Review

Prediction of Acute Kidney Injury by Fibroblast Growth Factor 23 (FGF-23) in Adult Patients, A Meta-analysis Study

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Introduction. The aim of the current meta-analysis was to assess the predictive value of blood fibroblast growth factor 23 (FGF-23) for acute kidney injury (AKI) in adult patients.
Methods. We retrieved relative publications from electronic databases including the Cochrane Library, PubMed, Google Scholar, Scopus, web of science, and Wanfang Data from their inception to Aug 2022.
Results. This meta-analysis study included seven prospective cohort trials comprising 1,655 adult patients. The overall pooled area under the receiver operating characteristic curve (AUC) from seven studies was 0.83 (95% CI: 0.80 to 0.86). Significant heterogeneity was identified (Q = 9.82, P = .004, I^2 = 80). Pooled sensitivity and specificity were 0.75 (95% CI: 0.59 to 0.87) and 0.77 (95% CI: 0.65 to 0.87), respectively. Pooled positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 3.3 (95% CI: 1.8 to 6.3), 0.32 (95% CI: 0.16 to 0.63), and 10 (95% CI: 3 to 38); respectively. Moreover, our sensitivity analysis showed that when a trial from Asia was excluded, the predictive value of FGF-23 was declined.
Conclusion. Our results of meta-analysis of seven prospective cohort trials suggested that blood FGF-23 is a candidate indicator for the prediction of AKI in adult patients. Results of future large and well-designed clinical trials are still needed.

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INTRODUCTION

Hitherto, effective therapies for acute kidney injury (AKI); a severe form of kidney disorder with high mortality,[1] are still lacking.[2] Accordingly, its early diagnosis, which could prevent its progression to severe stages, may be a promising approach to decrease its mortality and morbidity.[2] The main diagnostic criteria for AKI is the serum creatinine level.[1] However, the increase of serum creatinine is relatively late during the development of AKI.[1] Consequently, effective approaches for diagnosis of AKI at its early stage or the prediction of AKI are highly desired.

Fibroblast growth factor 23 (FGF-23) is a potent indicator for the early diagnosis of AKI in critically ill patients according to the recent meta-analysis research conducted by Sun *et al.*, which included eight studies in 2021.[3] Nevertheless, language restriction in their search strategy might have limited the inclusion of potent eligible trials. Moreover, data from three trials of pediatric patients were added to five studies from adult patients in that meta-analysis. Since the pathophysiological characteristics of children are different with adults, pooled results from adults and children may limit their use in clinical practices. Therefore, we performed a meta-analysis study with a focus on adult patients, and two new trials with 372 adult

patients were included in the present study.[4,5]

MATERIALS AND METHODS

As a systematic review and meta-analysis of a diagnostic accuracy test, no ethical approval was needed. The present research followed the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guideline.[6]

Search Strategies

A literature review was conducted in August 2022 by using the following search strategy: ("acute kidney injury" OR "AKI" OR "acute renal failure" OR "ARF" OR "acute kidney disease" OR "acute kidney stress" OR "renal insufficiency") AND ("fibroblast growth factor 23" OR "FGF-23"). Data sources including the Cochrane Library, PubMed, Google Scholar, Scopus, web of science, and Wanfang Data were electronically searched. No language or publication status restrictions were imposed.

Study Selection

Retrieved studies were screened by two reviewers separately. Duplicated papers were removed. The remaining studies were then screened based on titles and abstracts, and the entire text was reviewed if it attained the eligibility criteria and further included in this meta-analysis. Differences on study eligibility were resolved by consensus. Patients with AKI were those who fulfilled the Kidney Disease: Improving Global Outcomes (KDIGO), increase in serum creatinine level of > 0.3 mg/dL within 48h, Acute Kidney Injury Network (AKIN) or RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria.[7-9]

Inclusion Criteria

Inclusion criteria were: 1) studies that solely included adult population (age > 18 years), 2) prospective or retrospective observational, or cohort studies, 3) trials that investigated the impact of FGF-23 on the prediction of AKI in adult patients, and 4) if the data of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) could be obtained.

Exclusion Criteria

Studies that enrolled patients with preexisting chronic kidney disease at stages 3 to 5, and malignancies were excluded.

Quality Evaluation

Two reviewers assessed the methodological quality of eligible trials independently, by using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. [10]

Data Extraction

A standardized data collection sheet was used to extract predefined data from the included trials by two investigators, independently. If multiple values of sensitivity or specificity were reported in one study, the value with the highest Youden index was retrieved. Before analysis, the extracted data were reviewed by two authors. Disagreements on the extracted data were resolved by consensus.

Statistical Analysis

STATA/SE 12.0 for Windows 32-bit (StataCorp LP, TX, USA) was used for statistical analysis. The numbers of TP, FP, TN, and FN were calculated using Review Manager (version 5.3.5, for 32-bit Windows). We reported the pooled diagnostic accuracy indicators with 95% confidence interval (CI) in this meta-analysis. According to the area under the receiver operating characteristic curve (AUC) value, results were interpreted as excellent (0.90 to 1.0), good (0.80 to 0.89), fair (0.70 to 0.79), poor (0.60 to 0.69), and useless values (0.50 to 0.59).[11] Homogeneity between trials were evaluated by using the Cochran Q statistic. Significant heterogeneity was defined as $P \leq .10$. We also created I^2 statistics to test inconsistency across trials. A high inconsistency was defined as an I^2 statistic higher than 50%. Publication bias was investigated by Deeks' funnel plot asymmetry test. Sensitivity and subgroup analyses were also performed.

RESULTS

Search Results

A total of 9,927 articles were yielded at our initial electronic search. Ultimately, seven trials[4,5,12-16] were retrieved after two steps and following the screening. The screening procedure is shown in Figure 1.

Characteristics of Trials

As it is shown in Table 1, the retrieved seven

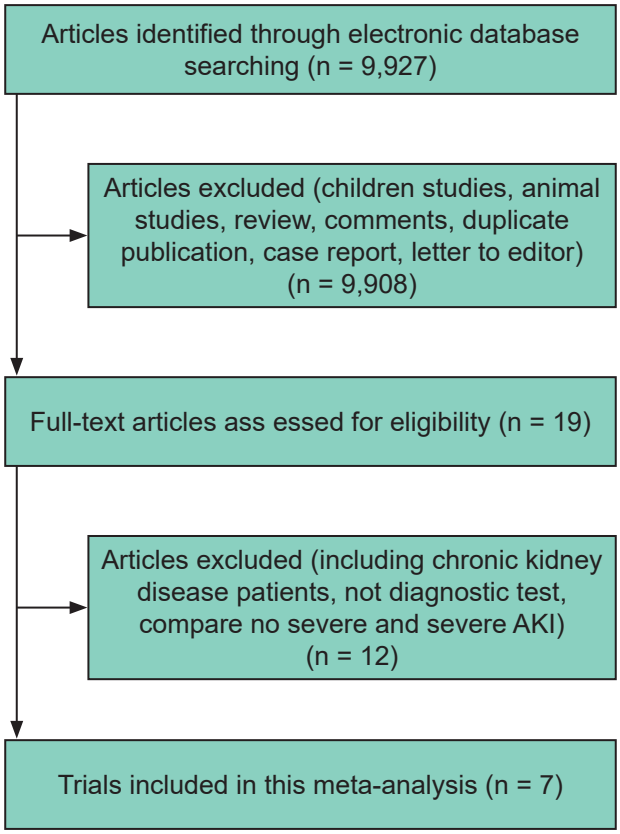

Figure 1. Flowcharts of Article Evaluation

studies comprising 1,655 adult patients were published between 2015 and 2022, and their population sizes ranged from 62 to 860 (median 162). Patients of four trials suffered from heart disorders.[12,13,15,16] Other three studies investigated the incidence of AKI in acute respiratory distress syndrome,[5] sepsis,[4] or critically ill patients.[14] Almost half of the seven trials had enrolled fewer than 80 patients.[14-16] The included studies were conducted in Europe,[12,14] or Asia.[5,13,15,16] Three trials[4,5,13] with a total of 574 patients were conducted in China. Four studies[4,5,14,16] employed the KDIGO criteria, one trial[12] the AKIN criteria, and two other studies[13,15] used serum creatinine values for the diagnosis of AKI. Four studies[5,12,14,16] measured plasma FGF23 while three trials,[4,13,15] detected serum FGF23 by using ELISA kits. All of the ELISA kits were produced by American companies (Table 1).

Risk of Bias Evaluation

We evaluated the risks of bias in included trials by using the QUADAS-2 tool. The detailed information of included studies is provided in additional files (Table S1).

FGF-23 Performance

First, we pooled sensitivity and specificity by

Table 1. Characteristics of 7 Prospective Cohort Studies Included

First author, Year of publication	Location	Age (year)	Population (AKI)	Period	AKI Diagnostic Criteria	FGF-23 Sample, Measurement
Speer, 2015	Germany	63.7 ± 1.46	859 (231)	2010/01 to 2011/03	AKIN criteria	Plasma, ELISA kit (Immutopics, Inc., USA)
Li,2018	China	59.95 ± 10.56	202 (30)	2015/04 to 2015/09	SCr >0.5mg/dL or ≥ 25% vs. baseline within 72 h after contrast administration	Serum, intact FGF23 ELISA kit (R&D, USA)
Rygasiewicz, 2018	Poland	61 (47 to 75)	79 (12)	2016/11 to 2017/05	KDIGO criteria	Plasma, C-terminal and intact FGF-23 ELISA kits (Immutopics, Inc., USA)
Shaker, 2018	Egypt	47.67 ± 12.8	80 (45)	2015/11 to 2017/01	SCr >50% vs. preoperative values, or >0.3 mg/dl during the first 48 h after operation	Serum, ELISA kit (Immutopics Inc., USA)
Pramong, 2021	Thailand	70.4 ± 11.8	62 (28)	2018/08 to 2019/01	KDIGO criteria (use serum creatinine criteria only)	Plasma, human c-FGF23 ELISA kit (Quidel, USA)
Xu, 2021	China	50 to 70	210 (86)	2018/09 to 2020/10	KDIGO criteria (SCr≥0.3 mg/dL within 48 hours; or ≥ 1.5 fold baseline eGFR)	Plasma, ELISA kit (R&D, USA)
Pei, 2022	China	72 (58.83)	162 (60)	2018/05 to 2020/11	KDIGO criteria	Serum, ELISA kit (R&D,USA)

Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury network; FGF-23, fibroblast growth factor 23; SCr, serum creatinine; KDIGO, Kidney Disease: Improving Global Outcomes

Table S1. Risk of Bias Evaluation by QUADAS-2 Tool

Risk of Bias	Speer, 2015	Li, 2018	Rygasiewicz, 2018	Shaker, 2018	Pramong, 2021	Xu, 2021	Pei, 2022
Patient Selection	Low	Low	Low	Low	Low	Low	Low
Index Test	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Reference Standard	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Study Flow and Timing	Unclear	Low	Unclear	Unclear	Low	Unclear	Low
Applicability Concerns							
Patient Selection	Low	Low	Low	Low	Low	Low	Low
Index Test	Low	Low	Low	Low	Low	Low	Low
Reference Standard	Low	Low	Low	Low	Low	Low	Low

Abbreviations: QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2

using Stata software's midas orders. As shown in Figure 2, the impact of serum or plasma FGF-23 on the prediction of AKI were analyzed in the included 7 trials. The pooled sensitivity and specificity were 0.75 (95% CI: 0.59 to 0.87) and 0.77 (95% CI: 0.65 to 0.87), respectively. As high heterogeneity was detected between included studies (Figure 2), we performed sensitivity analyses to investigate the potent source of heterogeneity. We noticed that one study[15] had significantly high sensitivity and specificity value and our sensitivity analyses revealed that when that trial[15] was excluded, the heterogeneity may not be improved (Table 2). Nevertheless, we found that pooled sensitivity (0.66 (95% CI: 0.58 to 0.74)) and specificity (0.72 (95% CI: 0.65 to 0.79)) were reduced when the mentioned trial was excluded (Table 2). In parallel, the pooled AUC values were good (0.83 (95% CI: 0.80 to 0.86), Figure 3) and fair (0.74 (95% CI: 0.70 to 0.78)), respectively, before and after excluding above mentioned trial.[15] We noticed that the average age of the patients in Shaker's[15] study was younger than other six trials. To determine whether FGF-23 performs better in middle-aged or younger people than it does in elderly patients, future trials will be necessary.

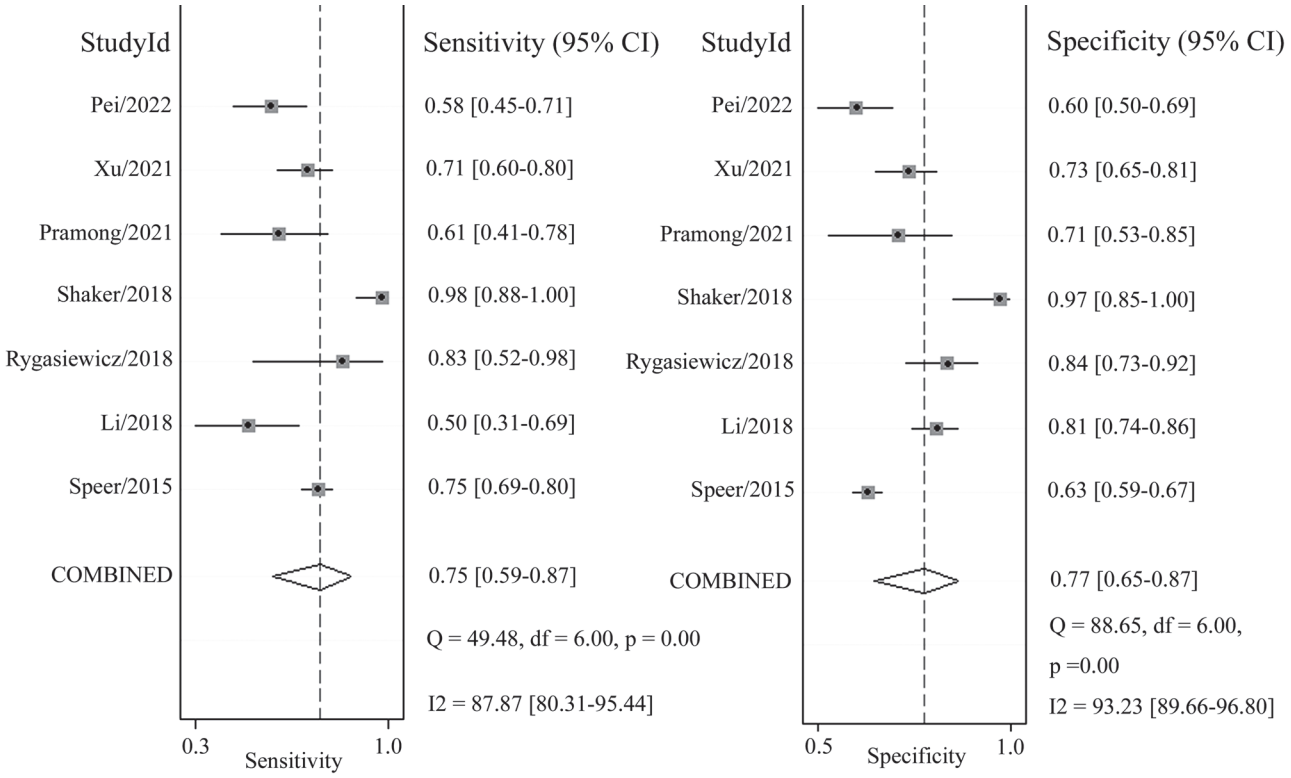

Figure 2. Forest Plots of Blood FGF-23 Predicting AKI

Table 2. Results of Sensitivity Analyses

Item	Before	After
Sensitivity	0.75 (95% CI: 0.59 to 0.87)	0.66 (95% CI: 0.58 to 0.74)
Heterogeneity	(Q = 49.48, *P* = .00, I^2 = 87)	(Q = 16.86, *P* = .00, I^2 = 70)
Specificity	0.77 (95% CI: 0.65 to 0.87)	0.72 (95% CI: 0.65 to 0.79)
Heterogeneity	(Q = 88.65, *P* = .00, I^2 = 93)	(Q = 36.03, *P* = .00, I^2 = 86)
AUC	0.83 (95% CI: 0.80 to 0.86)	0.74 (95% CI: 0.70 to 0.78)
Heterogeneity	(Q = 9.82, *P* = .004, I^2 = 80)	(Q = 12.74, *P* = .001, I^2 = 84)
PLR	3.3 (95% CI: 1.8 to 6.3)	2.4 (95% CI: 1.8 to 3.1)
Heterogeneity	NA	NA
NLR	0.32 (95% CI: 0.16 to 0.63)	0.47 (95% CI: 0.37 to 0.59)
Heterogeneity	NA	NA
DOR	10 (95% CI: 3 to 38)	5 (95% CI: 3 to 8)
Heterogeneity	NA	NA

Abbreviations: AUC, the area under the receiver operating characteristic curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio, NA, not available

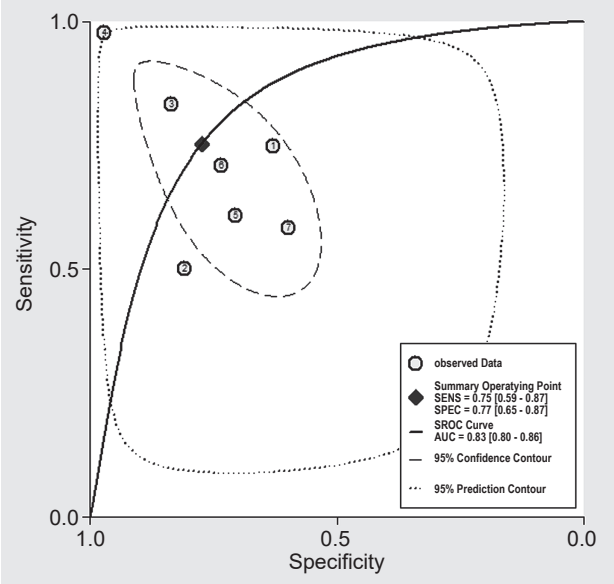

Figure 3. Summary ROC Plots of Blood FGF-23 Predicting AKI

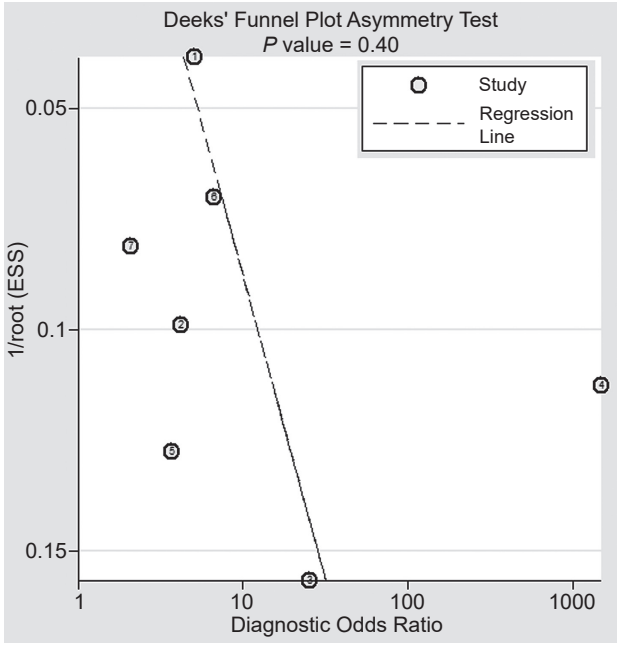

Figure 4. Deeks' Funnel Plots of Included Trials

As shown in Figure 4, the Deeks' funnel plot asymmetry test showed no significant publication bias (*P* = .40). However, the asymmetry distribution of trials in the figure makes it important to take publication bias into account.

Subgroup Analysis

Subgroup analysis was performed to investigate the effect of trial's location on diagnostic accuracy indicators. Our results showed that the pooled sensitivity, specificity, and AUC values of 5 trials from Asia were 0.74 (95% CI: 0.49 to 0.89), 0.80 (95% CI: 0.62 to 0.91), and 0.84 (95% CI: 0.81 to 0.87); respectively. The pooled positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 3.7 (95% CI: 1.4 to 9.8), 0.33 (95% CI: 0.13 to 0.83), and 11 (95% CI: 2 to 72); respectively. We found that the pooled diagnostic accuracy indicators of 5 trials from Asia with 716 patients were similar to the pooled results from both Asia and Europe. Since only two studies were conducted in Europe, we were unable to perform subgroup analysis on trials from Europe, as the Stata software could not conduct the analyses.

DISCUSSION

Results of the current meta-analysis which

included 7 prospective cohort trials with 1,655 adult patients, showed that blood FGF-23 may be an indicator for the prediction of AKI in adult population. However, the high heterogeneity between trials should be taken into account. Further larger and well-designed clinical trials are required to assess the significance of FGF-23 in the prediction of AKI in adult patients.

Mechanisms of FGF-23 Expression Regulation

FGF-23 is an important endogenous hormone that regulates phosphate homeostasis as well as metabolism of vitamin D via binding to a co-receptor.[17-19] Disorders of phosphates and vitamin D metabolism are common both in chronic kidney disease (CKD) and AKI[20,21] and increased levels of FGF-23 could be found in these disorders. [20,22,23] The major mechanism regulating FGF23 expression was reported in animal and *in vitro* studies. By using a vitamin D receptor knockout mice, Christov *et al.* found that the increase in FGF-23 level in AKI was independent of vitamin D signaling.[23] Increased erythropoietin in AKI may induce bone marrow FGF-23 expression.[24] Furthermore, the increased circulating FGF-23 levels in rodent AKI model could be partially inhibited by blocking the erythropoietin receptor.[24] This results suggest that regulation of FGF-23 expression in bone marrow was mediated by erythropoietin and its receptor. Additionally, FGF-23 production from bone and bone marrow could be stimulated by exogenous glycerol-3-phosphate, a byproduct of glycolysis, through local glycerol-3-phosphate acyltransferase-mediated lysophosphatidic acid synthesis in mice.[25] Interleukin-6 (IL-6) induces FGF-23 expression in AKI via soluble IL-6 receptor-mediated FGF-23 promoter activation.[26] A recent study showed that orphan nuclear receptor ERR-γ mediates IL-6-stimulated FGF-23 expression in liver as well as FGF-23 production in folic acid-induced AKI in mice.[27] In addition to bone, bone marrow and liver, increased FGF-23 expression was observed in other organs such as heart, spleen, and thymus in a mouse model of AKI induced by folic acid.[28] It has been shown that peroxisome proliferator-activated receptor α (PPARα) may play a role in transcriptional repressor in the regulation of FGF-23 expression, as the agonists of PPARα inhibit FGF-23 expression, but PPARα antagonist increase the expression of FGF-23 in osteoblast-like cells of rats (UMR106).[29] The elevated FGF-23 production in AKI may trigger by its upstream signals such as IL-6 and erythropoietin which are increased in AKI.[24,26]

Effects of increased FGF-23 in inflammation and AKI

Inflammation is linked to FGF-23,[30] however, there are controversial findings about the impact of increased FGF-23 on inflammation and AKI. Elevated FGF-23 level, as noted by Czaya *et al.* is a factor in various tissues' damage.[31] Inflammation of the airways was also exacerbated by cigarette smoke-activated FGF-23/FGF-23 receptor 4 signaling.[32] Zhang *et al.* discovered that the C-terminal of FGF-23, an antagonist of FGF-23, decreased inflammation and fibrosis in db/db mice with diabetic nephropathy.[33] This result suggests that intact FGF-23 may contribute to inflammation and fibrosis in diabetic nephropathy. A prospective cohort study involving 3,875 patients with chronic kidney disease at stages 2 to 4 showed that elevated FGF-23 is an independent risk factor for mortality.[34]

Several studies, however, suggested that FGF-23 might function as an anti-inflammatory factor, and protect the kidneys from AKI. FGF-23 inhibits leukocyte activation via binding to FGF receptor 2 on leukocytes.[35] The FGF-23/FGF receptor 2 signaling may prevent the activation of chemokines and selectins-triggered β2 integrin by triggering protein kinase A and blocking the activation of the small GTPase Rap1 activation.[35] Exogenous pretreatment with FGF-23 could reduce ischemia-reperfusion-induced AKI in mice probably through endothelial progenitor cells-mediated nephroprotection.[36] These controversial data suggest that further studies are still required to determine the contribution of increased FGF-23 generation in inflammation and AKI.

Previous Publications

A recent meta-analysis,[3] retrieved 8 studies including 3 pediatric trials and 5 adult patient studies, and concluded that the prediction of AKI using blood FGF-23 levels had a pooled sensitivity and specificity were 0.82 (95% CI, 0.66-0.91) and 0.77 (95% CI, 0.67-0.85), respectively. We observed that in in the eight included trials, three studies (including one adult study[15] and two pediatric trials[37,38]) had significant impacts on the pooled

sensitivity analysis. We further conducted sensitivity analyses and found that the performance of FGF-23 was dampened when the adult study,[15] but not the other two pediatric trials,[37,38] was excluded (sensitivity, specificity, and AUC values were 0.70 (95% CI: 0.62 to 0.77), 0.72 (95% CI: 0.64 to 0.78), and 0.77 (0.73 to 0.80); respectively).

LIMITATIONS

This meta-analysis has several limitations. One is the absence of standard diagnostic criteria for AKI in the included trials, which could create heterogeneity and results in incorrect findings. Significant heterogeneity is another problem that decreases the reliability of results from this meta-analysis. Given that the average age of patients in most research was greater than 60 years old, the majority of patients may be elderly. Thus, additional research is still required to address the impact of FGF-23 in adult patients younger than 60 years of age. Furthermore, this meta-analysis was not able to include any randomized control trials. It is also a limitation that may decrease the power of this study. We intended to carry out subgroup analysis to examine the impact of sample size and age on diagnostic accuracy indicators. However, limited available trials hurled us to abandon the try in this meta-analysis.

CONCLUSION

According to the finding of our meta-analysis which were based on seven prospective cohort trials, blood FGF-23 may be a potential indicator for predicting AKI in adult patients. Future, sizable, and carefully planned clinical trials are still needed.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAIABILTY STATEMENT

All data is contained within this manuscript.

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