Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: a systemic review and meta-analysis

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Research

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Abstract

Background The use of the furosemide stress test (FST) as an acute kidney injury (AKI) severity marker has been discussed in several different trials. However, the diagnostic performance of the FST in predicting AKI progression has not yet been fully discussed.

Methods In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched the PubMed, Embase, MEDLINE and Cochrane databases up to December, 31 2019. The diagnostic performance of the FST (in terms of sensitivity, specificity, number of events, number of true positives, and number of false positives) was extracted and evaluated.

Results We identified nine trials that enrolled a total of 1296 patients, including 432 patients and 864 patients for whom the outcomes in terms of AKI stage progression and renal replacement therapy (RRT), respectively, were reported. The pooled sensitivity and specificity results of the FST for AKI progression prediction were 0.83 (95% CI: 0.76 - 0.89) and 0.87 (95% CI: 0.80 - 0.92), respectively. The pooled positive likelihood ratio (LR) was 5.27 (95% CI: 3.75-7.39), the pooled negative LR was 0.22 (95% CI: 0.15 - 0.32), and the pooled diagnostic odds ratio (DOR) was 29.34 (95% CI: 16.35-52.66). The summary receiver operating characteristics (SROC) with pooled diagnostic accuracy was 0.87. The diagnostic performance of the FST in predicting AKI progression was not affected by different AKI criteria (relative DOR: 1.04, 95% CI: 0.18 - 5.94) or underlying chronic kidney disease (relative DOR: 0.66, 95% CI: 0.08 - 5.70). The pooled sensitivity and specificity results of the FST for RRT prediction were 0.87 (95% CI: 0.76 - 0.93) and 0.71 (95% CI: 0.56 - 0.83), respectively. The pooled positive LR and pooled negative LR were 2.85 (95% CI: 1.81-4.48) and 0.22 (95% CI: 0.11 - 0.43), respectively. The pooled diagnostic odds ratio (DOR) was 13.36 (95% CI: 4.79-37.27) and SROC with pooled diagnostic accuracy was 0.87.

Conclusion The FST is a simple tool for the identification of AKI populations at high risk of AKI progression, but the diagnostic performance of FST in RRT prediction is suboptimal.

Introduction

The incidence of in-hospital acute kidney injury (AKI), depending on the different AKI criteria used, ranges from 7.0-18.3% [1] among hospitalized patients in general and up to 20–50% in critically ill populations [2]. The progression of AKI with the presence of multiple organ failure can result in poor patient prognosis. Because of the high morbidities and mortalities associated with AKI, many investigators have focused on several novel biomarkers for the earlier detection of AKI, the discrimination of etiologies, and outcome prediction [3–7]. However, the availability of these novel biomarkers may be limited by its expense or reimbursement issues in different levels of healthcare systems or countries. In addition to the therapeutic role of furosemide on fluid balance, blood pressure control, and the management of hypercalcemia, Chawla et al. proposed that furosemide stress test (FST) as a tool for predicting AKI progression [8]. Several following studies also utilized FST to predict AKI progression or RRT prediction, but with heterogeneity in AKI criteria, urine output cut-off, duration of monitor or study designs. Meanwhile, a few recent studies have focused on the ability of FST to predict delayed post-kidney transplant graft function [9–10], whereas others were based on child populations [11–12]. As such, in order to more effectively explore the diagnostic accuracy of the FST for the prediction of AKI stage progression and RRT outcomes in different settings, we conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagnostic test accuracy guidelines [13].

Methods

Literature Search

In accordance with the PRISMA guidelines, our two investigators (JJ-C, G-K) systematically and independently conducted a review of the relevant published data. A computerized search of the Pubmed, Embase, MEDLINE and Cochrane electronic databases was performed using the keywords “furosemide,” “furosemide stress test,” “acute kidney injury,” “acute kidney failure,” and “acute renal insufficiency,” as well as the medical subject heading (MeSH) terms “Furosemide” [Mesh] AND “Acute Kidney Injury” [Mesh], in order to identify all the relevant English-language studies up to December 2019. Review articles or meta-analyses were not included for analysis, but their citations and references were searched for additional relevant studies.

Study Selection

After the initial screening, the two investigators Jia Jin Chen (JJ-C) and George Kuo (G-K) independently determined the eligibility of the identified studies based on evaluations of their titles, abstracts, and, subsequently, full texts. Any difference in opinion regarding eligibility was resolved by consensus through discussion. The full text of any article that was deemed potentially relevant was retrieved online. A study was included if it met the criteria of being a published English-language study, adult humans as its population, and reported the protocol and cut-off point of the FST. We enrolled studies with primary or secondary outcomes reporting the diagnostic value of the FST for AKI progression, RRT, or mortality. Studies were excluded if they met one or more of the following criteria: (1) focused on a population with transplanted kidneys, (2) used duplicate cohorts, (3) contained insufficient information for analysis, (4) were based on a child population, or (5) included no reported outcome of interest. Detailed results regarding excluded studies and the reasons for their exclusion are available in Supplemental Table 1. We have registered our work in PROSPERO with the study ID number 160934. However, till we finished our work, the registration was still under assessed by the editorial team of PROSPERO.

Data Extraction

The two investigators independently extracted relevant information from each study. The extracted data elements related to the study-level characteristics included the first author, year of publication, study location, study design, definition of AKI, total sample size, protocol of the FST (that is, furosemide dose,

time interval, cut-off point urine output), enrolled patients' AKI stages, reported outcomes of interest, whether or not the enrolled population had high plasma neutrophil gelatinase-associated lipocalin (NGAL) levels, and whether or not patients with chronic kidney disease were excluded (Table 1). As for diagnostic test performance, the extracted data included the cut-off point urine output based on the Youden index or pre-defined criteria, sensitivity, specificity, value of area under the receiver operating characteristics (AUROC), and the event number of AKI or RRT or mortality (Table 1 and Table 2).

Table 1
The characteristics of the nine included studies

First author/ year	Location	Design	AKI criteria	Population	Sample size	Furosemide dose	Urine output cutoff point	Outcome of interest	Enrolled patients AKI stage	High plasma NGAL	Exclusion of chronic kidney disease
Chawla, 2013	USA	PC + RC	AKIN	Mixed	77	1 mg/kg (furosemide naïve) or 1.5 mg/kg (furosemide non-naïve)	200 ml/2hr	AKIN stage 3	AKIN stage 1–2	Yes	Yes (eGFR < 30)
Elsaegh, 2018	Egypt	PC	KDIGO	Sepsis	60			KDIGO stage progression (included RRT)	Normal renal function & any stage of AKI	No	Yes
Lumlertgul, 2018	Thailand	PC	KDIGO	Mixed	162			RRT	Any stage of AKI	Yes	Yes (baseline Cr > 2)
Matsuura, 2018	Japan	RC	KDIGO	Mixed	51	NR	3.9 ml/2hr for per mg furosemide	KDIGO stage 3 & RRT	KDIGO stage 1–2 or high NGAL with normal renal function	Yes	No
Saber, 2018	Egypt	PC	AKIN	NR	40	1 mg/kg (furosemide naïve) or 1.5 mg/kg (furosemide non-naïve)	325 ml/6hr	AKIN stage 3 (included RRT)	AKIN stage 1–2	No	Yes (eGFR < 30)
Rewa, 2019	USA and Canada	PC	AKIN	Mixed	92	1 mg/kg (furosemide naïve) or 1.5 mg/kg (furosemide non-naïve)	200 ml/2hr	AKIN stage 3	AKIN stage 1–2	No	Yes (eGFR < 30)
Sakhuja, 2019	USA	RC	AKIN	NR	687	≥ 1 mg/kg	600 ml/6hr	RRT	AKIN stage 3	No	No
Vairakkani, 2019	India	NR	KDIGO	NR	80	1 mg/kg (furosemide naïve) or 1.5 mg/kg (furosemide non-naïve)	325 ml/2hr	KDIGO stage 3	KDIGO stage 1–2	No	Yes (eGFR < 30)
Venugopal, 2019	India	PC	AKIN	NR	62	1 mg/kg (furosemide naïve) or 1.5 mg/kg (furosemide non-naïve)	200 ml/2hr	AKIN-3 & RRT	AKIN stage 1–2	No	No
Abbreviation: AKI (acute kidney injury), AKIN (Acute Kidney Injury Network), Cr (Creatinine), eGFR (estimated Glomerular filtration rate), KDIGO (Kidney Disease Global outcomes), NR (not report), PC (prospective cohort), RC (Retrospective cohort), RRT (Renal replacement therapy)											

Table 2

Diagnostic test performance of furosemide stress test for AKI progression ,renal replacement therapy and mortality

Study	Sensitivity	Specificity	AUROC	sample size	Event (AKI progression)	TP	FP	FN	TN	Follow up period
Chawla, 2013	87.1	84.1	0.87	77	25	22	8	3	44	14 days
Elsaegh, 2018	89.3	93.4	NR	60	28	25	2	3	30	NR
Matsuura, 2018	76.5	94.1	0.84	51	17	13	2	4	32	7 days
Saber, 2018	86.7	68	NR	40	15	13	8	2	17	NR
Rewa, 2019	73.9	90	0.87	92	23	17	7	6	62	30 days
Vairakkani, 2019	82	80.8	NR	80	28	23	10	5	42	14 days
Venugopal, 2019	85.7	87.5	NR	62	14	12	6	2	42	NR
Study	Sensitivity	Specificity	AUROC	sample size	Event (RRT)	TP	FP	FN	TN	Follow up period
Lumlertgul, 2018	94.4	70.4	NR	94	108	102	16	6	38	NR
Matsuura, 2018	75	79	NR	51	8	6	9	2	34	7 days
Sakhuja, 2019	80.9	50.5	NR	687	162	131	260	31	265	1 days
Venugopal, 2019	83.3	84	NR	62	12	10	8	2	42	NR
Study	Sensitivity	Specificity	AUROC	sample size	Event (mortality)	TP	FP	FN	TN	Follow up period
Venugopal, 2019	66.7	77/3	NR	62	9	6	12	3	41	NR
Abbreviation: AUROC (Area Under the Receiver Operating Characteristics), AKI (Acute kidney injury), FN (False negative), FP (False positive), NR (not report), RRT (Renal replacement therapy), TN (True negative), TP (True positive)										

Outcome Measures

The diagnostic criteria for AKI were different in the nine enrolled studies. Four of the studies (Elsaegh, 2018; Lumlertgul, 2018; Matsuura, 2018; Vairakkani, 2019)[14–17] used the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [18]. Other studies used the Acute Kidney Injury Network (AKIN) criteria [19]. The reference test used in each study was based on the different AKI criteria used in each trial or on whether the patients received RRT. Four studies (Chawla, 2013; Rewa, 2019; Saber, 2018; Venugopal, 2019)[8, 20–22] used the AKIN stage 3 AKI criteria. Three studies (Elsaegh, 2018; Matsuura, 2018; Vairakkani, 2019)[14, 16–17] used the KDIGO stage 3 AKI criteria.

Risk of Bias Assessment

The risk of bias for each of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and Review Manager version 5.3 to identify the quality of the included studies [23]. The QUADAS-2 tool is based on four domains (patient selection, index test, reference standard, and flow and timing), which are used to judge the risk of bias. Each study was reviewed independently by JJ-C and G-K, with each investigator assigning a rating of high, low, or unclear risk for all four domains. The judgment principle of “applicability” was the same as the bias section, but there were no signaling questions. Disagreements between the reviewers were resolved by discussion. If the answer to all the signaling questions for a given domain was “yes,” then the domain was considered to entail a low risk of bias. If the answer to any of the signaling questions for a domain was “no,” then the domain was considered to entail a high risk of bias. The quality of evidence for the diagnostic performance of the FST in this meta-analysis was assessed based on the guidelines of the GRADE Working Group methodology [41]. We summarized the results in a table, which was constructed using the online GRADE Profiler (see Supplementary Table 2).

Statistical Analysis

We extracted the event number, total sample size, and true positive (TP), true negative (TN), false positive (FP), and false negative (FN) rates for each study or calculated these values according to the reported sensitivity and specificity. Based on these data, the positive likelihood ratio (+ LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR) could be obtained for each study. The summary measures were calculated using a bivariate model for the obtained pooled sensitivity and specificity. We used a random-effect model with maximum likelihood estimation to calculate the pooled DOR and LR. The above two tests were conducted by the ‘metabin’ function in the ‘meta’ package [24]. To assess the diagnostic performance of the FST regarding AKI progression for FST non-responders, a summary receiver operating characteristics (SROC) curve was constructed by the ‘restima’ function with restricted maximum likelihood estimation in the ‘mada’ package [42]. The threshold effect was examined by using the Spearman correlation coefficient between the logit of sensitivity and logit of “1 – specificity,” and $P < 0.05$ indicated the existence of a threshold effect. If there is no significant threshold effect, subgroup analysis or meta-regression analysis is warranted to clarify the sources of heterogeneity [25]. Heterogeneity from covariates other than the threshold effect among studies was evaluated using the I^2 index, with $I^2 < 25\%$, $25\% - 50\%$, and $> 50\%$ indicating mild, moderate, and high heterogeneity, respectively. The LRs indicate whether the accuracy of a particular test would be more accurate for patients with a disease than for subjects without the disease. Several relevant variables were identified, and these variables are summarized in Table 1 and Table 2 (with the specific variables including the AKI criteria used, whether or not the enrolled patients had high plasma NGAL, whether or not the enrolled patients had a clinical diagnosis of AKI, the pre-specific urine output cut-off point, the study design, and whether or not patients with chronic kidney disease were excluded). To explore possible sources of

heterogeneity, these variables were applied as moderators in meta-regression weighted by the inverse of the study variance. We performed the meta-regression by using Meta-DiSc (version 1.4) [26]. A sensitivity analysis was performed after excluding studies used the composite outcomes of AKI stage progression and RRT. All analyses were conducted using R version 3.6.2 (2019-12-12) [43]. A two-sided P value of < 0.05 was considered statistically significant.

Results

Literature Search

The initial search retrieved 128 records. After excluding duplicate articles and removing clearly irrelevant articles, the remaining 17 articles were screened based on their titles and abstracts in order to identify the potentially relevant articles, the full texts of which then were downloaded and reviewed to further determine their eligibility for inclusion in the final analysis. Of the 17 articles, one [27] was suspected of using a duplicate cohort from another study [8], two were focused on child populations [11–12], and two were based on kidney transplant outcomes [9–10]. Meanwhile, one study did not report a urine output cut-off point and one used an unclear AKI definition [28]. As such, nine studies were ultimately included in this meta-analytic study (Fig. 1).

Study Characteristics

The nine included trials enrolled a total of 1296 patients with clinical AKI or a risk of AKI. Among those patients, 432 patients and 864 patients, respectively, had reported outcomes of AKI stage progression (including the need for RRT) or RRT. Only one study reported the capability of the FST in predicting mortality (Venugopal, 2019(22)), with a sensitivity of 0.67 and specificity of 0.77 (Table 2). Four of the studies used prospective cohorts and three used non-prospective study designs (while another study had an unclear study design, Vairakkani, 2019)[17]. All of the studies except the one by Matsuura et al. used a standard furosemide dose and urine output cut-off point, while the study by Matsuura et al. used a urine output cut-off point defined by the furosemide dose (specifically, 3.9 ml of urine output 2 hours after per mg furosemide administration). Four studies used the AKIN [19] criteria and three used the KDIGO [18] criteria as AKI criteria. Two studies enrolled populations with high plasma NGAL levels (Chawla, 2013; Matsuura, 2018)[8, 16]. Most of the studies used a 2-hour time interval for the urine output cut-off point; only one study (Saber, 2018)[21] used a 6-hour time interval as the threshold.

Risk of Bias

With the QUADAS-2 tool, study characteristics or designs that might increase the risk of bias were identified. Domain 1 of the QUADAS-2 tool focuses on patient selection. One study (Elsaegh, 2018)[14] enrolled septic ICU population with normal renal function as the AKI population, and we considered this to entail a high risk of applicability concern. Another study (Matsuura, 2018)[16] enrolled a population of patients with clinical AKI or subclinical AKI (that is, those with high biomarker levels that still did not meet the clinical AKI criteria). Two trials (Vairakkani, 2019; Venugopal, 2019)[17, 22] provided insufficient information about their study designs; therefore, the domain 1 aspects of the study populations for these two studies were considered to entail unclear risks. Domain 2 of the QUADAS-2 tool addresses the aspect of index tests. Six trials selected the urine output threshold to optimize sensitivity and/or specificity; therefore, these six studies were considered to have a high risk of bias regarding domain 2. All of the studies that used the AKIN or KDIGO AKI criteria or RRT as reference standard was considered to have low risk of bias. Three studies (Elsaegh, 2018; Saber, 2018; Venugopal, 2019) [14, 21, 22] did not report a follow-up period for the primary or secondary outcomes. Therefore, these three studies were considered to have unclear risk of bias regarding domain 4. Because of the reasons mentioned above, we considered one study (Elsaegh, 2018)[14] to have high applicability concern regarding patient selection and another one (Matsuura, 2018)[16] to have unclear concern. The other two domains of applicability concern in the included studies were all rated as low risk. We conducted the risk of bias analysis for all the included studies using Review Manager (RevMan) Version 5.3 [44], and the results are summarized in Fig. 2.

Furosemide Stress Test for Acute Kidney Injury Stage Progression Prediction

The diagnostic values, cut-offs, and key results are summarized in Table 2. The pooled sensitivity and specificity values were 0.83 (95% CI: 0.76–0.89) and 0.87 (95% CI: 0.80–0.92), respectively. The pooled positive LR was 5.27 (95% CI: 3.75–7.39), and the negative LR was 0.22 (95% CI: 0.15–0.32) (Fig. 3). The heterogeneity of the aforementioned four pooled indices ranged from low to moderate (I^2 ranged from 0.0–49.0%) (Fig. 3). The pooled DOR was 29.34 (95% CI: 16.35–52.66), with low heterogeneity ($I^2 = 0$) (Supplementary Fig. 1). The area under the curve (AUC) for SROC to summarize diagnostic accuracy was 0.87 (Supplementary Fig. 2).

Furosemide Stress Test for Renal Replacement Therapy Prediction

Four trials provided information regarding the diagnostic value of the FST in terms of predicting further need for RRT in AKI populations. The diagnostic values, cut-offs, and key results are summarized in Table 2. The pooled sensitivity and specificity values were 0.87 (95% CI: 0.76–0.93) and 0.71 (95% CI: 0.56–0.83), respectively. The pooled positive LR was 2.85 (95% CI: 1.81–4.48), and the negative LR was 0.22 (95% CI: 0.11–0.43). The heterogeneity of the aforementioned four pooled indices was high (I^2 ranged from 58–87%) (Supplementary Fig. 3). The pooled DOR was 13.36 (95% CI: 4.79–37.27), with high heterogeneity ($I^2 = 84\%$) (Supplementary Fig. 4). The area under the curve (AUC) for SROC to summarize diagnostic accuracy was 0.87 (Supplementary Fig. 5).

Subgroup Analysis and Sensitivity Analysis

Due to the different study designs and study characteristics (that is, the criteria of AKI, prospective or non-prospective design, use or non-use of a pre-specified urine output cut-off point, enrolled high NGAL population, 2-hour or 6-hour protocol, and exclusion of underlying CKD population) used, these

designs and characteristics were used to explore the sources of heterogeneity. The analysis of threshold effect was performed with Spearman rank correlations ($\rho = 0.036$; $P = 0.96$). The results implied that there was no significant threshold effect and subgroup analysis was required. The results of the subgroup analysis are summarized and presented in Table 3. There were 2 studies that provided a composite outcome of the AKI stage progression and RRT (Elsaegh, 2018; Saber, 2018)[14, 21]. A sensitivity analysis was conducted after excluding these two trials. The pooled sensitivity and specificity values of the remaining 5 studies were 0.81 (95% CI: 0.73–0.88) and 0.87 (95% CI: 0.82–0.91), respectively. The pooled positive LR was 5.92 (95% CI: 4.26–8.22), and the negative LR was 0.23 (95% CI: 0.15–0.34) (Supplemental Fig. 6). The pooled DOR was 29.92 (95% CI: 15.94–56.18) (Supplemental Fig. 7). The SROC with pooled diagnostic accuracy was 0.90 (Supplemental Fig. 8).

Table 3
Heterogeneity analysis of meta-analyses (outcome included sensitivity analysis and meta-regression)

Variables	Subgroups	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Diagnostic odd ratio (95% CI)	Coeff.	SE	P value	RDOR (95% CI)
AKI criteria	AKIN	4	0.83 (0.73–0.91)	0.85 (0.79–0.90)	5.09 (3.15–8.23)	0.22 (0.13–0.36)	28.01 (13.43–58.43)				
	KDIGO	3	0.83 (0.71–0.92)	0.89 (0.81–0.94)	8.86 (2.51–31.22)	0.21 (0.12–0.39)	43.17 (9.64–193.22)	0.04	0.63	0.95	1.04 (0.18–5.94)
FST cutoff point time	6 hour	1	-	-	-	-	-				
	2 hour	6	0.83 (0.75–0.89)	0.88 (0.84–0.92)	6.12 (4.38–8.54)	0.22 (0.15–0.32)	32.43 (17.40–60.41)	0.56	1.17	0.64	1.80 (0.07–46.71)
Study design	Non-prospective	3	0.83 (0.72–0.91)	0.86 (0.79–0.91)	5.42 (3.42–8.60)	0.21 (0.12–0.35)	30.03 (13.29–67.82)				
	Prospective	4	0.84 (0.72–0.92)	0.87 (0.81–0.92)	5.75 (2.69–12.32)	0.23 (0.13–0.39)	29.82 (11.34–78.43)	-0.10	0.60	0.88	0.91 (0.17–4.79)
High NGAL	No	5	0.83 (0.74–0.90)	0.86 (0.80–0.90)	5.09 (3.03–8.55)	0.23 (0.14–0.36)	25.12 (12.65–49.86)				
	Yes	2	0.83 (0.69–0.93)	0.88 (0.80–0.94)	6.94 (3.44–14.04)	0.20 (0.10–0.39)	44.42 (14.50–136.10)	0.51	0.68	0.49	1.66 (0.25–10.82)
Exclusion of late CKD	No	2	0.81 (0.63–0.93)	0.90 (0.82–0.96)	8.02 (4.07–15.77)	0.22 (0.11–0.45)	46.48 (13.31–162.26)				
	Yes	5	0.84 (0.75–0.91)	0.85 (0.80–0.89)	4.87 (3.02–7.88)	0.22 (0.14–0.34)	25.81 (13.31–50.04)	-0.42	0.78	0.62	0.66 (0.08–5.70)
UOP cutoff point	Best cutoff point	5	0.82 (0.73–0.88)	0.85 (0.80–0.89)	4.98 (3.20–7.74)	0.23 (0.16–0.34)	25.76 (13.73–48.33)				
	Pre-defined	2	0.91 (0.72–0.99)	0.91 (0.82–0.97)	11.77 (1.76–78.49)	0.13 (0.04–0.42)	105.13 (7.10–1555.9)	0.96	0.87	0.33	2.60 (0.23–29.07)
Mixed outcome	No	5	0.81 (0.73–0.88)	0.87 (0.82–0.91)	5.92 (4.26–8.22)	0.20 (0.14–0.28)	29.92 (15.94–56.18)				
	Yes	2	0.92 (0.73–0.99)	0.83 (0.69–0.92)	8.50 (0.33–220.05)	0.15 (0.05–0.50)	70.29 (1.38–3570.5)	0.35	1.02	0.75	1.41 (0.08–23.81)
Abbreviation: AKI (Acute kidney injury), AKIN (Acute Kidney Injury Network), KDIGO (Kidney Disease Improving Global Outcomes), LR (likelihood ratio), NGAL (Neutrophil gelatinase-associated lipocalin), RDOR (Relative diagnostic odd ratio), SE (Standard error), UOP (urine output)											

Discussion

Furosemide has been used for decades. Its pharmacodynamics, pharmacokinetics, and adverse effects are well described in patients with chronic kidney disease or nephrotic syndrome, but less data is available regarding its effects in AKI populations. Because of its low cost and availability, the FST serves as a simple way to assess kidney function. In 1973, Beak et al. reported that the urinary free water excretion following intravenous furosemide

administration could serve as a diagnostic tool for acute tubular necrosis (ATN) [28]. In normal subjects or subjects with mild AKI, the infusion dose and creatinine clearance are major determinants of diuretic response [29]. After AKI, several tubular function alterations could affect diuretic response, including a decrease of Na-K-Cl cotransporter 2 expression, Na-K-ATPase redistribution [30], and organic acid transporter mis-targeting [31]. Therefore, the FST seems to provide a quick and easy method for the assessment of glomerular filtration and tubular damage. Despite this aforementioned role in diagnostics, furosemide is unlikely to reduce mortality or decrease the risk of RRT in AKI populations [32]. We thus performed this systematic review and meta-analysis to clarify the predictive value of the FST on AKI progression, the need for RRT, and in-hospital mortality. We also performed a subgroup analysis to investigate whether the FST has different diagnostic capabilities in different situations.

First, the analysis of the diagnostic accuracy of the FST for AKI progression yielded an AUROC of 0.87, with pooled sensitivity and specificity values of 0.83 and 0.87, respectively. This diagnostic accuracy of FST, though not compared to the accuracy levels of other biomarkers in a head-to-head manner, is not inferior to those previously reported for other biomarkers which with AUROC ranged from 0.70 to 0.85 for AKI stage progression or RRT prediction [3, 33–34]. In the enrolled studies, the diagnosis of AKI was based on the AKIN or KDIGO classifications, while only the studies by Chawla et al. and Matsuura et al. utilized NGAL levels in their cohorts. The study by Koyner et al. reported a higher AUROC for the FST compared with biomarkers alone in the same cohort investigated in the study by Chawla et al [27]. The prediction of AKI progression was better when the FST was used in patients with elevated biomarkers than in the whole cohort [27]. Most of the included studies, whether they pre-defined criteria or not, used 2 hours as the time point at which to observe furosemide responsiveness.

Second, our work demonstrated that use of the FST as a tool for RRT prediction had an AUROC of 0.87, but high heterogeneity was detected within the diagnostic indices. The optimal time for RRT initiation has been widely discussed for decades. Recently, several randomized controlled trials and meta-analyses considering this subject have been published, but their results have remained inconclusive [15, 35–36]. The pooled specificity and positive LR values of the FST for RRT prediction were relatively low according to our analysis. According to the study by Lumlertgul et al., 25% of the FST non-responder in a standard RRT group could still avoid the need for RRT because these patients did not meet the conventional RRT initiation criteria. Lumlertgul et al. also demonstrated that in FST non-responders, the early or late initiation of RRT did not affect short-term mortality or renal recovery [15]. Therefore, FST non-responsiveness alone might not be a good indicator for RRT initiation. We should also take clinical condition, patient's demand and residual renal capacity into consideration as suggested by Acute Disease Quality Initiative XVII conference (ADQI) [37].

Our study had several limitations. First, the risks of bias in the investigated studies were not low because of their use, in some cases, of non-prospective study designs, inconsistent diagnostic cut-off values, and mixed patient populations. Second, the serum albumin level has been considered as a factor of diuretic resistance based on early experimental data [38], and recent studies have shown that the co-administration of albumin and loop diuretics might transiently increase urine water and sodium excretion [39–40]. However, we did not have information about the serum albumin level in most study and whether loop diuretics were co-administered with albumin in the enrolled studies. Third, due to the lack of large prospective studies meeting our criteria for inclusion, the total number of enrolled patients was relatively small. A larger clinical study is thus required in the future.

Conclusion

In conclusion, FST non-responsiveness has a good predictive ability for AKI progression regardless of different AKI criteria or underlying chronic kidney disease. However, FST has only a modest predictive capability for RRT initiation with some application concern. Further trials with larger sample sizes or high quality study design are still needed to clarify the benefit of FST in clinical setting.

Abbreviations

AKI
acute kidney injury
AKIN
Acute Kidney Injury Network
FST
furosemide stress test
KDIGO
Kidney Disease:Improving Global Outcomes
NGAL
neutrophil gelatinase-associated lipocalin
PC
prospective cohort
RC
retrospective cohort

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Not applicable

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Figure Legends

Figure 1. PRISMA Flow chart of study inclusion

Figure 2. Summary of risk of bias and applicability concern

Figure 3. Forest plot of FST diagnostic accuracy for AKI progression prediction

Supplemental Figure 1. Diagnostic odd ratio of FST for prediction of AKI progression

Supplemental Figure 2. SROC curves of FST for prediction of AKI progression, SROC (summary receiver operating characteristic)

Supplemental Figure 3. Forest plot of FST diagnostic accuracy for RRT prediction, RRT (renal replacement therapy)

Supplemental Figure 4. Diagnostic odd ratio of FST for prediction of RRT

Supplemental Figure 5. SROC curves of FST for prediction of RRT

Supplemental Figure 6. Forest plot of FST diagnostic accuracy for AKI stage progression (exclusion of RRT)

Supplemental Figure 7. Diagnostic odd ratio of FST for prediction of AKI stage progression (exclusion of RRT)

Supplemental Figure 8. SROC curves of FST for prediction of AKI stage progression (exclusion of RRT)

Figures

Figure 1

PRISMA Flow chart of study inclusion

		Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Chawla, 2013	?	+	+	+	+	+	+	+
Eisaegh, 2018	?	+	+	+	?	-	+	+
Lumertgul, 2018	+	+	+	+	+	+	+	+
Matsuura, 2018	?	-	-	+	+	?	+	+
Rewa, 2019	+	-	-	+	+	+	+	+
Saber, 2018	+	-	+	+	?	+	+	+
Sakhija, 2019	+	-	+	+	+	+	+	+
Varakkani, 2019	?	-	+	+	+	+	+	+
Venugopal, 2019	?	+	+	+	?	+	+	+

Legend: High (Red), Unclear (Yellow), Low (Green)

Figure 2

Summary of risk of bias and applicability concern

Figure 3

Forest plot of FST diagnostic accuracy for AKI progression prediction

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