Am J Transl Res 2021;13(11):12141-12151
www.ajtr.org /ISSN:1943-8141/AJTR0137789

Review Article

Serum fibroblast growth factor 23 for early detection of acute kidney injury in critical illness

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Received July 28, 2021; Accepted October 12, 2021; Epub November 15, 2021; Published November 30, 2021

Abstract: Background: Serum fibroblast growth factor 23 (FGF23) is associated with acute kidney injury (AKI) and mortality in patients with critical illnesses. However, the accurate predictive performance of FGF23 on AKI remains inconclusive. Methods: Meta-analysis was performed using data sources including PubMed, Web of Science, EMBASE, and Cochrane (until June 1, 2021). Cohort or observational studies including patients with AKI and serum FGF23 level as the index test were included. The primary outcome was the AKI detective accuracy. This study has been registered in PROSPERO (CRD42021249930). Results: Eleven studies with 1946 patients in seven countries were included. Across all settings, the sensitivity and specificity for serum FGF23 levels to predict AKI were 82% (95% CI, 66-91%) and 77% (95% CI, 67-85%), respectively. The diagnostic odds ratio of FGF23 was 15.51 (95% CI, 4.89-49.19), with the pooled positive likelihood ratio of 3.62 (95% CI, 2.25-5.83) and a negative likelihood ratio of 0.23 (95% CI, 0.11-0.50). The area under the receiver operating characteristic curve to detect AKI was 0.86 (95% CI, 0.82-0.88). C-terminal FGF23 had a better performance than intact FGF23. Conclusions: Plasma FGF23 is a valuable biomarker for incident AKI in critically ill patients. Comparisons of FGF23 with other biomarkers in AKI still need more studies to prove.

Keywords: Acute kidney injury, fibroblast growth factor 23, diagnosis, meta-analysis

Introduction

Acute kidney injury (AKI) is a frequent complication of critical illness, with a prevalence varying from 5% in hospitalized patients to 30-50% in patients from intensive care units or after cardiac surgery [1]. AKI is frequently associated with high mortality and prolonged hospitalization [2]. Therefore, quick, accurate, early, and appropriate biomarkers for predicting or diagnosing AKI are very important for early therapeutic strategies. Serum creatinine (SCr) level is widely used to diagnose AKI, but SCr level does not increase until half the estimated glomerular filtration rate (eGFR) has been lost. Besides, SCr can be affected by factors including sex, hydration status, and muscle mass [3]. Moreover, serum or urinary biomarkers such as cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) [4], interleukin-18 (IL-18) [3], n-acetyl-β-(D)-glucosaminidase, etc., have been studied to predict or diagnose AKI [5]. However, current findings are inconclusive or not widely used. Moreover, anuria during AKI sometimes limits the use of urine biomarkers [6]. Considering the limitations, there is an urgent need to find other early diagnostic biomarkers for the synthetic detection of AKI.

Fibroblast growth factor 23 (FGF23) is an osteocyte-derived phosphaturic hormone that increases urinary phosphate excretion and decreases 1,25-dihydroxy vitamin D levels [7]. Metabolism of FGF23 included the cleavage of bioactive intact FGF23 (iFGF23, 30 kD) into

C-terminal (cFGF23, 12 kD) and N-terminal (18 kD) fragments. FGF23 could be cleared by kidneys through filtration and catabolism. As early as 2010, Leaf et al. found that circulating FGF23 levels were increased in AKI [8]. In recent years, FGF23 was reported to be positively associated with the risk of AKI and mortality in critically ill patients [9-11]. Elevated FGF23 levels also could predict or detect AKI [11]. However, inconclusive results raised question about performances of FGF23 across clinical settings or in different FGF23 types. Therefore, this systematic review and meta-analysis were performed to explore current evidence supporting the role of FGF23 in AKI detection.

Material and methods

This study was carried out according to MOOSE (Meta-analysis of Observational Studies in Epidemiology) reporting criteria (Table S1) [12] and has been registered in PROSPERO (CRD42021249930).

Literature search

Authors (CX and ZL) performed a literature search using PubMed, MEDLINE, EMBASE, Web of Science, and Cochrane database (up to April 30th, 2021). The search terms (both as medical subject headings and combined free text terms) were: ("fibroblast growth factors" OR "fibroblast growth factor 23" OR "FGF-23" OR "FGF 23") and ("acute kidney injury" OR "acute renal failure" OR "acute tubular necrosis" OR "contrast-induced nephropathy" OR "AKI"). We also reviewed references of included articles or reviews for other eligible studies.

Study selection

Two authors (CX and ZL) evaluated all the abstracts or full texts of articles independently and screened out studies for eligibility and inclusion. A third reviewer adjudicated the disagreement. Studies were included according to the following criteria: (1) Cohort or observational studies; (2) Including patients with AKI; (3) Serum FGF23 level was the diagnostic indicator; (4) Outcomes of interest were diagnostic accuracy data or 2×2 tables or area under the curve (AUC) with OR without corresponding 95% confidence interval (CI), or there was enough data to calculate the sensitivity and specificity. If duplicate studies were published, the study with more detailed data was included. Exclusion criteria: (1) Case reports, reviews, or basic researches; (2) Studies including patients with chronic kidney disease (CKD) or receiving long-term dialysis, cancer, and pregnancy; (3) Studies without sufficient data. When data were missing, corresponding authors were contacted. The language restriction was English. Abstracts and unpublished studies were included if eligible.

Data collection and methodological quality assessment

Two authors (CX and ZL) independently extracted the following data: the first author, publication year, country, population type, clinical settings, sample size, gender, average age, baseline kidney function, AKI definition, time of FGF23 measurement, FGF23 type, and cut-off value. The fractions of patients with true-positive, false-negative, true-negative, and false-positive results were calculated. The methodological quality of included studies was evaluated by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria. When there were different sensitivity and specificity values for multiple cut-off values in one study, data with the highest Youden index were used.

Statistical analysis

The bivariate mixed-effects regression model was used for meta-analysis of diagnostic test data [13]. The primary outcome was the AKI event based on traditional SCr or urine volume changes. The secondary outcome was the mortality event. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and 95% CIs were obtained based on this model. The hierarchical summary receiver operating characteristic curves were constructed, and the area under the curve (AUROC) was calculated. The I^2 statistic was used to assess the heterogeneity in studies. I^2>50% was considered as remarkable heterogeneity. Significant heterogeneity was explored by meta-regression analysis. Subgroup analysis was conducted by the clinical design, FGF23 type, and ages. A two-sided P value <0.05 was considered statistically significant. Data were analyzed using Stata 12.0 (Stata Corp. LP) with 'Midas' related commands.

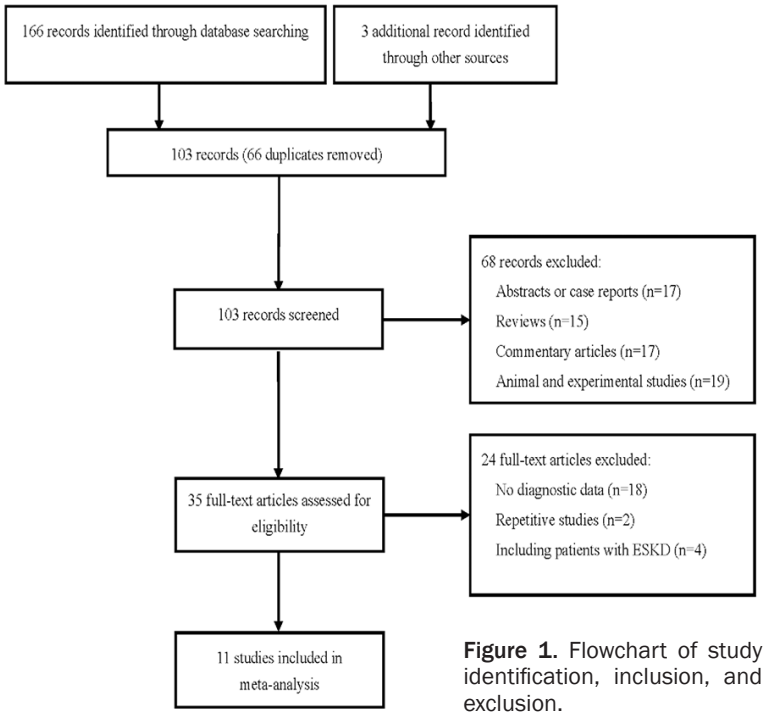

Figure 1. Flowchart of study identification, inclusion, and exclusion.

Results

Literature search

The combined searches identified 169 published studies. After screening abstracts according to the inclusion criteria, we excluded 68 studies. After reviewing the full text of the remaining studies, another 24 studies were excluded (**Figure 1**). Eventually, 11 studies with 1946 patients were included [11, 14-23].

Baseline characteristics

Characteristics of included studies were listed in **Table 1**. Eight of 11 studies could be analyzed by meta-analysis [11, 16-19, 21-23]. Studies came from seven countries and included Caucasians, Asians, and Egyptians. All of them were single-center trials. Sample sizes were from 19 to 859. There were nine prospective cohort studies, one retrospective cohort study [19], and one case-control study [23]. Eight studies were conducted in adults [11, 14, 15, 17-20, 22], and three studies in children [16, 21, 23]. Studies were conducted in different AKI settings: Six studies included AKI after cardiac surgery with cardiopulmonary bypass (CPB), three studies in intensive care unit (ICU) patients [14, 15, 18], one study in patients with contrast-induced nephropathy (CIN) [19], and one study in patients with acute decompensated heart failure (ADHF) [11]. Two studies focused on mortality included AKI patients only [14, 15]. Most studies used cFGF23 assays for FGF-23 measurements, while two studies utilized iFGF23 assays. Most studies used the KDIGO criteria of AKI, while two studies [14, 22] used Acute Kidney Injury Network (AKIN) criteria, and one study [23] used pediatric modified RIFLE class score. Nine studies assessed the diagnostic value of FGF23 in AKI, and four studies [14, 15, 18, 22] assessed FGF23 on mortality in AKI patients. Cut-off values for serum FGF23 varied across studies and were different between iFGF23 and cFGF23 (**Table 1**).

Quality assessment

The quality of included studies according to QUADAS-2 criteria was summarized in **Figure 2**. The scale included the assessment of risk-of-bias and applicability. No patient selection bias was reported, but the study of Ali et al. [23] used a case-control design. However, most studies did not report whether FGF23 test results were interpreted without knowledge of AKI.

Diagnostic value of serum FGF23 in AKI prediction

Across all AKI settings, serum FGF23 level had a pooled sensitivity of 82% (95% CI, 66-91%; **Figure 3**) and specificity of 77% (95% CI, 67-85%). The pooled PLR was 3.62 (95% CI, 2.25-5.83), NLR was 0.23 (95% CI, 0.11-0.50), and the DOR was 15.51 (95% CI, 4.89-49.19). The AUROC was 0.86 (95% CI, 0.82-0.88; **Figure 4**) with the I^2 statistic as 80.66%, indicating high heterogeneity. Deeks' funnel plot asymmetry test (**Figure 5A**) showed no significant publication bias of the results (P=0.307). The sensitivity and specificity of individual studies for serum FGF23 to predict AKI were listed in **Table 2**. Scattergram of the PLR and NLR was shown in **Figure 5B**, which suggested FGF23 as a moderate biomarker for AKI detec-

Table 1. Characteristics of included studies

Author	Year	Country	Age	Clinical Setting	Design	Sample size (n)	Gender male (%)	Age (y)	Baseline eGFR	Definition of AKI	Time of Measurement
Pramong	2020	Thailand	Adults	ADHF	PC	62	26 (41.9%)	70.4±11.8	55.6±26.6	SCr >0.3 mg/dl within 48 hours or >50% in 7 d	24 h after diagnosing ADHF
Li	2018	China	Adults	CIN	RC	202	141 (82%)	59.95±10.56	NA	SCr >0.5 mg/dl or a minimum of 25% increase within 72 h after contrast administration	1 day after PCI
Rygasiewicz	2018	Poland	Adults	ICU	PC	79	51 (65%)	61 (47-75)	93.80 (70.61-109.69)	KDIGO criteria	Within 24 h of ICU admission
Shaker	2018	Egypt	Adults	CPB	PC	80	54 (67.5%)	47.67±12.8	89.17±27.9	SCr >0.3 mg/dl or >50% within 48 hours after surgery	24 h after surgery
Hanudel	2016	USA	Children	CPB	PC	32	18 (56%)	3 (1-7)	141±42	SCr >50% within 48 hours after surgery	Pre-operative
Ali	2013	USA	Children	CPB	NCC	19	8 (60%)	4 (2-7)	81.80±18.73	Pediatric-modified RIFLE class score using eGFR	Pre-operative
Speer	2015	Germany	Adults	CPB	PC	859	589 (68.6%)	63.7±1.46	NA	Acute Kidney Injury Network (AKIN) criteria	24 h before surgery
Fayed	2019	Egypt	Adults	ICU AKI	PC	30	17 (56.7%)	60.7±19	NA	Acute Kidney Injury Network (AKIN) criteria	Within 24 h of diagnosis of AKI
Wu	2018	Taiwan	Adults	ICU AKI	PC	257	167 (65.0%)	65.7±16.6	55.6±41.0	NA	Within 24 h of diagnosis of AKI
Leaf	2016	USA	Adults	CPB	PC	250	143 (57%)	79 (72-83)	50 (41-66)	SCr >0.3 mg/dl within 48 hours or >50% in 7 d	CPB end/postoperative day 1
Volovelsky	2018	USA	Children	CPB	PC	76	42 (55.5%)	0.7 (0.3, 4.7)	96 (68, 122)	KDIGO stages II-III	12-24 h after CPB

AKI, acute kidney injury; CPB, cardiopulmonary bypass; ADHF, acute decompensated heart failure; ICU, intensive care unit; CIN, contrast-induced nephropathy; Y, year; RC, retrospective cohort; PC, prospective cohort; NCC, Nested case-control; n, number; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; NA, not available.

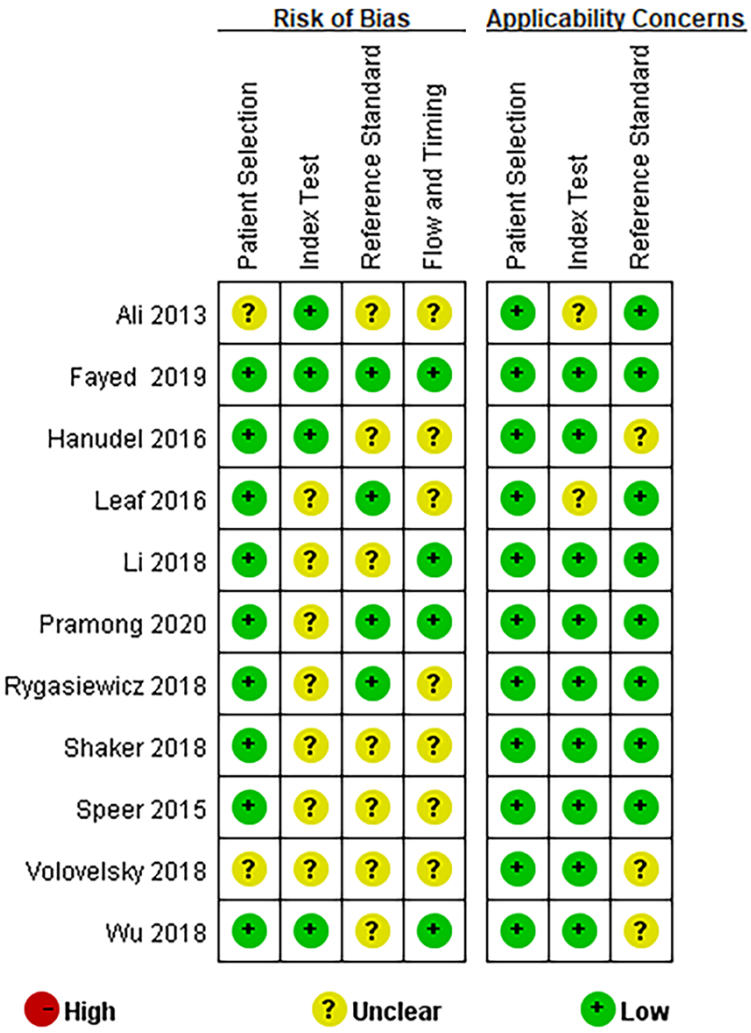

Figure 2. Risk of bias and applicability concerns graph using the QUADAS-2 tool. Key domains: patient selection, index test, reference standard, study flow and timing.

tion. Fagan's nomogram (**Figure 6**) indicated that with a pre-test probability of a positive AKI of 50%, the post-test probabilities of positive and negative AKI were 80% and 20% after the index FGF23 result was acquired.

Subgroup analysis and heterogeneity analysis

Subgroup analyses were performed to report specific test accuracy indexes and explore the heterogeneity source (**Table 3**). The predictive role of cFGF23 level for AKI was moderate (DOR/AUROC, 6.74 (95% CI 3.84-11.86)/0.74± 0.03) but the heterogeneity was low (I^2 26.1%). In contrast, studies for iFGF23 generated a high DOR (68.9) but a high heterogeneity (I^2 94.3%). However, this result was not reliable due to the limited number of studies. DOR of FGF23 in prospective cohort studies was significantly higher compared with that in retrospective studies (13.69 vs. 5.57). Meanwhile, the DOR of FGF23 in children was greater than that in adults (12.88 vs. 9.71). There was no heterogeneity of the results in children while the heterogeneity in adults was high (I^2 0% vs. 80.3%). Moreover, the DOR of FGF23 in patients after CPB was 22.6 (95% CI 4.39-116.69). Only one study [19] showed FGF23 performance in patients with CIN (AUROC, 0.64, 95% CI 0.52-0.77), one study [18] in ICU patients (AUROC 0.81), and one study [11] in patients with ADHF (AUROC 0.81, 95% CI, 0.73-0.89), making data merging impossible. Meta-regression analysis further found that the heterogeneity of results mainly came from the FGF23 type, study design, and ages (P all <0.05).

Value of FGF23 on mortality prediction

In-hospital mortality was reported in four studies [14, 15, 18, 22] in adults. Among them, two studies [14, 15] included AKI patients only. There were insufficient data to merge for the prognosis of AKI. Two studies [18, 22] focused on cFGF23, one [14] on iFGF23, and one [15] on both of them. The AUROC of cFGF23 on mortality was 0.69 in AKI patients, and 0.8 and 0.85 in critically ill patients, respectively. The AUROC of iFGF23 on mortality was 0.5 and 0.88 respectively in AKI patients.

Discussion

Principal findings

Biomarkers for the early diagnosis of AKI have been studied for decades. Multiple biomarkers

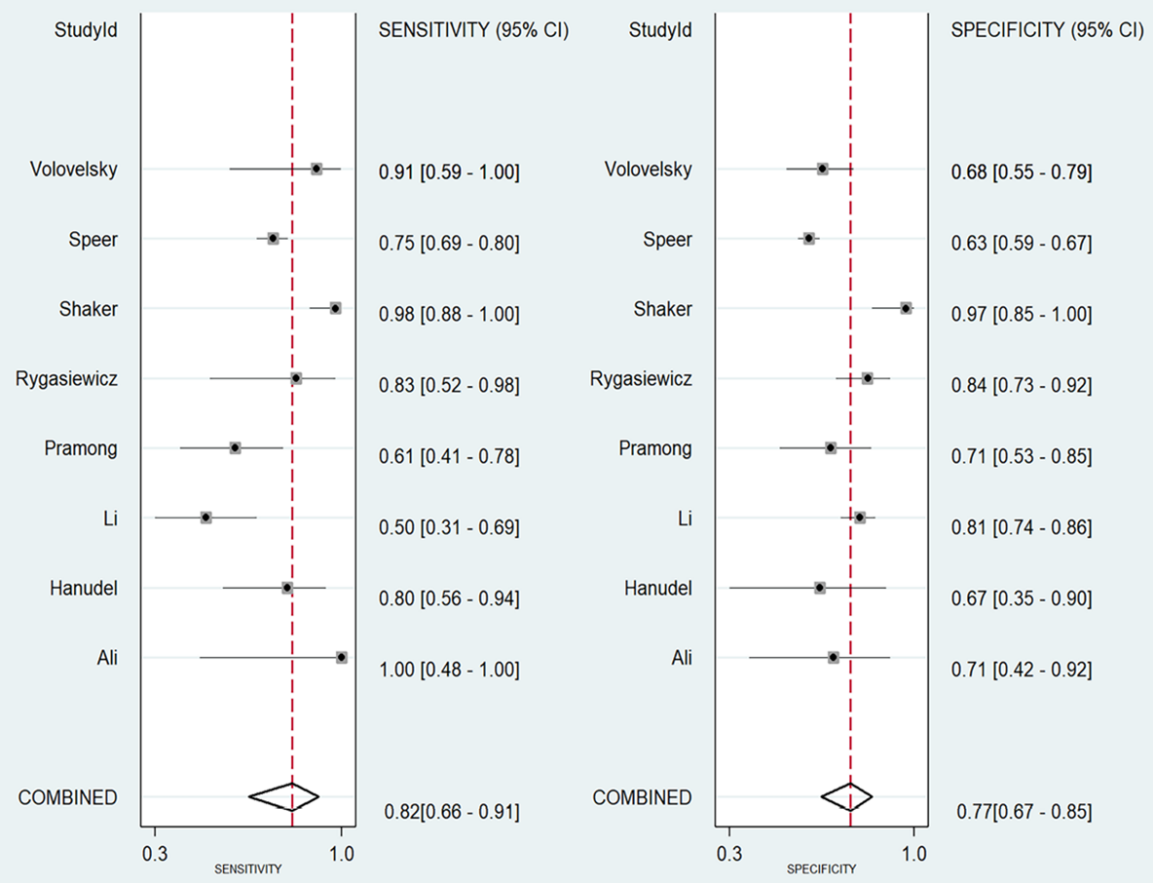

Figure 3. Forest plot of the pooled sensitivity and specificity of serum FGF23 level in predicting AKI across all settings.

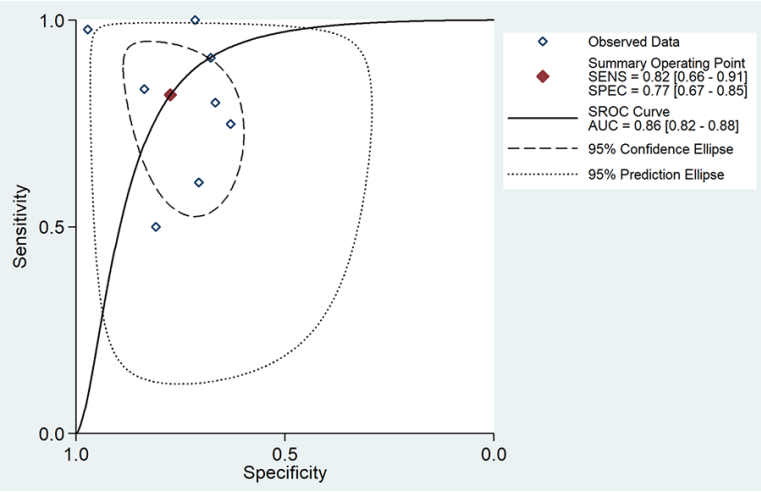

Figure 4. Hierarchical summary receiver operating characteristic plot of serum FGF23 level to predict AKI across all settings. The curve was represented by the straight line; each of the analyzed studies is represented by a diamond. The point estimate to which summary sensitivity (SENS) and specificity (SPEC) correspond was represented by the diamond shape, and the respective 95% CIs by the dashed line, whereas the 95% confidence area in which a new study would be located was represented by the dotted line. AUC, the area under the curve.

have been investigated such as KIM-1, NGAL, liver-type fatty acid-binding protein (LA-BP), and IL-18 [3]. This meta-analysis assessed the diagnostic performance of the relative new biomarker, serum FGF23, for detecting AKI in patients with critical illnesses. Our results showed that the performance of serum FGF-23 level was suboptimal but promising, with a high sensitivity of 82% and a moderate specificity of 77%. The overall predictive accuracy was good with an AUROC of 0.86. In addition, the detection accuracy of FGF23 on mortality was evaluated. However, the AUROC results are moderate and need more studies to prove in the future.

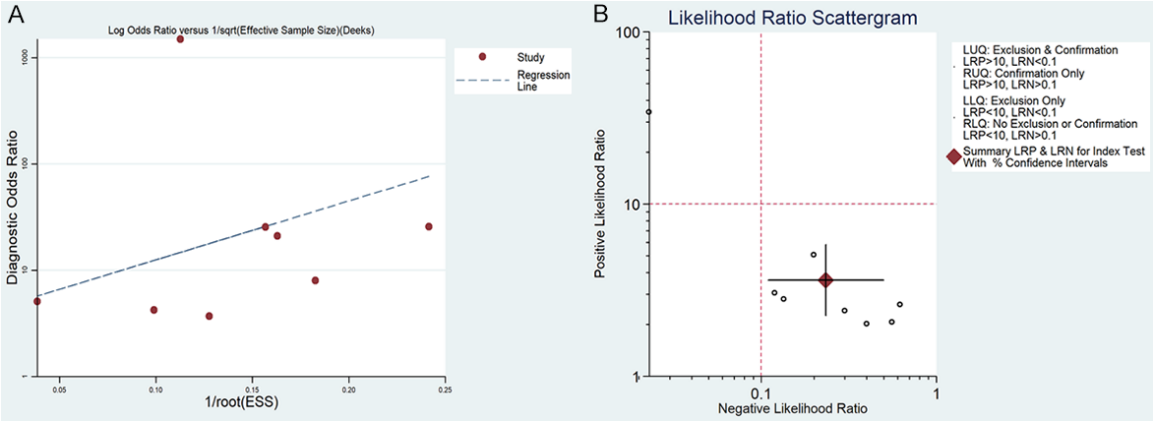

Figure 5. Deeks' funnel plot and scattergram of the positive likelihood ratio and negative likelihood ratio.

Table 2. Sensitivity and specificity of individual studies for serum FGF23 to predict AKI

Study	Year	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV
Ali	2013	5	4	0	10	100%	71%	56%	100%
Hanudel	2016	16	4	4	8	80%	67%	80%	67%
Li	2018	15	33	15	139	50%	81%	31%	90%
Pramong	2020	17	10	11	24	61%	71%	63%	69%
Rygasiewicz	2018	10	11	2	56	83%	84%	48%	97%
Shaker	2018	44	1	1	34	98%	97%	98%	97%
Speer	2015	173	233	58	396	75%	63%	43%	87%
Volovelsky	2018	10	21	1	44	91%	68%	32%	98%

TN, true negative; TP, true positive; FN, false negative; FP, false positive; PPV, positive predictive value; NPV, negative predictive value.

Comparison with other studies

Studies have proven that elevated FGF23 levels could predict the risk of mortality, cardiovascular events, and renal events in patients with CKD or ESKD [24]. However, only a few studies evaluated the diagnostic role of FGF23 in AKI. The first evidence was a case report in 2010 by Leaf et al. reporting that circulating FGF23 levels were increased in AKI [8]. Subsequent studies confirmed the initial observation and included studies performed in children and adults across various AKI settings. As we know, this meta-analysis was the first one trying to summarize the existing evidence.

Possible interpretations

Increased FGF23 production could be affected by multiple factors in kidney diseases [25, 26]. Studies found that the increase of FGF23 in AKI could be independent of serum phosphate, parathyroid hormone, and vitamin D, but was associated with reduced kidney clearance, increased production in bones, and extra-skeletal tissues like liver and spleen, inflammation factors, and excessive erythropoietin [25, 27-34]. Moreover, FGF23 itself could increase inflammation and result in a vicious circle in AKI [27]. Therefore, abnormal levels of serum FGF23 in the early AKI stage are evidential, which makes FGF23 a credible biomarker of AKI. However, multiple mechanisms of increasing FGF23 could be a double-edged sword. For example, the diagnostic ability of FGF23 on AKI also could be weakened by the multiple factors mentioned above. In comparison with other biomarkers, there are few pieces of evidence. FGF23 was found to be superior to urinary kidney injury biomarkers like urinary NGAL and KIM-1 [20].

According to the subgroup analysis, we found that the FGF23 level had better diagnostic accuracy in children compared with adults. This might be attributed to the complicated comorbid conditions (such as cardiovascular events, CKD, and mineral disorder) that were more prevalent in adults and affect FGF23 concentrations. The value of FGF23 in prospective cohort studies was significantly higher than that in retrospective studies. This could be explained by the prospective design which is

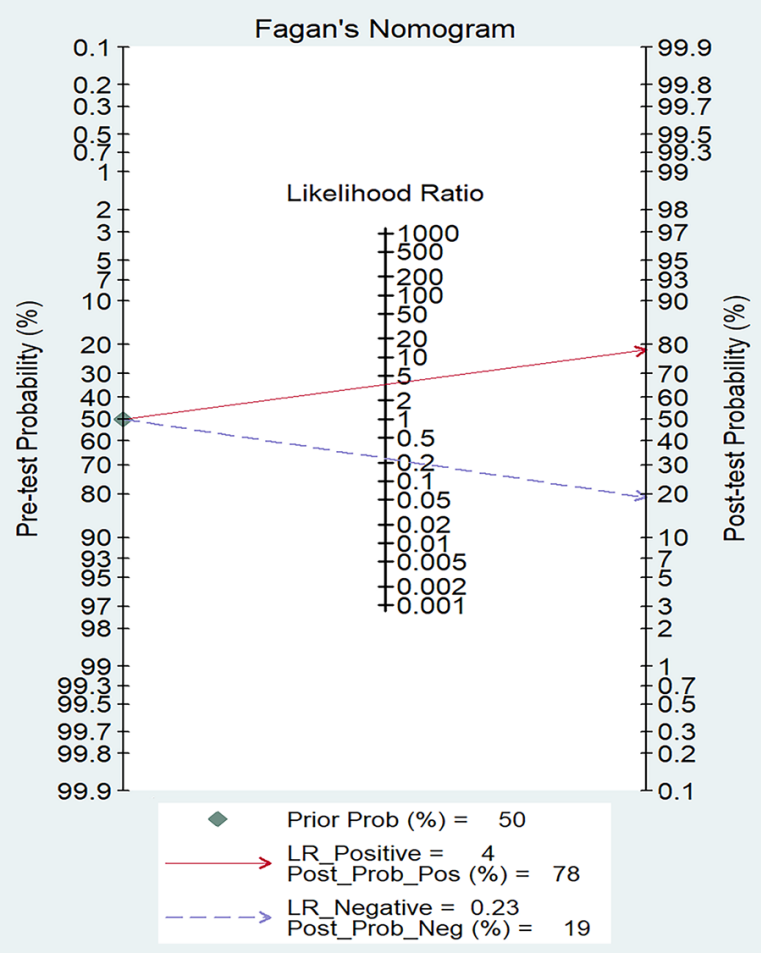

Figure 6. Fagan's nomogram plot analysis to evaluate the serum FGF23 for the detection of AKI. In each plot, a vertical axis on the left showed the fixed pre-test probability. Using the likelihood ratio in the middle axis, post-test probability (patient's probability of having AKI after the index FGF23 result was known) was acquired. With a pre-test probability of a positive AKI of 50%, the post-test probability of positive AKI gave positive and negative results of 80% and 20%.

better in diagnostic tests by avoiding bias. The subgroup results in CPB were good with a high DOR. Studies have shown that the severity of CPB time or heart failure could increase the elevated degree of serum FGF23 [11]. Therefore, the predictive value of FGF23 in patients after CPB may be better. However, more studies are needed to prove this hypothesis.

Results of the AKI detection varied between the cFGF23 and iFGF23 but were not significantly different. The immunometric assay for measurement of cFGF23 detects both the intact and c-terminal cleavage molecules, referred to as 'total FGF23', while the iFGF23 assay detects only the intact product [35]. About 64% of the included studies in this meta-analysis reported cFGF-23 levels exclusively. Although both cFGF23 and iFGF23 rose in AKI, cFGF23 levels were about 25-75 fold higher and more sensitive than iFGF23 (only two-fold) [20]. These data were consistent with significant increases in both the production and cleavage of FGF23 in AKI, which was different from CKD and ESKD (increased FGF23 production and less cleavage due to the loss of FGF23 catabolism in kidneys). Although the clinical application of cFGF23 or iFGF-23 still needs more studies to investigate, cFGF23 may be a more suitable indicator for detecting AKI.

On the other side, whether increased FGF23 is simply a biomarker of AKI or directly contributes to kidney injury or mortality is still unsolved. Smith et al. [36] found that FGF23 produced in kidneys could activate myofibroblasts and fibrogenesis via transforming growth factor β related pathways in an obstructed kidney model. Thus, locally produced FGF23 by injured kidneys could aggravate kidney damage.

The temporal change of FGF23 levels is of great importance. FGF23 levels were increased from the first or second hour after AKI in a folic acid induced mouse model [27]. Hanudel et al. [21] showed that plasma cFGF23 and iFGF23 levels increased dramatically within four hours in AKI patients after CPB, and cFGF23 peaked at 24 hours while iFGF23 peaked at four hours. Leaf et al. [20] found that the plasma cFGF23 level increased significantly from the preoperative period to the end of CPB, but almost peaked at day 1 post-operation. The detectable elevation of plasma FGF23 was shown with a relatively broad window, which might be associated with AKI severity and multiple pathways, such as renal ischemia-reperfusion injury and inflam-

Table 3. Pooled diagnostic accuracy of FGF23 in various settings

Setting	N	Sensitivity	95% CI		Specificity	95% CI		PLR	95% CI		NLR	95% CI		DOR	95% CI		I^2	AUROC	SE
cFGF23	6	0.75	0.7	0.8	0.655	0.622	0.688	2.61	1.95	3.5	0.4	0.031	0.51	6.744	3.84	11.86	0.261	0.735	0.029
iFGF23	2	0.79	0.68	0.87	0.84	0.78	0.88	8.73	0.2	385.7	0.13	0.002	8.91	68.9	0.15	31598.4	0.943	NA	NA
Prospective studies	6	0.78	0.73	0.82	0.67	0.63	0.7	2.93	1.93	4.47	0.29	0.17	0.51	13.69	4.59	40.85	0.768	0.87	0.08
Retrospective studies	2	0.57	0.39	0.74	0.8	0.74	0.86	2.71	1.8	4.08	0.44	0.11	1.77	5.57	1.52	20.4	0.207	NA	NA
Adults	5	0.75	0.7	0.79	0.69	0.66	0.72	3.06	1.85	5.07	0.39	0.23	0.64	9.71	3.58	26.31	0.803	NA	NA
Children	3	0.86	0.71	0.95	0.68	0.58	0.78	2.78	2	3.86	0.24	0.11	0.54	12.88	3.91	42.36	0	0.7	0.24
CPB	5	0.8	0.75	0.84	0.65	0.62	0.69	2.79	1.78	4.4	0.19	0.08	0.48	22.6	4.39	116.69	0.786	NA	NA

Abbreviations: N, number of studies; AUROC, area under the receiver operating characteristic curve; CPB, cardiopulmonary bypass; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; SE, standard error of AUROC; NA, not available.

mation cytokine release across different clinical settings.

Limitations

There were several limitations of this study. First, there was significant heterogeneity among the included studies in terms of population characteristics, definitions of AKI, and FGF23 assays. However, part of the heterogeneity could be illustrated by the FGF23 type, the study design, and ages. Second, all included studies used SCr or urine volume which was not ideal gold standard as the reference standard for AKI diagnosis. Third, we could not compare the predictive value of the FGF23 level at different times due to limited data. Fourth, although there was no significant publication bias in the results, the exclusion of non-English language citations may lead to potential bias. Last, it was important to determine the cut-off value between AKI and the non-AKI groups for a predictive biomarker. However, we could not determine the ideal cut-off values for serum FGF23 results because of the various cut-off values across the included studies and there were few raw data to map out ROCs.

Conclusions

In summary, this study indicates that plasma FGF23 especially cFGF23 may serve as a promising predictive biomarker of AKI across different clinical settings. Further studies based on a panel of biomarkers and stratified AKI subgroups are required to optimize the clinical use of serum FGF23. Comparison of FGF23 with other biomarkers in AKI also needs more studies to prove in the future.

Acknowledgements

We thank Dr. Chenchen Zhou and Dr. Daoji Xue for their help and guidance. This work was supported by the National Nature Science Fund of China (No. 81970640, 81873595, 81370844), Shanghai science and technology talent program (19YF1450300), and Shanghai Municipal Key Clinical Specialty (shslczdzk02503).

Disclosure of conflict of interest

None.

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Table S1. MOOSE checklist for meta-analyses of observational studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	3
5	Type of study designs used	4
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	4
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	4
14	Method of addressing articles published in languages other than English	4
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	4
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	4
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	5
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5
24	Provision of appropriate tables and graphics	6
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	6, 7
26	Table giving descriptive information for each study included	6
27	Results of sensitivity testing (eg, subgroup analysis)	7
28	Indication of statistical uncertainty of findings	7
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10
30	Justification for exclusion (eg, exclusion of non-English language citations)	10
31	Assessment of quality of included studies	8
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8, 9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	8, 9
34	Guidelines for future research	9
35	Disclosure of funding source	11

From: Stroup DF, Berlin JA, Morton SC, et al., for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology. A proposal for reporting. JAMA 2000; 283: 2008-2012. Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.