICU patients, sepsis/non-sepsis patients, and different AKI criteria (RIFLE/AKIN/KDIGO). In the subgroup analysis, biomarkers only reported in 1 study could not be compared and were therefore excluded. Potential publication bias was assessed visually using funnel plots. A two-sided P value < 0.05 was considered statistically significant. The bivariate model was conducted using SAS version 9.4 (SAS Institute, Cary, NC) with the “METADAS” macro (version 1.3) which is recommended by the Cochrane Diagnostic Test Accuracy Working Group. The HSROC analysis and funnel plots were performed using R software version 3.6.3 with the “meta4diag” package (version 2.0.8) based on Bayesian inference.

Results
Search results and study characteristics
The study selection process is summarized in Additional file 1: Appendix. A total of 23,882 articles were identified through the electronic search, and after excluding duplicate and non-relevant articles, the titles and abstracts of the remaining 1803 articles were screened. A total of 242 studies were eligible for full-text review, of which 110 studies including 38,725 patients reported data on the occurrence of AKI with any one of the biomarkers of interest and were included in the meta-analysis [24–133]. The details of the included studies and population characteristics as well as definitions used for the diagnosis of AKI are shown in Tables 1 and 2.

All 110 studies provided quantifiable results for AKI. Seventy-nine studies exclusively enrolled ICU patients, and 31 studies enrolled non-ICU patients. Fifty-seven studies exclusively enrolled surgery patients, and 55 studies enrolled patients from mixed surgical/medical settings. Only 8 studies enrolled patients with sepsis, and therefore, analysis of sepsis was not conducted. Of the enrolled studies, 44 used the KDIGO classification as the only definition for AKI, 23 used AKIN, 21 used RIFLE, 6 used two or more definitions, 6 used a 50% increase in SCr, 1 used an increase in SCr from normal to > 3 mg/dL,
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|--------------|------------|---------|--------------|-----------------------|
| 1  | Qian et al. 2019 [24] | Patients who underwent cardiac surgery | Urinary NGAL | AKI within post-op 7 days | AKIN | No | 91 | 58 (63.7) | 33 (36.3) | AKI stage 1, 2, 3 | Post-op 0, 2, 4 h |
| 2  | Prowle et al. 2015 [25] | Cardiopulmonary bypass, ICU patients | Urinary NGAL, Urinary Klotho | AKI within post-op 5 days | RIFLE | No | 93 | 68 (73.1) | 25 (26.9) | AKI stage R, I, F | Pre-op, and post-op 24 h |
| 3  | Lei et al. 2018 [26] | Decompensated cirrhosis | Urinary NGAL, Urinary KIM-1, Serum CyC, Serum Cr | AKI within 7 days | KDIGO | Yes | 150 | 82 (54.7) | 68 (45.3) | AKI stage 1, 2, 3 | At hospital admission |
| 4  | van Wolswinkel et al. 2016 [27] | Patients with imported falciparum malaria | Urinary NGAL, Urinary KIM-1, Serum NGAL | AKI within 7 days | KDIGO | No | 39 | 33 (84.6) | 6 (15.4) | AKI stage 1, 2, 3 | At hospital admission |
| 5  | Srisawat et al. 2015 [28] | Hospitalized patients with Leptospirosis | Urinary NGAL, Serum NGAL | AKI within 7 days | KDIGO | No | 113 | 71 (62.8) | 42 (37.2) | AKI stage ≥ 1 | At hospital admission |
| 6  | Zeng et al. 2014 [29] | Major surgery | Urinary NGAL, Urinary L-FABP | Post-op AKI within 2 days | AKIN | No | 197 | 160 (81.2) | 37 (18.8) | AKI stage ≥ 1 | Pre-op, and post-op 0, 4, 12 h and 1, 2, 7, 14 days |
| 7  | Aydoğdu et al. 2013 [30] | Critically ill patients with and without sepsis | Urinary NGAL, Urinary CyC, Serum CyC | AKI within 7 days | RIFLE | Yes | 151 | 88 (58.3) | 63 (41.7) | AKI stage R, I, F | Every day since ICU admission to the day of AKI |
| 8  | Liu et al. 2013 [31] | Cardiac surgery | Urinary NGAL, Urinary L-FABP | Post-op AKI within 3 days | AKIN | No | 109 | 83 (76.1) | 26 (23.9) | AKI stage 1, 2, 3 | Pre-op, and post-op 0, 2 h |
| 9  | Wagener et al. 2011 [32] | Orthotopic liver transplantation | Urinary NGAL, Urinary L-FABP | Post-op AKI within 7 days | RIFLE | No | 92 | 55 (59.8) | 37 (40.2) | AKI stage ≥ R | Pre-op, post-op 3, 18, 24 h |
| 10 | Makris et al. 2009 [33] | Critically ill multiple trauma patients | Urinary NGAL | AKI within 3 days | RIFLE | No | 31 | 20 (64.5) | 11 (35.5) | AKI stage R, I, F | At ICU admission and post-admission 24, 48 h |
| 11 | Constantin et al. 2010 [34] | Critically ill patients | Serum NGAL | AKI at ICU admission | RIFLE | No | 88 | 36 (40.9) | 52 (59.1) | AKI stage ≥ R | At ICU admission |
| 12 | Cruz et al. 2010 [35] | Critically ill patients | Serum NGAL | AKI during ICU stay | RIFLE | No | 301 | 168 (55.8) | 133 (44.2) | AKI stage R, I, F | Daily from ICU admission to 4 days after ICU admission |
| 13 | de Geus et al. 2011 [36] | Critically ill patients | Urinary NGAL, Urinary CyS/Cr, Urinary IL-18/Cr, Urinary KIM-1/Cr | AKI with 7 days of ICU stay | AKIN and RIFLE | No | 632 | 461 (72.9) | 171 (27.1) | AKI stage R, I, F | At ICU admission |
| 14 | Endre et al. 2011 [37] | Critically ill patients | Urinary NGAL, Urinary CyS/Cr, Urinary IL-18/Cr, Urinary KIM-1/Cr | AKI mortality within 7 days | AKIN and RIFLE | No | 528 | 381 (72.2) | 147 (27.8) | AKI stage ≥ R or ≥ 1 | At ICU admission, and at 12 and 24 h after admission |
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|----------------|-------------|---------|---------------|-----------------------|
| 15 | Breidthardt et al. 2012 [38] | Acute heart failure patients presented to emergency department | Serum NGAL | AKI | AKIN | No | 207 | 147 (71) | 60 (29) | AKI stage 1, 2, 3 | Every 6 h from ER presentation to 48 h after ER |
| 16 | Camou et al. 2013 [39] | Critically ill adult with septic shock | Serum NGAL | AKI at ICU admission, and 24 h, 48 h | RIFLE/AKIN | No | 50 | 7 (14) | 43 (86) | AKI stage R, I, F, AKI stage 1, 2, 3 | at ICU admission, and 24 h, 48 h |
| 17 | Doi et al. 2013 [40] | Cardiac surgical patients | Serum NGAL | AKI | AKIN | No | 146 | 93 (63.7) | 53 (36.3) | AKI stage ≥ 1 | Pre-op, post-op 0, 2, 4, 12, 24, 36, 60 h |
| 18 | Gaipov et al. 2015 [41] | Cardiac surgical patients | Urinary NGAL, Serum NGAL | Post-op AKI within 12 h, 24 h, 48 h and RRT | KDIGO | No | 60 | 40 (66.7) | 20 (33.3) | AKI stage 1, 2, 3, RRT | Post-op 2 h |
| 19 | Cuartero et al. 2019 [42] | Critically ill patients | Serum NGAL | AKI and ICU admission and 48 h later | AKIN and KDIGO | No | 100 | 57 (57) | 43 (43) | AKI stage 1, 2, 3 | At ICU admission, and 24, 48 h later |
| 20 | Khawaja et al. 2019 [43] | Critically ill patients with suspected sepsis | Serum NGAL | Sepsis-related AKI | RIFLE | No | 46 | 22 (47.8) | 24 (52.2) | AKI stage ≥ R | 12, 24, and 48 h after ICU admission |
| 21 | Mosa et al. 2018 [44] | Cardiothoracic surgery using cardiopulmonary bypass | Serum NGAL | Post-op AKI | KDIGO | No | 182 | 117 (64.3) | 65 (35.7) | AKI stage ≥ 1 | Before CPB and at 0, 2, 12, 24 h after CPB |
| 22 | Sun et al. 2017 [45] | Scrub typhus-associated AKI | Serum NGAL | Serum KIM-1 | Scrub typhus-associated AKI | RIFLE | Yes | 138 | 113 (81.9) | 25 (18.1) | AKI stage R, I, F | Admission (n = 138) and 3 days after taking the initial sample (n = 37) |
| 23 | Ghanomy et al. 2014 [46] | Cardiac surgery (CPB & valve replacement surgery) | Serum NGAL | Serum CysC | Post-op AKI | N.A | No | 50 | 33 (66) | 17 (34) | Creatinine level at 24 h being elevated either by 25% of the basal level or by 0.3 mg/dL above the basal level | Baseline and post-op 3, 6, 24 h |
| 24 | Padhy et al. 2014 [47] | Patients received percutaneous coronary intervention | Serum NGAL | Contrast-induced AKI | N.A | No | 60 | 30 (50) | 30 (50) | by a rise in serum creatinine level of at least 0.5 mg/dL from the baseline value at 48 h | 0, 4, 24, 48 h after coronary angiography |
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|-------------|-------------------|-----------|----------|--------------|-----|---------------|------------|---------|--------------|----------------------|
| 25 | Geus et al. 2013 [48] (no sepsis) | ICU patients | Serum NGAL | AKI within 24 h after ICU admission | AKIN | No | 542 | 427 (78.8) | 115 (21.2) | AKI stage ≥ 1 | ICU Admission (0 h) and at 4, 8, 24 h after ICU Admission |
| 25 | Geus et al. 2013 [48] (sepsis) | ICU patients | Serum NGAL | AKI within 24 h after ICU admission | AKIN | No | 75 | 25 (33.3) | 50 (66.7) | AKI stage ≥ 1 | ICU Admission (0 h) and at 4, 8, 24 h after ICU Admission |
| 26 | Haase-Fielitz et al. 2009 [49] | Cardiac surgery | Serum NGAL, Serum CysC | Post-op AKI and 24 h after OP | SCr increase > 50% from baseline; RIFLE | No | 100 | 77 (77) | 23 (23) | AKI stage R, I, F | Baseline, post-op 6 h and 24 h |
| 27 | Hanson et al. 2011 [50] | Severe malaria | Urinary NGAL, Serum Cr | RRT | N.A | No | 163 | 79 (48.5) | 84 (51.5) | RRT | On study enrollment |
| 28 | Introcaso et al. 2018 [51] | Cardiac surgery | Serum NGAL | Post-op AKI | KDIGO | Yes | 69 | 45 (65.2) | 24 (34.8) | AKI stage 1, 2, 3 | Pre-op and within post-op 4 h in ICU |
| 29 | Kim et al. 2017 [52] | Critically ill patients with suspected sepsis | Serum NGAL | AKI mortality | KDIGO | Yes | 167 | 126 (75.4) | 41 (24.6) | AKI stage ≥ 1, RRT | On study enrollment |
| 30 | Ferrari et al. 2019 [53] | Critically ill adult | Urinary TIMP-2 × IGFBP-7 | AKI within 12 h, 24 h, 48 h and 7 days | KDIGO | Yes | 442 | 254 (57.5) | 188 (42.5) | AKI stage ≥ 1, RRT | ICU admission |
| 31 | Xie et al. 2019 [54] | ICU patients | Urinary TIMP-2 × IGFBP-7 | CRRT, mortality, length of ICU stay | KDIGO Stage AKI 1, 2, 3 | Yes | 719 | 480 (66.8) | 239 (33.2) | AKI stage ≥ 1 | immediately upon enrollment |
| 32 | Adler et al. 2018 [55] | Out-of-hospital cardiac arrest | Urinary TIMP-2 × IGFBP-7 | AKI | KDIGO Stage AKI 1, 2, 3 | Yes | 48 | 17 (35.4) | 31 (64.6) | AKI stage ≥ 1 | 3 h and 24 h after OHCA |
| 33 | Oezkur et al. 2017 [56] | Cardiac surgery | Urinary TIMP-2 × IGFBP-7 | AKI within 48 h after op | KDIGO | Yes | 100 | 80 (80) | 20 (20) | Unknown | Before surgery (baseline), ICU admission (directly after Surgery), 24 h post-surgery |
| 34 | Wang et al. 2017 [57] | Cardiac surgery | Urinary TIMP-2 × IGFBP-7 | AKI within 7 days after op | KDIGO | Yes | 57 | 37 (64.9) | 20 (35.1) | AKI stage 2 or 3 | Before surgery, ICU admission (in 2-h intervals from 0 to 12 h after Surgery), 24 h after ICU admission |
| 35 | Finge et al. 2017 [58] | Cardiac surgery with cardiopulmonary bypass | Urinary TIMP-2 × IGFBP-7 | AKI within 48 h after op | KDIGO | Yes | 93 | 59 (63.4) | 34 (36.6) | AKI stage ≥ 1 | Before surgery and 3-h postoperative period |
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|---------------|------------|---------|--------------|----------------------|
| 36 | Cuartero et al. 2017 [59] | Septic and non-septic critically ill patients | Urinary TIMP-2 x IGFBP-7 | AKI | AKIN | Yes | 98 | 49 (50) | 49 (50) | AKI stage ≥ 2, RRT at ICU admission and up to 12 h later simultaneously with the morning blood work | Pre-op and at 1, 4, 24 h after surgery |
| 37 | Mayer et al. 2017 [60] | Cardiac surgery with cardiopulmonary bypass | Urinary TIMP-2 x IGFBP-7 | Post-op AKI | KDIGO and RIFLE | Yes | 110 | 101 (91.8) | 9 (8.2) | AKI stage 1, 2, 3; stage R, l, F | Pre-op and 4, 12, 24 h after CPB |
| 38 | Meersch et al. 2014 [61] | Cardiac surgery with cardiopulmonary bypass | Urinary TIMP-2 x IGFBP-7 | Post-op AKI | AKIN or KDIGO | Yes | 50 | 24 (48) | 26 (52) | AKI stage 1, 2, 3 | Pre-op and 4, 12, 24 h after CPB |
| 39 | Dusse et al. 2016 [62] | Cardiac surgery | Urinary TIMP-2 x IGFBP-7 | AKI stage 2 or 3 within 48 h after op | KDIGO | Yes | 40 | 3 (80) | 8 (20) | AKI stage 2, 3 | post-op 4 h and then twice daily until discharge from ICU (maximum 4 days) |
| 40 | Gunnerson et al. 2016 [63] | Critically ill patients | Urinary TIMP-2 x IGFBP-7 | AKI stage 2 or 3 | KDIGO | No | 375 | 340 (90.7) | 35 (9.3) | AKI stage 2, 3 | Within 12 h of ICU admission |
| 41 | Wetz et al. 2015 [64] | Cardiac surgery | Urinary TIMP-2 x IGFBP-7 | Post-op AKI Stage 1 or 2 | KDIGO | No | 42 | 26 (61.9) | 16 (38.1) | AKI stage 1, 2 | Baseline; End of surgery; 4 h after arrest of CPB; 1 day after surgery |
| 42 | Kimmel et al. 2016 [65] | ER patient | Urinary TIMP-2 x IGFBP-7 | Positive U scores at enrollment | KDIGO | No | 362 | 347 (95.9) | 15 (4.1) | Unknown | Unknown |
| 43 | Pilarsczyk et al. 2015 [66] | Post-cardiac surgery | Urinary TIMP-2 x IGFBP-7 | Post-op AKI stage 2 or 3 within 48 h | KDIGO | No | 60 | 41 (68.3) | 19 (31.7) | AKI stage 1,2,3 | Post-op 4 h and every 12 h until discharge |
| 44 | Hoste et al. 2014 [67] | Critically ill patients | Urinary TIMP-2 x IGFBP-7 | AKI stage 2 or 3 within 12 h | KDIGO | Partial | 153 | 27 (17.6) | 126 (82.4) | AKI stage 1,2,3 | ICU admission |
| 45 | Cummings et al. 2018 [68] | Cardiac surgery | Urinary TIMP-2 x IGFBP-7 | Post-op AKI stage 2 or 3 within 48 h | KDIGO | No | 400 | 309 (77.3) | 91 (22.7) | AKI stage 1, 2, 3 | Immediately after CPB |
| 46 | Katagiri et al. 2012 [69] | Cardiac surgery | Urinary L-FABP | Post-op AKI | AKIN | No | 77 | 49 (63.6) | 28 (36.4) | Unknown | Unknown |
| 47 | Doiet et al. 2011 [70] | Critically ill patients admitted to medical-surgical mixed ICU | Urinary L-FABP Urinary NGAL Urinary IL-18 | AKI during admission | RIFLE | No | 339 | 208 (61.4) | 131 (38.6) | Unknown | 12 h after ICU admission |
Table 1 (continued)

| No  | Study (year)                  | Population setting                     | Biomarker                        | Endpoint                  | AKI criteria                                      | UOC   | Total patient No | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|-----|-------------------------------|----------------------------------------|----------------------------------|---------------------------|-------------------------------------------------|-------|------------------|------------|---------|--------------|------------------------|
| 48  | Ferguson et al. 2010 [71]     | Ordinary ward and ICU                 | Urinary L-FABP Urinary NGAL Urinary KIM-1 Urinary IL-18 Urinary NAG | AKI                       | ≥ 50% increase in SCr from baseline              | No    | 160              | 68 (42.5)  | 92 (57.5) | unknown      | NA                     |
| 49  | Li et al. 2012 [72]           | Liver transplantation                  | Urinary L-FABP Urinary NGAL     | AKI                       | AKIN                                            | No    | 25               | 14 (56)    | 11 (44)  | Unknown      | 0,2,4,6,12,24,48,72,120 h after the anhepatic phase on day 0,1 and 2 after contrast medium exposure |
| 50  | Manabe et al. 2012 [73]       | Cardiac catheterization               | Urinary L-FABP                  | Contrast-induced AKI within 48 h | AKIN                                            | No    | 220              | 201 (91.4) | 19 (8.6)  | Unknown      | Before OP, 0,3,6,18,24 and 48 h after OP |
| 51  | Matsui et al. 2012 [74]       | Cardiac surgery                       | Urinary NGAL Urinary L-FABP     | Post-op AKI within 48 h    | AKIN                                            | No    | 85               | 37 (43.5)  | 48 (56.5) | Unknown      | Before OP, 0,3,6,18,24 and 48 h after OP |
| 52  | Khreba et al. 2019 [75]       | Post-cardiopulmonary bypass in open heart surgery | Urinary KIM-1                  | Post-op AKI                | KDIGO                                           | No    | 45               | 18 (40)    | 27 (60)   | Unknown      | Post-op 3 h              |
| 53  | Tu et al. 2014 [76]           | Sepsis                                | Urinary KIM-1                  | Sepsis-related AKI         | AKIN                                            | No    | 150              | 101 (67.3) | 49 (32.7) | Unknown      | 0,1,3,6,24,48 h after ICU admission |
| 54  | Parikh et al. 2005 [77]       | ARDS                                  | Urinary IL-18                  | AKI within the first 6 days of ARDS | Increase in Scr by at least 50% | No    | 138              | 86 (62.3)  | 52 (37.7) | Unknown      | ICU admission 0,1,3 day |
| 55  | Parikh et al. 2004 [78]       | Kidney transplant patients            | Urinary IL-18                  | ATN                       | S<sub>C</sub>r from normal to > 3 mg/dL (>265 umol/L) | No    | 72               | 50 (69.4)  | 22 (30.6) | Unknown      | 24 h after OP            |
| 56  | Han et al. 2009 [79]          | Cardiac surgery                      | Urinary KIM-1/Cr               | Post-op AKI within 72 h after surgery | AKIN                                            | No    | 90               | 54 (60)    | 36 (40)   | Unknown      | 0,3,18,24 h after op     |
| 57  | Liangos et al. 2009 [80]      | Cardiac surgery (Cardiopulmonary bypass) | Urinary KIM-1 Urinary NAG Urinary NGAL Urinary IL-18 Urinary CysC Urinary α1-microglobulin | Post-op AKI within 72 h | Cre inc > 50% in 72 h | No    | 103              | 90 (87.4)  | 13 (12.6) | Unknown      | 2 h                    |
| 58  | Naggar et al. 2012 [81]       | Critically ill patients               | Urinary KIM-1                  | AKI                       | RIFLE                                           | No    | 40               | 20 (50)    | 20 (50)   | Unknown      | 0,24,48 h               |
### Table 1 (continued)

| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|---------------|------------|---------|--------------|-----------------------|
| 59 | Nickolas et al. 2012 [82] | ER patients | Urinary KIM-1 | AKI | RIFLE | No | 1635 | 1539 (94.1) | 96 (5.9) | Unknown | 0 h ER |
| 60 | Vaidya et al. 2008 [83] | Inpatient nephrology consultation service | Urinary KIM-1 | AKI | RIFLE | No | 204 | 102 (50) | 102 (50) | Unknown | 0 h |
| 61 | Nisula et al. 2015 [84] | ICU patients | Urinary IL-18 | AKI | KDIGO on Day 2 or Day 3 | YES | 1439 | 942 (65.5) | 497 (34.5) | AKI Stage3 RRT | 0-24 h |
| 62 | Nickolas TL et al. 2008 [85] | ER patients | Urinary NGAL | AKI | RIFLE-R | No | 635 | 605 (95.3) | 30 (4.7) | RRT | ED presentation |
| 63 | Cho et al. 2013 [86] | Critically ill patients admitted to medical-surgical mixed ICU | Urinary NGAL | AKI | AKIN | No | 145 | 91 (62.8) | 54 (37.2) | AKIN stage 1,2,3 RRT | ICU admission |
| 64 | Park et al. 2019 [87] | Sepsis | Urinary NGAL | Sepsis-related AKI | KDIGO | No | 140 | 121 (86.4) | 19 (13.6) | Unknown | 0 h |
| 65 | Perry et al. 2010 [88] | Cardiac Surgical | Serum NGAL | Post-op AKI within 4 days | 50% increase in serum | No | 879 | 804 (91.5) | 75 (8.5) | Unknown | 0 h |
| 66 | Shapiro et al. 2010 [89] | Sepsis | Serum NGAL/Cr | AKI | AKI/ > 0.5 mg/dL in 72 h | No | 661 | 637 (96.4) | 24 (3.6) | RIFLE-I RIFLE-R | 12,24,48,72 h |
| 67 | Thanakitcharu et al. 2014 [90] | Open cardiac surgery | Urinary NGAL | Post-op AKI | AKIN | No | 130 | 84 (64) | 46 (35.3) | Unknown | 0.36 h after surgery |
| 68 | Valette et al. 2013 [91] | Contrast-induced | Serum NGAL | Contrast-related AKI within 72 h | AKIN | No | 98 | 68 (64) | 30 (35.4) | RRT | 0.26,24 h |
| 69 | Varela et al. 2015 [92] | Cardiac surgery | Urinary NGAL | Post-op AKI | AKIN | No | 66 | 50 (75.8) | 16 (24.2) | Unknown | 0.16,24 h after surgery |
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|---------------|------------|---------|--------------|----------------------|
| 70 | Chen et al. 2012 [93] | CCU, AMI | Serum NGAL, Urinary NGAL/Cr Urinary IL-18/Cr Urinary Cystatin C | AKI | AKIN | No | 150 | 107 (71.3) | 43 (28.7) | Unknown | after CCU admission |
| 71 | Nisula et al. 2014 [94] | Critically ill | Urinary NGAL | AKI < 72 h | KDIGO | No | 1042 | 663 (63.6) | 379 (36.4) | AKI Stage 1,2,3 RRT | ICU arrival, 12 h 24 h after admission |
| 72 | Maisel et al. 2016 [95] | Acute heart failure | Serum NGAL | Worsening renal function < 5 days increase in plasma creatinine of 0.5 mg/dL or ≥ 50% above first value or initiation of acute renal replacement therapy | No | 927 | 855 (92.2) | 72 (7.8) | Unknown | Acute heart failure requiring intravenous diuretic agents, 2,6 h, 1,2,3d |
| 73 | Matsa et al. 2014 [96] | Critically ill | Serum NGAL, Urinary NGAL | AKI < 72 h | RIFLE | No | 194 | 135 (69.6) | 59 (30.4) | Unknown | 0.24,48,72 h ICU arrival |
| 74 | Munir et al. 2013 [97] | Cardiopulmonary bypass | Urine NGAL | Post-op AKI < 48 h | AKIN | No | 88 | 77 (87.5) | 11 (12.5) | Unknown | 4 h after CPB |
| 75 | Onk et al. 2016 [98] | Cardiac surgery | Serum IL-6, Serum NGAL, Serum Scr | Post-op AKI < 7 days | RIFLE | No | 90 | 45 (50) | 45 (50) | RIFLE-R,F | Pre-op 1,6,12,24,36 h,7d |
| 76 | AZRINA MD RALIB et al. 2017 [99] | Critically ill | Serum NGAL | AKI | KDIGO | No | 225 | 138 (61.3) | 87 (38.7) | Unknown | within 24 h of ICU admission |
| 77 | Yang et al. 2016 [100] | Heart failure | Urinary NGAL, Urinary KIM-1, Urinary NGAL/Cr, Urinary KIM-1/Cr, Serum CysC | AKI | KDIGO | No | 103 | 54 | 49 | Unknown | Admission to ICU |
| 78 | Ueta et al. 2014 [101] | Endovascular stent graft repair of aortic aneurysm | Urinary NGAL/Cr, Urinary NGAL, Serum NGAL, Serum L-FABP, Serum L-FABP/Cr | Post-op AKI | AKIN | No | 42 | 36 | 6 | Unknown | 2 h post-op 0 h, 2 h, 6 h, 1d, 3d, 4d |
| 79 | Chang et al. 2015 [102] | CCU patients | Urinary NGAL, NGAL/Cr | Pre-renal and intrinsic AKI | KDIGO | No | 147 | 76 | 71 | Unknown | Admission to CCU |
| 80 | Hjortrup et al. 2014 [103] | ICU severe sepsis | Serum NGAL, Urinary NGAL | AKI | KDIGO | No | 222 | 191 | 31 | AKI stage ≥ 1, RRT | On study enrollment |
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|---------------|------------|---------|--------------|------------------------|
| 81 | Chen et al. 2020 [104] | CCU patients | Serum IL-18, Serum NGAL, Serum CysC, Urinary NGAL, Urinary NGAL/Cr | AKI | KDIGO | No | 269 | 217 | 52 | Unknown | Admission to CCU |
| 82 | Wybraniec et al. 2017 [105] | Contrast-induced acute kidney injury | Urinary KIM-1, Urinary IL-18 | Contrast-induced AKI | KDIGO | No | 95 | 86 | 9 | Unknown | 6 h after procedure |
| 83 | Sinkala et al. et al. 2016 [106] | Hospitalized patients | Urinary KIM-1 | AKI | unknown | unknown | 40 | 27 | 13 | Unknown | Cross-sectional |
| 84 | Toregrosa et al. et al. 2014 [107] | Acute coronary syndrome or heart failure or undergoing coronary angiography | Urinary L-FABP, Urinary KIM-1, Urinary NGAL | AKI | RIFLE | No | 144 | 124 | 20 | Unknown | 12 h after procedure |
| 85 | Tekce et al. 2014 [108] | Patient received cisplatin | Urinary KIM-1, Serum KIM-1 | AKI | Cre > 1.5–twofold | No | 22 | 14 | 8 | Unknown | Day 0, 1, 3, 5 |
| 86 | Toregrosa et al. 2012 [109] (M) | Acute coronary syndrome | Urinary IL-18, Urinary NGAL | AKI | KDIGO | No | 89 | 77 | 12 | Unknown | 12 h after procedure |
| 87 | Toregrosa et al. 2012 [109] (S) | Cardiac surgery | Urinary IL-18, Urinary NGAL | Post-op AKI | RIFLE, Cre inc > 50% | No | 46 | 32 | 14 | Unknown | 12 h after surgery |
| 88 | Matsui et al. et al. 2011 [110] | ICU patients | Urinary L-FABP/Cr, Urinary NAG/Cr | AKI | AKIN (inc > 0.3, 50%) | No | 25 | 11 | 14 | Unknown | 0 h after ICU |
| 89 | Parikh et al. et al. 2011 [111] | Cardiac surgery | Serum NGAL, Urinary NGAL, Urinary IL-18 | Post-op AKI | RIFLE | R | 1219 | 1159 | 60 | Unknown | 0–5 day after surgery |
| 90 | Wang 2017 [112] | Cardiopulmonary bypass | Urinary IL-18 | Post-op AKI | Cre increase > 50% | No | 103 | 81 | 22 | Unknown | Before CPB, at 2 h, 4 h, 6 h, 8 h and 12 h after CPB |
| 91 | Haase-Fielitz et al. 2009 [113] | Cardiac surgery | Serum NGAL | Post-op AKI | Cre increase > 50% within 168 h | No | 100 | 77 | 23 | RIFLE-LF, AKIN-2,3, RRT | 6 h after start CPB |
| 92 | Waskowski 2021 [114] | Cardiac surgery | 11. TIMP-2 × IGFBP-7: 0.3, 12. TIMP-2 × IGFBP-7: 2 | Post-op AKI | KDIGO | Yes | 93 | 62 (67) | 31 (33) | AKI stage ≥ 1 | Post-op day 1 |
| 93 | Imoto 2021 [115] | ICU patients | 07. NGAL | AKI | KDIGO | Yes | 106 | 35 (3) | 71 (67) | AKI Stage 3 | Day 1 |
| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|-------------|---------------------|-----------|----------|--------------|-----|----------------|------------|---------|--------------|----------------------|
| 93 | Lee 2021    | Cardiac surgery     | 05. L-FABP 06. L-FABP/Cr | Post-op AKI | KDIGO       | Yes | 144            | 85 (59)    | 59 (41) | AKI stage ≥ 1 | Post-op 16–18 h       |
|    |             |                     |           |          |              |     |                |            |         |              |                      |
| 94 | Szymanowicz 2021 | Cardiac surgery | 07. NGAL | Post-op AKI | KDIGO       | No  | 114            | 96 (84)    | 18 (16) | AKI stage ≥ 1 | 3 h after OP          |
| 95 | Zhen 2021   | Acute coronary syndrome | 09. Serum NGAL | AKI | AKIN       | No  | 172            | 149 (87)   | 23 (13) | AKI stage ≥ 1 | 6 h after admission   |
| 96 | Obata 2021  | Open abdominal aortic aneurysm repair | 06. L-FABP/Cr 08. NGAL/Cr | Post-op AKI | KDIGO       | No  | 64             | 45 (70)    | 19 (30) | AKI stage ≥ 1 | Pre-op, post-induction, 2 h post-AXC, Post-op, 4 h and 2 day |
| 97 | Qiu 2021    | Sepsis              | 07. NGAL 09. Serum NGAL | Sepsis-related AKI AKI | KDIGO       | Yes | 90             | 46 (51)    | 44 (49) | AKI stage ≥ 1 | at ICU admission       |
| 98 | Shakked 2022 | COVID-19 patients | 07. NGAL | Post-op AKI | KDIGO       | No  | 52             | 30 (58)    | 22 (42) | AKI stage ≥ 1, RRT | ER presentation         |
| 99 | Vogel 2021  | COVID-19 patients   | 04. KIM-1/Cr 09. Serum NGAL | AKI | Post-op AKI | AKIN | Yes            | 60         | 46 (78) | AKI stage ≥ 1 | ER presentation | Pre-op, Post-op 6 h, 24 h |
| 100| Ergun 2021  | Major surgery       | 10. TIMP-2 × IGFBP-7: custom | Post-op AKI | KDIGO       | Yes | 101            | 74 (73)    | 27 (27) | AKI stage 2 or 3 | Pre-op, Post-op 2 h, 6 h, POD 1 |
| 101| Pilarczyk 2022 | Thoracic aortic surgery | 10. TIMP-2 × IGFBP-7: custom | Post-op AKI | KDIGO       | Yes | 48             | 38 (79)    | 10 (21) | AKI stage ≥ 1 | Pre-op, Post-op 2 h, 4 h, 6 h, 24 h, 48 h, 72 h |
| 102| Okuda 2022  | Emergency laparotomy | 06. L-FABP/Cr | Post-op AKI | KDIGO       | Yes | 162            | 102 (63)   | 60 (37) | AKI stage ≥ 1 | ER presentation | 24 h after ICU admission |
| 103| Pei 2022    | Sepsis              | 09. Serum NGAL | Sepsis-related AKI | KDIGO       | Yes | 366            | 168 (63)   | 98 (37) | AKI stage ≥ 1 | The first day of vancomycin use |
| 104| Jahaj 2021  | ICU patients        | 09. Serum NGAL | Sepsis-related AKI | RIFLE       | Yes | 94             | 71 (76)    | 23 (24) | AKI stage ≥ 1 | The first day of vancomycin use |
| 105| Garms 2021  | Patients received vancomycin | 07. NGAL | Drug-related AKI | KDIGO       | Yes | 50             | 36 (72)    | 14 (28) | AKI stage ≥ 1 | Post-op 0.5 h, 1 h and 0, 6, 12, and 24 h after ICU admission |
Table 1 (continued)

| No | Study (year) | Population setting | Biomarker | Endpoint | AKI criteria | UOC | Total patient | No AKI (%) | AKI (%) | AKI severity | Timing of measurement |
|----|--------------|---------------------|-----------|----------|--------------|-----|---------------|------------|---------|--------------|-----------------------|
| 107 | Guray 2021 [130] | Patients undergoing coronary angiography | 09 Serum NGAL | Contrast-induced nephropathy | an increase of over 25% or equal to or over 44.2 μmol/L in baseline SCr at 48–72 h after cardiac catheterization | No | 84 | 68 (81) | 16 (19) | AKI stage ≥ 1 | Before and at 4 and 24 h after the procedure |
| 108 | Tan 2022 [131] | Ureteroscopic lithotripsy-related urosepsis | 01 IL-18 03 KIM-1 07 NGAL | Sepsis-related AKI | KDIGO | Yes | 157 | 121 (77) | 36 (23) | AKI stage ≥ 1 | 0, 4, 12, 24 and 48 h after the surgery |
| 109 | Lakhal 2021 [132] | Cardiac surgery patients | 02 TIMP-2 × IGFBP-7.0.3 | Post-op AKI | KDIGO | Yes | 65 | 38 (58) | 27 (42) | AKI stage ≥ 1 | before CPB and post-CPB 6 h, 24 h |
| 110 | Sahu 2022 [133] | Patients undergoing percutaneous coronary intervention | 03 09 Serum NGAL | Contrast-induced nephropathy | an increase in SCr by > 0.5 mg/dL or > 25%, assessed at 48 h after the procedure | No | 212 | 187 (88) | 25 (12) | AKI stage ≥ 1 | 4 and 48 h after the procedure |

AKI acute kidney injury, AKIN Acute Kidney Injury Network, ARDS acute respiratory distress syndrome, ATN acute tubular necrosis, CCU cardiac care unit, Cr creatinine, CPB cardiothoracic surgery using cardiopulmonary bypass, CysC cystatin C, ER emergency room, ICU intensive care unit, IL-18 interleukin-18, KDIGO Kidney Disease Improving Global Outcomes, KIM-1 kidney injury molecule-1, L-FABP liver-type fatty acid-binding protein, NGAL neutrophil gelatinase-associated lipocalin, PENK proenkephalin, RIFLE Risk, Injury, Failure, Loss, and End-stage renal disease, SCr serum creatinine, TIMP-2 × IGFBP-7 tissue inhibitor of metalloproteinases-2 × insulin-like growth factor-binding protein-7, UOC urine output criteria
Table 2  Summary of included comparative studies for outcome evaluation

| No | Study (year)          | Mean age | Male gender % | Diabetes% | Chronic kidney disease% | Heart failure% | Sepsis% | Surgery% | SOFA score |
|----|----------------------|----------|---------------|-----------|-------------------------|---------------|---------|----------|------------|
| 1  | Qian et al. 2019 [24] | 61.8     | 58 (63.7)     | 14 (15.4) | 0%                      | 13 (14.3)     | Unknown | 100%     | Unknown    |
| 2  | Prowle et al. 2015 [25] | 70       | 64 (69)       | 7 (7)     | 37%                     | 6 (6)         | Unknown | 100%     | Unknown    |
| 3  | Lei et al. 2018 [26]  | 60.6     | 91 (60.7)     | 0%        | 0%                      | 0%            | 0%      | 0%       | Unknown    |
| 4  | van Wolfswinkel et al. 2016 [27] | 45.5 | 33 (84.6) | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown |
| 5  | Srisawat et al. 2015 [28] | 39.8 | 94 (83.2) | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown |
| 6  | Zeng et al. 2014 [29]  | 55.3     | 109 (55.3)    | 46 (23.4) | 0%                      | Unknown       | Unknown | 100%     | Unknown    |
| 7  | Aydoğdu et al. 2013 [30] | 67.7 | 98 (64.9) | 44 (29.1) | 0%                      | 55 (36.4)     | 129 (85.4) | Unknown | 6          |
| 8  | Liu et al. 2013 [31]   | 63       | 72 (66.1)     | 28 (25.7) | 10 (9.2)                | 22 (20.2)     | 19 (17.4) | 100%     | Unknown    |
| 9  | Wagener et al. 2011 [32] | 54.3 | 60 (65.2) | Unknown | Unknown | Unknown | Unknown | 100%     | Unknown    |
| 10 | Makris et al. 2009 [33] | 46       | 25 (80.6)     | Unknown | Unknown | Unknown | Unknown | Unknown | 7          |
| 11 | Constantin et al. 2010 [34] | 57 | Unknown | Unknown | 0%                      | Unknown       | 45 (51) | 36 (40.9) | 7          |
| 12 | Cruz et al. 2010 [35]   | 64       | 207 (68.8)    | 47 (15.6) | 20 (6.6)               | Unknown       | 115 (38.2) | 137 (45.5) | 5          |
| 13 | de Geus et al. 2011 [36] | 60.1 | 369 (58.4) | Unknown | 0 (0)          | Unknown       | 43 (6.8) | 192 (30.4) | 8          |
| 14 | Endre et al. 2011 [37]  | 60       | 318 (60.2)    | Unknown | Unknown | Unknown | 101 (19.1) | 310 (58.7) | 6.3        |
| 15 | Breithardt et al. 2012 [38] | 80   | 122 (58.9)    | 69 (33)  | 92 (44)                | 103 (50)      | Unknown | Unknown | 12         |
| 16 | Camou et al. 2013 [39]  | 60.3     | 38 (76)       | Unknown | Unknown | Unknown | 100%     | Unknown | 12         |
| 17 | Doi et al. 2013 [40]    | 69       | 92 (63)       | 59 (40.4) | 68 (46.6)              | Unknown       | Unknown | 100%     | Unknown    |
| 18 | Gaipov et al. 2015 [41] | 56.7 | 42 (70)       | 18 (45)  | Unknown | 6 (15)       | 3 (7.5)    | 100%     | Unknown    |
| 19 | Cuartero et al. 2019 [42] | 59.1 | 60 (60)     | Unknown | Unknown | Unknown | 29 (29)   | 39%      | 6.5        |
| 20 | Khawaja et al. 2019 [43] | 46.5 | 32 (69)       | 2 (4.3)   | Unknown | Unknown | 100%     | Unknown    |
| 21 | Mosa et al. 2018 [44]   | 64       | 97 (53.3)     | 57 (31.3) | Unknown | Unknown | 100%     | Unknown    |
| 22 | Sun et al. 2017 [45]    | 65       | 49 (36)       | 26 (19)  | 9 (7)         | Unknown       | Unknown | Unknown | Unknown    |
| 23 | Ghonemy et al. 2014 [46] | 43     | 32 (64)       | 0%        | 0%                    | Unknown       | Unknown | 100%     | Unknown    |
| 24 | Padhy et al. 2014 [47]  | 55.9     | 44 (73.3)     | 7 (11.7)  | Unknown | Unknown | 100%     | Unknown    |
| 25 | Geus et al. 2013 [48]   | 57.9     | 347 (59.9)    | Unknown | 0%                  | 0%            | 0%      | 0%       | Unknown    |
| 26 | Geus et al. 2013 [48]   | 57.6     | 38 (47.5)     | Unknown | 0%                  | Unknown | 100%     | 0%       | Unknown    |
| 27 | Haase-Fielitz et al. 2009 [49] | 71.8 | 61 (61) | 28 (28) | 0% | Unknown | 100%     | Unknown | 100% |
| No | Study (year) | Mean age | Male gender % | Diabetes% | Chronic kidney disease% | Heart failure% | Sepsis% | Surgery% | SOFA score |
|----|--------------|----------|---------------|-----------|------------------------|---------------|---------|----------|------------|
| 27 | Hanson et al. 2011 [50] | 35 | 130 (80) | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown |
| 28 | Introcaso et al. 2018 [51] | 77 | 44 (63.8) | Unknown | Unknown | Unknown | Unknown | 100% | Unknown |
| 29 | Kim et al. 2017 [52] | 70 | 99 (59.3) | Unknown | Unknown | Unknown | 100% | Unknown | Unknown |
| 30 | Ferrari et al. 2019 [53] | 68 | 276 (62.4) | 76 (17.2) | 0% | Unknown | 80 (18.1) | 64 (14.5) | 6 |
| 31 | Xie et al. 2019 [54] | 68.2 | 439 (61.1) | 114 (15.9) | 98 (13.6) | Unknown | 87 (12.1) | 103 (14.3) | 7 |
| 32 | Adler et al. 2018 [55] | 63 | 44 (91.7) | 8 (17) | 11 (23) | 42 (88) | 6 (12.5) | Unknown | Unknown |
| 33 | Oezkur et al. 2017 [56] | 68.5 | 70 (70) | Unknown | 0% | 46 (46) | Unknown | 100% | Unknown |
| 34 | Wang et al. 2017 [57] | 60 | 41 (71.9) | 8 (14) | 2 (3.5) | 100% (I-I-V) | Unknown | 100% | Unknown |
| 35 | Finge et al. 2017 [58] | 70.5 | 53 (57) | 21 (22.6) | 0% | Unknown | Unknown | 100% | Unknown |
| 36 | Cuartero et al. 2017 [59] | 55 | 65 (66.3) | 15 (15.3) table S1 | 6 (6.1) table S1 | Unknown | 40 (40.8) | Unknown | 7.5 |
| 37 | Mayer et al. 2017 [60] | 68 | 87 (79.1) | 9 (8.2) | 9 (8.2) | 6 (5.5) | Unknown | 100% | Unknown |
| 38 | Meersch et al. 2014 [61] | 71 | 33 (66) | 20 (40) | 15 (30) | 46 (92) | Unknown | 100% | Unknown |
| 39 | Dusse et al. 2016 [62] | 81.2 | 16 (40) | 13 (32.5) | Unknown | Unknown | 2 (5) | 100% | Unknown |
| 40 | Gunneron et al. 2016 [63] | 64.3 | 242 (64.5) | 101 (26.9) | 40 (10.7) | 61 (16.3) | 44 (11.7) | 261 (69.6) | Unknown |
| 41 | Wetz et al. 2015 [64] | 72 | 29 (69) | IDDM 10 (23.8) | 26 (61.9) | 18 (42.9) | Unknown | 41 (97.6) | Unknown |
| 42 | Kimmel et al. 2016 [65] | 67 | 241 (67) | 82 (23) | 39 (11) | 81 (22) | Unknown | Unknown | Unknown |
| 43 | Pilarczyk et al. 2015 [66] | 69.6 | 48 (80) | 21 (35) | Unknown | 4 (6.7) | 8 (13.3) | 100% | Unknown |
| 44 | Hoste et al. 2014 [67] | 64.5 | 87 (56.9) | unknown | 13 (8.5) | Unknown | 29 (19) | 23 (15) | Unknown |
| 45 | Cummings et al. 2018 [68] | 67 | 269 (67.3) | 123 (30.8) | 132 (33) | 163 (40.8) | Unknown | 100% | Unknown |
| 46 | Katagiri et al. 2012 [69] | 64.25 | 47 (61) | 23 (29.9) | 6 (7.8) | Unknown | Unknown | 100% | Unknown |
| 47 | Doi et al. 2011 [70] | 66 | 223 (65.8) | 94 (27.7) | Unknown | Unknown | 66 (19.5) | 175 (51.6) | Unknown |
| 48 | Ferguson et al. 2010 [71] | 58 | 111 (69.4) | Unknown | Unknown | Unknown | AKI group 33 (35.9) | 54 (33.8) | Unknown |
| 49 | Li et al. 2012 [72] | 47 | 22 (88) | Unknown | Unknown | Unknown | Unknown | 100% | Unknown |
| 50 | Manabe et al. 2012 [73] | 71.7 | 29 (13.2) | 69 (31.4) | 220 (100) | Unknown | Unknown | 0% | Unknown |
| 51 | Matsui et al. 2012 [74] | 71.7 | 64 (75) | 27 (36) | Unknown | Unknown | Unknown | 100% | Unknown |
| 52 | Kheeba et al. 2019 [75] | 46.3 | 23 (51.1) | 15 (33.3) | Unknown | Unknown | Unknown | 100% | Unknown |
| 53 | Tu et al. 2014 [76] | 57.3 | 93 (62) | 17 (11.3) | Unknown | Unknown | Unknown | 100% | Unknown |
| No | Study (year)          | Mean age | Male gender % | Diabetes% | Chronic kidney disease% | Heart failure% | Sepsis% | Surgery% | SOFA score |
|----|----------------------|----------|---------------|-----------|-------------------------|----------------|---------|----------|------------|
| 54 | Parikh et al. 2005   | 50       | 72 (52.2)     | Unknown   | Unknown                 | 29 (21)        | Unknown | Unknown  | Unknown    |
| 55 | Parikh et al. 2004   | 44       | 44 (61.1)     | Renal Transplant group 8 (36.4) | 22 (30.6)        | Unknown  | ATN group 6 (42.9) | 26 (36.1) | Unknown   |
| 56 | Han et al. 2009      | 63.56    | 61 (67.8)     | Unknown   | Unknown                 | Unknown        | Unknown | Unknown  | 100%       |
| 57 | Liangos et al. 2009  | 68       | 74 (72)       | 29 (28.2) | Unknown                 | 23 (22.3)      | Unknown | Unknown  | 100%       |
| 58 | Naggar et al. 2012   | 51       | 16 (40)       | Unknown   | Unknown                 | Unknown        | Unknown | Unknown  | 13         |
| 59 | Nickolas et al. 2012 | 64.4     | (52.3)        | 29.4%     | 25.2                    | 8.2%           | 3.4%    | Unknown  | Unknown    |
| 60 | Vaidya et al. 2008   | 61.2     | 55%           | Unknown   | Unknown                 | Unknown        | 34%     | Unknown  | Unknown    |
| 61 | Nisula et al. 2015   | 63       | 920 (63.9)    | 326 (22.7) | 86 (6)                  | 165 (11.5)     | 89 (6.2) | 485 (33.7) | 7          |
| 62 | Nickolas TL et al.   | 60.1     | 331 (51)      | Unknown   | 106 (16.7)              | Unknown        | Unknown | Unknown  | Unknown    |
| 63 | Cho et al. 2013      | 62.9     | 85 (58.6)     | 41 (28.3) | 20 (13.8)               | Unknown        | 70 (48.3) | Unknown  | Unknown    |
| 64 | Park et al. 2019     | 75       | 67 (47.9)     | Unknown   | Unknown                 | Unknown        | 85 (60.7) | Unknown  | Unknown    |
| 65 | Perry et al. 2010    | 65       | 704 (80)      | 298 (33.9) | Unknown                 | Unknown        | 100%    | Unknown  | Unknown    |
| 66 | Shapiro et al. 2010  | 59       | 318 (48)      | 188 (28)  | Unknown                 | 100%           | Unknown | Unknown  | Unknown    |
| 67 | Thanakitcharu et al. | 51.1     | 76 (58.5)     | 21 (16.2) | Unknown                 | 54 (35.8)      | 100%    | Unknown  | Unknown    |
| 68 | Valette et al. 2013  | 60       | 74 (75)       | 15 (15)   | 4 (4)                   | 8 (8)          | Unknown | Unknown  | 8          |
| 69 | Varela et al. 2015   | 68       | 49 (74)       | 15 (23)   | Unknown                 | Unknown        | 100%    | Unknown  | Unknown    |
| 70 | Chen et al. 2012     | 66       | 113 (75)      | 92 (61)   | Unknown                 | 30 (20)        | Unknown | Unknown  | Unknown    |
| 71 | Nisula et al. 2014   | 63       | 673 (64.6)    | 242 (23.2) | 74 (7.1)                | 139 (13.5)     | 67 (6.4) | 362 (34.7) | 8          |
| 72 | Maisel et al. 2016   | 68.5     | (62)          | (43.6)    | (25.9)                  | Unknown        | Unknown | Unknown  | Unknown    |
| 73 | Matsa et al. 2014    | 60.1     | 104 (56)      | Unknown   | Unknown                 | 15 (8)         | 76 (39) | Unknown  | Unknown    |
| 74 | Munir et al. 2013    | 52       | 76 (86)       | Unknown   | Unknown                 | Unknown        | 100%    | Unknown  | Unknown    |
| 75 | Onk et al. 2016      | 66       | 52 (58)       | 26 (29)   | Unknown                 | Unknown        | 100%    | Unknown  | Unknown    |
| 76 | Azrina Md Ralib et al. 2017 | 47 | 151 (67) | Unknown | Unknown               | Unknown        | 129 (57) | 98 (43.6) | 8          |
| 77 | Yang et al. 2016     | 68       | 71 (68.9)     | Unknown   | Unknown                 | Unknown        | Unknown | Unknown  | Unknown    |
| 78 | Ueta et al. 2014     | 69.7     | 60%           | 25        | Unknown                 | Unknown        | 100%    | Unknown  | Unknown    |
| 79 | Chang et al. 2015    | 67       | 100 (68)      | 63 (43)   | 47 (32)                 | 60 (41)        | 17 (12) | Unknown  | Unknown    |
| 80 | Hjortrup et al. 2014 | 66       | 126 (57)      | 16 (7)    | 47 (21)                 | Unknown        | 100%    | 98 (44)  | 8          |
| No | Study (year) | Mean age | Male gender % | Diabetes% | Chronic kidney disease% | Heart failure% | Sepsis% | Surgery% | SOFA score |
|----|-------------|----------|---------------|-----------|------------------------|---------------|--------|----------|------------|
| 81 | Chen et al. 2020 [104] | 64 | 202 (75) | 110 (41) | unknown | Unknown | 15 (5.6) | Unknown | Unknown |
| 82 | Wybraniec et al. 2017 [105] | 65 | 69.50% | 39% | Unknown | Unknown | Unknown | Unknown | Unknown |
| 83 | Sinkala et al. et al. 2016 [106] | 35.6 | 50 (62.5) | Unknown | 27 (33.75) | Unknown | Unknown | Unknown | Unknown |
| 84 | Torregrosa et al. et al. 2014 [107] | 65.2 | 110 (76.4) | Unknown | Unknown | Unknown | Unknown | Unknown | 49% | Unknown |
| 85 | Tekce et al. 2014 [108] | 57.2 | 16 (73) | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown |
| 86 | Torregrosa et al. 2012 [109] (M) | 62.6 | 67 (75) | Unknown | Unknown | Unknown | Unknown | Unknown | 0% | Unknown |
| 86 | Torregrosa et al. 2012 [109] (S) | 68.8 | 34 (74) | Unknown | Unknown | Unknown | Unknown | Unknown | 100% | Unknown |
| 87 | Matsui et al. 2011 [110] | 73 | 15 (60) | 6 (24%) | 5 (20) | Unknown | Unknown | 8 (32) | Unknown |
| 88 | Parkh et al. 2011 [111] | 71 | 826 (68) | 511 (42%) | Unknown | 314 (26%) | Unknown | 100% | Unknown |
| 89 | Wang 2017 [112] | 58.2 | 54 (54.4) | Unknown | Unknown | Unknown | Unknown | 100% | Unknown |
| 90 | Haase-Fielitz et al. 2009 [113] | 69.5 | 61 (61%) | 28 (28%) | 27 (27%) | 25 (25%) | Unknown | 100% | Unknown |
| 91 | Waskowski 2021 [114] | 69.4 | 77 (82.8) | 15 (16.1) | 27 (29) | 14 (15.1) | No | 71 (76.3) | Unknown |
| 92 | Imoto 2021 [115] | 72 | 58 (54.7) | Unknown | Unknown | 10 (9.4) | No | No | Unknown |
| 93 | Lee 2021 [116] | 62 | 95 (66.0) | 53 (36.8) | Unknown | Unknown | No | 100% | Unknown |
| 94 | Szymanowicz 2021 [117] | 68 | 57 (50) | 36 (31.5) | Unknown | 74 (64.9) | No | 100% | Unknown |
| 95 | Zhen 2021 [118] | 61.7 | 110 (63.9) | 48 (27.9) | Unknown | Unknown | No | No | Unknown |
| 96 | Obata 2021 [119] | 69.8 | 57 (89) | 56 (87.5) | Unknown | Unknown | No | 100% | Unknown |
| 97 | Qiu 2021 [120] | 74.7 | 60 (66.7) | 24 (26.7) | Unknown | Unknown | 100% | No | 6.0 |
| 98 | Shakked 2022 [121] | 52 | 31 (59.6) | 21 (40.4) | Unknown | Unknown | No | No | Unknown |
| 99 | Vogel 2021 [122] | 55 | 34 (63) | 7 (13) | 7 (13) | 1 (1.9) | No | No | Unknown |
| 100 | Ergun 2021 [123] | 71.6 | 33 (55) | Unknown | Unknown | Unknown | No | 100% | Unknown |
| 101 | Piłarczyk 2022 [124] | 69.1 | 33 (32.7) | Unknown | 5 (4.9) | Unknown | No | 100% | Unknown |
| 102 | Okuda 2022 [125] | 75.2 | 33 (68.8) | 9 (18.8) | 12 (25) | Unknown | No | 100% | Unknown |
| 103 | Pei 2022 [126] | 72 | 97 (59.9) | 49 (30.2) | 17 (10.5) | 43 (26.5) | 100% | No | 2 |
| 104 | Jahaj 2021 [127] | 47.2 | 199 (74.8) | Unknown | Unknown | Unknown | No | No | 6.4 |
| 105 | Garms 2021 [128] | 49.6 | 63 (67) | 27 (28.7) | 5 (5.3) | Unknown | No | 43 (45.7) | Unknown |
| 106 | Irqsusi 2021 [129] | 68.5 | 50 (100) | 17 (34) | 8 (16) | 47 (94) | No | 100% | Unknown |
| 107 | Guray 2021 [130] | 67.6 | 48 (57.1) | 23 (27.3) | Unknown | Unknown | No | No | Unknown |
| 108 | Pan 2022 [131] | 50.5 | 62 (39.5) | 33 (2.1) | Unknown | Unknown | 100% | Unknown | Unknown |
3 used a 0.5 mg/dL increase in SCr within 48–72 h, and 6 were at the discretion of the attending physicians.

Quality of the enrolled trials
The studies were published over 18 years and varied in sample size from 22 to 1635 patients (Tables 1, 2). The QUADAS-2 tool revealed that the quality of the enrolled studies varied. There was a low and/or unclear risk in each study in most domains of bias evaluation (Additional file 1: Figs. S1, S2). The risk of bias was low for patient selection in 84 studies (76.4%); index test in 26 studies (23.6%); reference standard in 30 studies (27.3%); and flow and timing in 96 studies (87.3%). The applicability concerns were low for patient selection in 89 studies (80.9%); index test in 106 studies (96.4%); and reference standard in 95 studies (86.4%). Therefore, according to the criteria of overall quality, 70 studies (63.6%) were rated as low risk, 15 studies (13.6%) as unclear risk, and 25 studies (22.7%) as high risk.

Primary outcomes
The occurrence of AKI was based on all of the included studies with a total of 38,725 patients, of whom 8,340 had incident AKI. Among the 11 candidate biomarkers, the diagnostic accuracy (defined as the DOR value) was numerically highest for NGAL/creatinine (NGAL/Cr) (DOR 16.2, 95% CI 10.1–25.9), which was reported in 9 studies. The results demonstrated that urinary NGAL had high diagnostic accuracy (DOR 13.8, 95% CI 10.2–18.8), which was significantly better than IL-18 (relative DOR 0.60, 95% CI 0.44–0.82), and TIMP-2 × IGFBP-7: 0.3 (relative DOR 0.42, 95% CI 0.22–0.81) for the occurrence of AKI (Table 3). The HSROCs depicting the overall discriminative accuracy of the biomarkers to diagnose AKI are shown in Fig. 1A. Of the biomarkers, urinary NGAL (HSROC 85.2%, 95% CI 80.4–89.4%), urinary NGAL/Cr (HSROC 91.4%, 95% CI 79.4–96.5%), serum NGAL (HSROC 84.7%, 95% CI 80.7–87.9%), IL-18 (HSROC 82.1%, 95% CI 70.2–88.9%), KIM-1 (HSROC 84.4%, 95% CI 72.7–95.5%), and L-FABP/Cr (HSROC 85.8%, 95% CI 80.7–87.9%) were highly accurate.

| Table 2 (continued) | No | Study (year) | Mean age | Male gender % | Diabetes% | Chronic kidney disease% | Heart failure% | Sepsis% | Surgery% | SOFA score |
|---------------------|----|--------------|----------|---------------|-----------|------------------------|---------------|---------|----------|------------|
| 109 Lakhal 2021 [132] | 78.6 | 32 (49.2) | 14 (21.5) | Unknown | Unknown | No | 100% | Unknown | |
| 110 Sahu 2022 [133] | 58.3 | 182 (85.8) | 59 (27.8) | Unknown | 3 (1.4) | No | No | Unknown | |

SOFA sequential organ failure assessment

| Table 3 | Summary of the diagnostic meta-analysis in the whole population |
|---------|---------------------------------------------------------------|
| Marker | No. of study | Sensitivity, % (95% CI) | Specificity, % (95% CI) | DOR (95% CI) | Relative sensitivity (95% CI) | Relative specificity (95% CI) | Relative DOR (95% CI) |
| NGAL | 35 | 76.8 (72.3–80.8) | 80.7 (77.1–83.8) | 13.8 (10.2–18.8) | Reference | Reference | Reference |
| IL-18 | 12 | 67.6 (60.4–74.0) | 80.0 (76.1–83.5) | 8.4 (5.7–12.1) | 0.88 (0.80–0.96)* | 0.99 (0.97–1.02) | 0.60 (0.44–0.82)* |
| IL-18/Cr | 3 | 71.9 (63.3–79.1) | 80.6 (75.0–85.3) | 10.6 (6.4–17.6) | 0.94 (0.84–1.04) | 1.00 (0.95–1.05) | 0.77 (0.48–1.23) |
| KIM-1 | 14 | 76.3 (70.4–81.4) | 79.4 (75.2–83.1) | 12.4 (8.5–18.1) | 0.99 (0.93–1.06) | 0.98 (0.96–1.01) | 0.90 (0.65–1.23) |
| KIM-1/Cr | 6 | 69.9 (60.1–78.1) | 83.8 (78.8–87.7) | 12.0 (7.0–20.3) | 0.91 (0.80–1.03) | 1.04 (0.99–1.09) | 0.86 (0.52–1.43) |
| L-FABP | 10 | 69.8 (62.0–76.5) | 81.0 (77.0–84.4) | 9.8 (6.5–14.8) | 0.91 (0.83–0.998)* | 1.00 (0.98–1.03) | 0.71 (0.50–1.01) |
| L-FABP/Cr | 8 | 81.8 (74.0–87.7) | 69.6 (58.5–78.7) | 10.3 (5.4–19.7) | 1.07 (0.97–1.17) | 0.86 (0.75–0.99)* | 0.74 (0.38–1.44) |
| NGAL/Cr | 9 | 71.6 (63.5–78.5) | 86.5 (82.5–89.7) | 16.2 (10.1–25.9) | 0.93 (0.84–1.03) | 1.07 (1.03–1.11)* | 1.17 (0.75–1.82) |
| Serum NGAL | 40 | 76.3 (71.6–80.4) | 79.7 (75.9–83.0) | 12.6 (9.3–17.3) | 0.99 (0.94–1.05) | 0.99 (0.96–1.01) | 0.91 (0.69–1.21) |
| TIMP-2 × IGFBP-7: custom | 6 | 86.3 (74.8–93.0) | 57.6 (43.1–70.9) | 8.5 (3.4–21.4) | 1.12 (0.999–1.26) | 0.71 (0.56–0.92)* | 0.62 (0.23–1.63) |
| TIMP-2 × IGFBP-7: 0.3 | 17 | 68.0 (58.1–76.4) | 73.5 (64.1–81.1) | 5.9 (3.3–10.4) | 0.88 (0.76–1.02) | 0.91 (0.80–1.03) | 0.42 (0.22–0.81)* |
| TIMP-2 × IGFBP-7: 2 | 11 | 18.5 (12.4–26.8) | 97.3 (95.7–98.4) | 8.3 (4.3–16.1) | 0.24 (0.16–0.36)* | 1.21 (1.15–1.26)* | 0.60 (0.29–1.24) |

CI confidence interval, Cr creatinine, DOR diagnostic odds ratio, IL-18 interleukin-18, KIM-1 kidney injury molecule-1, L-FABP liver-type fatty acid-binding protein, NGAL neutrophil gelatinase-associated lipocalin, TIMP-2 × IGFBP-7 tissue inhibitor of metalloproteinases-2 × insulin-like growth factor-binding protein-7

*Numbers in bold indicate significant difference (P<0.05) versus the referent category: "NGAL"
74.9–93.8%) had HSROC values greater than 80%. Additional file 1: Figs. S3, S4 and Fig. 1B illustrate the pairwise comparisons of the biomarkers for pooled sensitivity, specificity, and DOR in the whole population.

Subgroup analyses
In the setting of ICU patients, the diagnostic accuracy was numerically highest for NGAL/Cr (DOR 12.6, 95% CI 7.8–20.2), followed by L-FABP/Cr and urinary NGAL. The diagnostic accuracy of urinary NGAL was significantly better than TIMP-2 × IGFBP-7: 0.3 (relative DOR 0.51, 95% CI 0.28–0.92) (upper panel in Table 4). In contrast, urinary NGAL (DOR 17.1, 95% CI 7.8–37.5), urinary NGAL/Cr (DOR 99.3, 95% CI 7.7–1285.0), and serum NGAL (DOR 15.0, 95% CI 7.1–32.0) had better diagnostic accuracy for AKI than IL-18 (DOR 9.6, 95% CI 4.2–21.9) in the non-ICU patients (lower panel in Table 4). Additional file 1: Figs. S5–S7 illustrate the pairwise comparisons of the biomarkers for pooled sensitivity, specificity, and DOR in the ICU patients.

On the other hand, urinary NGAL had the highest diagnostic accuracy (DOR 17.9, 95% CI 12.3–26.3),
which was significantly better than IL-18 (relative DOR 0.31, 95% CI 0.21–0.47), IL-18/Cr (relative DOR 0.56, 95% CI 0.34–0.94), KIM-1 (relative DOR 0.57, 95% CI 0.40–0.82), L-FABP (relative DOR 0.46, 95% CI 0.30–0.71), and TIMP-2 x IGFBP-7: 0.3 (relative DOR 0.28, 95% CI 0.10–0.79) for the occurrence of AKI in the setting of medical/mixed patients (upper panel in Table 5). Furthermore, urinary NGAL had a low diagnostic accuracy in the setting of surgical patients. Urinary NGAL/Cr (DOR 34.3, 95% CI 9.0–130.6), KIM-1 (DOR 26.2, 95% CI 9.6–71.6), L-FABP (DOR 14.9, 95% CI 7.0–31.5), and IL-18 (DOR 11.8, 95% CI 6.1–22.9) had better diagnostic accuracy than urinary NGAL (lower panel in Table 5). Additional file 1: Figs. S8–S12 and Fig. 1C illustrate the pairwise comparisons of the biomarkers for pooled sensitivity, specificity, and DOR in the medical/mixed and surgical patients.

Only twelve studies recruited patients with sepsis, and therefore analysis of sepsis was not conducted. The results of the non-sepsis patients were similar to those of the overall cohort: Urinary NGAL (DOR 16.3, 95% CI 11.8–22.4) had significantly better diagnostic accuracy for AKI than IL-18 (relative DOR 0.52, 95% CI 0.37–0.72), L-FABP (relative DOR 0.65, 95% CI 0.46–0.93), and TIMP-2 x IGFBP-7: 0.3 (relative DOR 0.36, 95% CI 0.19–0.67) (Additional file 1: Table S1). Additional file 1: Figs. S13–S15 illustrate the pairwise comparisons of the biomarkers for pooled sensitivity, specificity, and DOR in the non-sepsis patients.

Only 10 studies recruited patients without using standard AKI criteria (RIFLE/AKIN/KDIGO), and therefore, the analysis was not conducted. In the 100 studies which adopted standard AKI criteria, NGAL/Cr had the highest diagnostic accuracy (DOR 15.4, 95% CI 9.6–24.4),
followed by KIM-1 (DOR 12.8, 95% CI 8.7–18.7), and urinary NGAL (DOR 12.5, 95% CI 9.2–16.9). Urinary NGAL had significantly better diagnostic accuracy for AKI than IL-18 (relative DOR 0.62, 95% CI 0.45–0.85) and TIMP-2 × IGFBP-7: 0.3 (relative DOR 0.46, 95% CI 0.24–0.86) (Table 6). Additional file 1: Figs. S16–S18 illustrate the pairwise comparisons of the biomarkers for pooled sensitivity, specificity, and DOR in the studies using standard AKI criteria.

Only 30 studies diagnosed AKI using urine output criteria, and the diagnostic accuracy was numerically highest for KIM-1 (DOR 14.6, 95% CI 5.9–35.9), followed by IL-18 (DOR 13.1, 95% CI 6.7–25.7), and TIMP-2 × IGFBP-7: 2 (DOR 12.0, 95% CI 5.2–27.8). Among the other 80 studies that diagnosed AKI without using urine output criteria, NGAL had the highest diagnostic accuracy (DOR 18.6, 95% CI 12.8–27.0), followed by urinary NGAL/Cr (DOR 17.6, 95% CI 10.7–29.1). Urinary NGAL had significantly better diagnostic accuracy for AKI than IL-18 (relative DOR 0.38, 95% CI 0.26–0.56), IL-18/Cr (relative DOR 0.60, 95% CI 0.37–0.98), KIM-1 (relative DOR 0.61, 95% CI 0.42–0.88), and L-FABP (relative DOR 0.61, 95% CI 0.41–0.88) (Table 7). Additional file 1: Figs. S19–S20 and Fig. 1D illustrate the pairwise comparisons of the biomarkers for pooled sensitivity, specificity, and DOR in the studies that did not use urine output criteria.

Sensitivity analyses
To determine the robustness of the study results, we examined the extent to which the results were influenced by the quality of the enrolled study, the economic situation of the countries in which they were conducted, and the definition of the study outcome.
Table 6  Summary of the diagnostic meta-analysis for the studies using standard AKI criteria (any of RIFLE, AKIN, and KDIGO)

| Marker   | No. of study | Sensitivity, % (95% CI) | Specificity, % (95% CI) | DOR (95% CI) | Relative sensitivity (95% CI) | Relative specificity (95% CI) | Relative DOR (95% CI) |
|----------|--------------|-------------------------|-------------------------|--------------|-------------------------------|-----------------------------|-----------------------|
| NGAL     | 33           | 75.9 (71.2–80.0)         | 79.9 (76.0–83.3)        | 12.5 (9.2–16.9) | Reference                     | Reference                  | Reference             |
| IL-18    | 11           | 66.2 (58.9–72.8)         | 79.8 (75.7–83.4)        | 7.7 (5.3–11.2) | 0.87 (0.79–0.96)              | 1.00 (0.98–1.02)           | 0.62 (0.45–0.85)*     |
| IL-18/Cr | 3            | 71.4 (62.8–78.6)         | 80.1 (74.3–84.9)        | 10.0 (6.1–16.5) | 0.94 (0.84–1.05)              | 1.00 (0.95–1.06)           | 0.80 (0.50–1.29)      |
| KIM-1    | 12           | 76.2 (70.2–81.4)         | 80.0 (75.6–83.7)        | 12.8 (8.7–18.7) | 1.01 (0.94–1.08)              | 1.00 (0.97–1.03)           | 1.03 (0.74–1.42)      |
| KIM-1/Cr | 6            | 69.3 (59.5–77.5)         | 83.4 (78.3–87.5)        | 11.3 (6.7–19.1) | 0.91 (0.84–1.02)              | 1.02 (1.00–1.05)           | 0.85 (0.59–1.22)      |
| L-FABP   | 9            | 70.4 (62.6–77.1)         | 81.7 (77.7–85.2)        | 10.6 (7.0–16.1) | 0.93 (0.84–1.02)              | 1.02 (1.00–1.05)           | 0.85 (0.59–1.22)      |
| L-FABP/Cr| 8            | 81.9 (74.2–87.7)         | 70.0 (59.0–79.1)        | 10.6 (5.6–20.1) | 1.08 (0.99–1.18)              | 0.88 (0.76–1.01)           | 0.85 (0.44–1.63)      |
| NGAL/Cr  | 9            | 71.1 (63.0–78.1)         | 86.2 (82.1–89.5)        | 15.4 (9.6–24.4) | 0.94 (0.85–1.04)              | 1.08 (1.04–1.12)*          | 1.23 (0.79–1.91)      |
| Serum NGAL | 35         | 74.3 (69.4–78.8)         | 78.9 (74.8–82.5)        | 10.8 (7.9–14.8) | 0.98 (0.92–1.04)              | 0.99 (0.96–1.01)           | 0.87 (0.65–1.15)      |
| TIMP-2 × IGFBP-7: custom | 6     | 85.9 (74.4–92.7)         | 58.1 (43.6–71.4)        | 8.4 (3.4–20.7) | 1.13 (1.00–1.28)*              | 0.73 (0.57–0.93)*          | 0.67 (0.26–1.75)      |
| TIMP-2 × IGFBP-7: 0.3 | 16     | 66.6 (56.7–75.2)         | 74.0 (64.5–81.7)        | 5.7 (3.2–10.0) | 0.88 (0.75–1.02)              | 0.93 (0.82–1.05)           | 0.46 (0.24–0.86)*     |
| TIMP-2 × IGFBP-7: 2 | 10     | 17.5 (11.6–25.6)         | 97.5 (95.8–98.5)        | 8.3 (4.2–16.1) | 0.23 (0.15–0.35)              | 1.22 (1.16–1.28)           | 0.66 (0.32–1.38)      |

AKI acute kidney injury, RIFLE Risk, Injury, Failure, Loss, and End-stage renal disease, AKIN Acute Kidney Injury Network, KDIGO Kidney Disease Improving Global Outcomes, CI confidence interval, DOR diagnostic odds ratio, NGAL neutrophil gelatinase-associated lipocalin, IL-18 interleukin-18, Cr urine creatinine, KIM-1 kidney injury molecule-1, L-FABP liver-type fatty acid-binding protein; TIMP-2 × IGFBP-7, tissue inhibitor of metalloproteinases-2 × insulin-like growth factor-binding protein-7.

*Numbers in bold indicate significant difference (P<0.05) versus the referent category: “NGAL”

We first stratified the studies according to their quality. Seventy studies were of high quality and 40 studies were of low or middle quality. Among the high-quality studies, the diagnostic accuracy was numerically highest for urinary NGAL (DOR 12.95, 95% CI 8.88–18.87), followed by urinary NGAL/Cr (DOR 12.34, 95% CI 5.85–26.02), and serum NGAL (DOR 12.32, 95% CI 8.41–18.06). Urinary NGAL had significantly better diagnostic accuracy for AKI than IL-18 (relative DOR 0.56, 95% CI 0.39–0.78), L-FABP (relative DOR 0.66, 95% CI 0.45–0.97), and TIMP-2 × IGFBP-7: 0.3 (relative DOR 0.43, 95% CI 0.22–0.87). Among the low- or middle-quality studies, KIM-1/Cr had the highest diagnostic accuracy (DOR 33.33, 95% CI 9.87–126.47), followed by KIM-1 (DOR 34.60, 95% CI 17.16–69.77), and IL-18 (DOR 30.43, 95% CI 12.80–72.33). Both KIM-1 (relative DOR 3.00, 95% CI 1.53–5.87) and IL-18 (relative DOR 2.64, 95% CI 1.11–6.28) had significantly better diagnostic accuracy for AKI than NGAL, while IL-18/Cr had significantly worse diagnostic accuracy for AKI than NGAL (relative DOR 0.42, 95% CI 0.22–0.81) (Additional file 1: Table S2).

Seventy-eight studies were conducted in high-income countries, and the diagnostic accuracy was numerically highest for urinary NGAL/Cr (DOR 15.23, 95% CI 9.56–24.26), and urinary NGAL (DOR 14.13, 95% CI 10.03–19.89). Urinary NGAL had significantly better diagnostic accuracy for AKI than IL-18 (relative DOR 0.46, 95% CI 0.33–0.64), L-FABP (relative DOR 0.54, 95% CI 0.36–0.79), and TIMP-2 × IGFBP-7: 0.3 (relative DOR 0.40, 95% CI 0.21–0.74). Among the other 32 studies conducted in middle- or low-income countries, L-FABP had the highest diagnostic accuracy (DOR 45.15, 95% CI 14.56–140.05), which was significantly better than urinary NGAL (relative DOR 2.89, 95% CI 1.12–7.42) (Additional file 1: Table S3).

Thirty-seven studies focused on early onset AKI (AKI developed within 48 h), and the diagnostic accuracy was numerically highest for L-FABP (DOR 33.1, 95% CI 11.5–95.1), serum NGAL (DOR 21.4, 95% CI 10.5–43.7), L-FABP/Cr (DOR 21.4, 95% CI 2.9–158.8), and urinary NGAL (DOR 15.4, 95% CI 7.2–32.9) (Additional file 1: Table S4).

Twenty-four studies focused on severe AKI (AKI stage 2 or 3), and the diagnostic accuracy was numerically highest for TIMP-2 × IGFBP-7: custom (DOR 19.6, 95% CI 7.0–55.3), and serum NGAL (DOR 11.5, 95% CI 6.1–21.9) (Additional file 1: Table S5). Ten studies focused on renal replacement therapy, and both urinary NGAL (DOR 15.2, 95% CI 5.3–43.5) and serum NGAL (DOR 12.1, 95% CI 4.7–31.1) had good diagnostic accuracy (Additional file 1: Table S6).

The findings were not materially different from the standard analysis and remained robust in the sensitivity analyses.
Publication bias was assessed visually using funnel plots. There were apparent asymmetrical patterns in the funnel plots for all the biomarkers except TIMP-2 × IGFBP-7: custom, TIMP-2 × IGFBP-7: 0.3, and TIMP-2 × IGFBP-7: 2.0. These results suggested that publication bias was obvious in this meta-analysis (Additional file 1: Appendix).

Assessment of quality of evidence and summary of findings
The quality of evidence was assessed using the GRADE system. We evaluated the primary outcomes and presented them as summary of findings in Additional file 1: Appendix.

Table 7 Summary of the diagnostic meta-analysis according to AKI criteria with or without UO

| Population/marker | No. of study | Sensitivity, % (95% CI) | Specificity, % (95% CI) | DOR (95% CI) | Relative sensitivity (95% CI) | Relative specificity (95% CI) | Relative DOR (95% CI) |
|-------------------|-------------|------------------------|-------------------------|-------------|-----------------------------|-----------------------------|---------------------|
| Non-UO            |             |                        |                         |             |                             |                             |                     |
| NGAL              | 27          | 81.1 (76.6–84.9)        | 81.3 (72.2–84.7)        | 18.6 (12.8–27.0) | Reference                   | Reference                   | Reference           |
| IL-18             | 9           | 63.7 (55.1–71.6)        | 80.1 (75.5–84.1)        | 7.1 (4.5–11.2)  | 0.79 (0.70–0.89)*           | 0.99 (0.96–1.02)          | 0.38 (0.26–0.56)*   |
| IL-18/Cr          | 3           | 72.4 (63.8–79.6)        | 81.0 (75.2–85.7)        | 11.2 (6.6–19.0) | 0.89 (0.80–0.99)*           | 1.00 (0.95–1.05)          | 0.60 (0.37–0.98)*   |
| KIM-1             | 12          | 73.8 (67.0–79.7)        | 80.1 (75.4–84.0)        | 11.3 (7.3–17.5) | 0.91 (0.84–0.99)*           | 0.99 (0.96–1.01)          | 0.61 (0.42–0.88)*   |
| KIM-1/Cr          | 6           | 70.8 (61.2–78.8)        | 84.1 (79.0–88.2)        | 12.8 (7.3–22.3) | 0.87 (0.77–0.99)*           | 1.04 (0.99–1.08)          | 0.69 (0.41–1.16)    |
| L-FABP            | 9           | 72.2 (64.2–79.0)        | 81.2 (76.7–85.0)        | 11.2 (7.0–18.0) | 0.89 (0.81–0.98)*           | 1.00 (0.97–1.03)          | 0.61 (0.41–0.88)*   |
| L-FABP/Cr         | 6           | 80.3 (70.4–87.4)        | 74.8 (59.4–85.8)        | 12.1 (4.9–29.7) | 0.99 (0.89–1.11)            | 0.92 (0.77–1.10)          | 0.65 (0.26–1.64)    |
| NGAL/Cr           | 9           | 72.9 (65.0–79.6)        | 86.8 (82.6–90.0)        | 17.6 (10.7–29.1) | 0.90 (0.82–0.99)*           | 1.07 (1.03–1.11)*         | 0.95 (0.60–1.50)    |
| Serum NGAL        | 34          | 79.0 (74.3–83.1)        | 79.5 (75.1–83.3)        | 14.6 (10.0–21.2) | 0.97 (0.92–1.03)            | 0.98 (0.95–1.01)          | 0.78 (0.56–0.99)    |
| TIMP-2 × IGFBP-7: 0.3 | 5  | 82.2 (67.8–91.0)        | 61.8 (41.3–78.9)        | 7.5 (2.3–24.6)  | 1.01 (0.87–1.18)            | 0.76 (0.55–1.05)          | 0.40 (0.12–1.40)    |
| TIMP-2 × IGFBP-7: 2  | 5  | 25.4 (13.7–42.2)        | 95.3 (89.4–98.0)        | 6.8 (2.1–22.8)  | 0.31 (0.18–0.55)*           | 1.17 (1.10–1.25)*         | 0.37 (0.10–1.30)    |
| UO                |             |                        |                         |             |                             |                             |                     |
| NGAL              | 7           | 68.2 (54.7–79.2)        | 78.5 (67.8–86.3)        | 7.8 (4.6–13.1)  | Reference                   | Reference                   | Reference           |
| IL-18             | 2           | 77.4 (62.9–87.4)        | 79.3 (68.5–87.1)        | 13.1 (6.7–25.7) | 1.14 (0.98–1.31)            | 1.01 (0.97–1.05)          | 1.68 (0.94–3.01)    |
| KIM-1             | 2           | 84.9 (71.6–92.6)        | 72.2 (55.1–84.6)        | 14.6 (5.9–35.9) | 1.25 (1.08–1.44)*           | 0.92 (0.79–1.08)          | 1.87 (0.81–4.31)    |
| L-FABP/Cr         | 2           | 70.4 (38.1–90.2)        | 77.5 (46.5–93.2)        | 8.2 (2.4–28.2)  | 1.03 (0.67–1.60)            | 0.99 (0.71–1.38)          | 1.05 (0.27–4.02)    |
| Serum NGAL        | 6           | 67.8 (53.3–79.6)        | 79.2 (68.6–86.8)        | 8.0 (4.5–14.1)  | 1.00 (0.83–1.19)            | 1.01 (0.97–1.05)          | 1.03 (0.57–1.84)    |
| TIMP-2 × IGFBP-7: custom | 5 | 88.2 (76.1–94.6)        | 55.8 (39.1–71.2)        | 9.5 (4.0–22.6)  | 1.29 (1.05–1.60)*           | 0.71 (0.52–0.98)*         | 1.21 (0.44–3.36)    |
| TIMP-2 × IGFBP-7: 0.3 | 12  | 59.0 (46.3–70.6)        | 77.2 (66.8–85.1)        | 4.9 (3.0–7.9)   | 0.87 (0.65–1.14)            | 0.98 (0.83–1.16)          | 0.63 (0.31–1.27)    |
| TIMP-2 × IGFBP-7: 2  | 6  | 16.7 (9.6–27.4)         | 98.4 (96.5–99.3)        | 12.0 (5.2–27.8) | 0.24 (0.14–0.43)*           | 1.25 (1.11–1.41)*         | 1.54 (0.57–4.13)    |

CI confidence interval, DOR diagnostic odds ratio, NGAL neutrophil gelatinase-associated lipocalin, IL-18 interleukin-18, Cr urine creatinine, KIM-1 kidney injury molecule-1, L-FABP liver-type fatty acid-binding protein, TIMP-2 × IGFBP-7 tissue inhibitor of metalloproteinases-2 × insulin-like growth factor-binding protein-7, UO urine output

*Numbers in bold indicate significant difference (P<0.05) versus the referent category: “NGAL”

Discussion
The current study is the most comprehensive systematic review to date including the highest number of studies of candidate AKI biomarkers. In this systematic review of 110 studies including 38,725 patients, the overall AKI rate was 21.5% (8340/38725). Serum NGAL and urinary NGAL were the most commonly used biomarkers for AKI (Table 3). In the whole population, both serum and urine NGAL had the best diagnostic accuracy regardless of whether or not they were adjusted by urinary creatinine (Table 3). For the critical patients, all of the biomarkers had similar predictive performance for AKI (upper panel in Table 4). However, for the non-critical patients, NGAL, NGAL/Cr, and serum NGAL had better diagnostic accuracy for AKI than IL-18 (lower panel in Table 4). In the medical patients, NGAL had the best diagnostic...
In the present study, we demonstrated that several biomarkers are a major limitation for large-scale population studies. As demonstrated in the present study, NGAL/Cr, L-FABP/Cr, TIMP-2 × IGFBP-7: custom seemed to have good predictive performance in the setting of critically ill patients, while NGAL/Cr and KIM-1 were the best biomarkers in surgical patients (Tables 4, 5).

There is an unmet need for the early detection of AKI due to an increase in the incidence of AKI in hospitalized patients [134, 135]. In clinical practice, it is difficult to recognize AKI before the level of creatinine changes, at which time the damage may be irreversible [4]. Therefore, researchers are increasingly interested in identifying biomarkers that can identify AKI at an early stage. The 23rd ADQI consensus meeting proposed combining clinical assessments, traditional tests, and validated novel biomarkers to identify patients at risk of AKI [136]. In susceptible patients exposed to high-risk events, biomarkers can predict the development or progression of AKI and may guide targeted therapy [137]. In the literature, many biomarkers have performed better than SCr when histologic evidence of kidney injury was used as the reference standard [138]. Although various biomarkers have been associated with AKI and adverse outcomes, the clinical application of any single biomarker has failed to demonstrate troponin-like diagnostic performance in myocardial infarction. The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study [37, 111, 139] showed the heterogeneity of AKI subtype is a major limitation for large-scale population studies. In the present study, we demonstrated that several biomarkers had good predictive performance for AKI. In addition, the damage biomarkers had better predictive ability for AKI than the stress biomarker in various clinical settings. It is likely that the ability to identify different etiologies, mechanisms, and types of AKI will be critical in developing targeted therapies and designing pharmacological trials to enable more precise medicine or therapeutic interventions.

The complexity of the pathogenesis of AKI due to factors such as hemodynamics, inflammatory status, genetic background, the use of nephrotoxic compounds, and interventions means that the clinical course of AKI differs in different clinical situations [140]. In critically ill or surgical patients, the potential benefits of reducing kidney injury-related complications may outweigh the loss caused by over-monitoring the patient, such as related length of stay. Appropriate biomarkers should improve the detection rate of AKI with high sensitivity and good negative predictive value, thus enabling timely initiation of preventive strategies for AKI [141]. Previous investigations have reported that TIMP-2 × IGFBP-7 was a good biomarker to identify patients who will develop AKI and reduce the need for renal replacement therapy [136, 137, 142]. As demonstrated in the present study, NGAL/Cr, IGFBP-7 was a good negative predictive value, thus enabling timely initiation of preventive strategies for AKI [141]. In our study, the clinical performance of TIMP-2 × IGFBP-7 with a cutoff value of 2 was significantly better than that of TIMP-2 × IGFBP-7 with a cutoff value of 0.3 in the medical patients. Urinary NGAL, KIM-1, and serum NGAL seemed to be the best biomarkers in the setting of non-critically ill patients and medical patients (Tables 4, 5).

However, the sensitivity and specificity in the enrolled studies were heterogeneous because they depended on the circumstances and the threshold effects of the biomarkers. Considering the potential threshold effects and the correlation between sensitivity and specificity, HSROC analysis proved the good predictive performance of L-FABP/Cr and the NGAL series (Fig. 1A). There were differences in the applied diagnostic criteria for AKI between the enrolled studies. The subgroup analysis also demonstrated that the relative diagnostic accuracy of the AKI biomarkers remained consistent in the studies using current standard AKI criteria (RIFLE/AKIN/KDIGO) (Table 6). NGAL series seemed to have the best predictive performance for AKI, especially in the high-quality studies and in the studies which were conducted in high-income countries. Other biomarkers outperformed the NGAL series only in low- or moderate-quality studies or in the studies conducted in middle- or low-income countries (Additional file 1: Tables S2-S3). Sensitivity analysis also demonstrated the good predictive performance of serum NGAL, urinary NGAL, and TIMP-2 × IGFBP-7: custom for early onset AKI (AKI developed within 48 h) and severe AKI (stage 2–3 or renal replacement therapy) (Additional file 1: Tables S4-S6). These findings enhance the robustness of the study results.

Although the damage and stress biomarkers in this study had good predictive performance, unlike troponin in acute coronary syndrome, none of the reported biomarkers are completely specific for AKI. Previous studies have reported that NGAL, IL-18, and KIM-1 may be elevated in the setting of sepsis and CKD [143–146]. Of note, these biomarkers can be used to recruit more homogeneous patient populations when implementing a clinical trial [147]. Biomarkers to identify and characterize AKI sub-types are necessary and may have the potential to provide individualized timely etiology-based management of AKI. In addition, considering the...
complex and multifactorial etiology of AKI, a panel of multiple biomarkers including stress, injury, and kidney reserve biomarkers could provide better discrimination for AKI. Furthermore, more kidney tissue-specific markers may help localize and quantify the severity of AKI and provide a deeper understanding of the pathophysiology of AKI. These biomarkers may offer opportunities for personalized management of AKI and support the call for a refinement of the existing AKI criteria.

**Strengths and limitations**

The strength of our analysis is the extensive literature search of related studies. We used standard Cochrane protocols and included the largest cumulative study sample size to date in comparison with previous reports. The strength of our meta-analysis also lies in the comprehensive data search with subgroup analyses across several clinical scenarios. We used the GRADE approach to rate the certainty of evidence [148].

Besides limitations in the meta-analysis, there were several limitations in the individual studies. First, most studies had a small sample size, and this contributed to the high heterogeneity of the meta-analysis. Second, our funnel meta-regression and Cochrane Collaboration tool analysis showed significant publication bias (Additional file 1: Appendix). Third, in some scenarios, the limited number of enrolled studies, such as trials focusing on sepsis, made subgroup analysis difficult. Of note, these new biomarkers are most effective in conditions where the time of renal insult is known, for instance, post-cardiac surgery or coronary angiography, compared to situations where the onset of kidney injury is less clear, for instance, in sepsis. To ensure the robustness of the findings, we did not emphasize the diagnostic accuracy of biomarkers extracted from fewer than three articles. Fourth, we did not perform additional analyses to assess the additional predictive value of Scr levels. Most of the included studies did not measure Scr levels with biomarkers to predict AKI. In the literature, Scr has poor predictive performance for AKI due to delayed rise and cannot accurately estimate the timing of injury [118, 127]. Traditionally, the diagnosis of AKI is based on a rise in serum creatinine and the creatinine could be hard to wear two hats, having an administrative role as well as patrolling the beat. Furthermore, the use of Scr as a comparison has several limitations and limits the full interpretation of biomarker performance. For example, Scr may be elevated in pre-renal azotemia, which is not true for renal tissue damage, and biomarkers may not be elevated. On the other hand, in the setting of true renal injury with fluid overload, biomarkers may be elevated but Scr may remain unchanged, which may underestimate the predictive performance of biomarkers [149, 150]. Fifth, the kits for specific biomarker analysis varies among the studies, so it was difficult to determine the optimal cutoff value of biomarkers to predict AKI. Sixth, the occurrence of AKI was diagnosed according to several different criteria in the enrolled studies. However, the KDIGO classification was the mostly commonly used, which has been proposed to provide a uniform definition of AKI, essentially combining the RIFLE and AKIN criteria. Finally, the definition of AKI varied between the studies, and this may have unduly influenced pooled effect estimates. Nonetheless, our conclusions were drawn from studies with different study designs and different clinical scenarios. Further research efforts are certainly needed for the pursuit of better precision medicine, especially with regard to the use of multiple biomarkers. It could be more fruitful to investigate whether different etiologies of AKI (pre-renal versus renal versus obstructive, cardiogenic shock, hypovolemic shock, sepsis-related, etc.) affect the predictive accuracy of biomarkers, and to evaluate whether the efficacy of biomarkers is affected by the severity of AKI. These issues can be incorporated into the design of future randomized controlled trials to evaluate the optimal biomarkers for different clinical settings in order to improve the timely diagnosis of AKI. Moreover, further investigations to improve the diagnosis and manage the underlying mechanisms of AKI may help to mitigate the current high mortality rate of patients with AKI.

**Conclusion**

Based on our pairwise meta-analysis of biomarkers to predict AKI, NGAL series had the best diagnostic accuracy for the prediction of AKI, regardless of whether or not they were adjusted by urinary creatinine, especially in medical patients. However, the predictive performance of urinary NGAL was limited in surgical patients, and NGAL/Cr seemed to be the best biomarker in these patients. All of the biomarkers had similar predictive performance in critically ill patients. Future pragmatic clinical trials are warranted to evaluate the real-world predictive accuracy of AKI biomarkers.

**Abbreviations**

AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; CKD: Chronic kidney disease; CI: Confidence interval; DOR: Diagnostic odds ratio; ESRD: End-stage renal disease; HSROC: Hierarchical summary receiver operating characteristic curve; ICU: Intensive care unit; IL-18: Interleukin-18; KDIGO: Kidney Disease: Improving Global Outcomes; KIM-1: Kidney injury molecule-1; L-FABP: Liver-type fatty acid-binding protein; NGAL: Neutrophil gelatinase-associated lipocalin; OR: Odds ratio; PRISMA: Preferred Reporting Items of Systematic Reviews and Meta-Analyses; RIFLE: Risk, injury, failure, loss, ESRD; Scr: Serum creatinine; TIMP-2 x IGFBP-7: Tissue inhibitor of metalloproteinases-2 x insulin-like growth factor-binding protein-7.
Supplementary Information

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Additional file 1: Supplementary appendix.

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Author contributions

VCW chaired the group, conceived and designed the study, performed statistical analysis, and contributed to data collection, data interpretation, and critical revision of the manuscript. HCP, YY, TYC, CCS, CHW, CTH, TJW, and JYC conducted a literature search. HWL, SYC, TMH, YPY, YHL, MXC, CYC, YTC, and YCC performed statistical analysis. HCP SYY, TYU, and VCW wrote the manuscript and performed a critical review of the manuscript. All authors contributed to subsequent drafts and examined the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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