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Article

Diagnostic Performance of Fractional Excretion of Sodium for the Differential Diagnosis of Acute Kidney Injury

A Systematic Review and Meta-Analysis

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Abstract

Background and objectives AKI is classified as prerenal, intrinsic, and postrenal. Prerenal AKI and intrinsic AKI represent the most common causes for AKI in hospitalized patients. This study aimed to examine the accuracy of the fractional excretion of sodium for distinguishing intrinsic from prerenal AKI.

Design, setting, participants, & measurements We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, the Cochrane Library, and Scopus for all available studies that met the criteria until December 31, 2021. We included studies that evaluated fractional excretion of sodium in differentiating AKI etiologies in adults, whereas studies that did not have sufficient data to extract a 2×2 table were excluded. We assessed the methodologic quality using the Quality Assessment of Diagnostic Accuracy Studies-2 tool and extracted the diagnostic accuracy data for all included studies. We conducted a meta-analysis using the bivariate random effects model. We performed subgroup analysis to investigate sources of heterogeneity and the effect of the relevant confounders on fractional excretion of sodium accuracy.

Results We included 19 studies with 1287 patients. In a subset of 15 studies (872 patients) that used a threshold of 1%, the pooled sensitivity and specificity for differentiating intrinsic from prerenal AKI were 90% (95% confidence interval, 81% to 95%) and 82% (95% confidence interval, 70% to 90%), respectively. In a subgroup of six studies (511 patients) that included CKD or patients on diuretics, the pooled sensitivity and specificity were 83% (95% confidence interval, 64% to 93%) and 66% (95% confidence interval, 51% to 78%), respectively. In five studies with 238 patients on diuretics, the pooled sensitivity and specificity were 80% (95% confidence interval, 69% to 87%) and 54% (95% confidence interval, 31% to 75%), respectively. In eight studies with 264 oliguric patients with no history of CKD or diuretic therapy, the pooled sensitivity and specificity were 95% (95% confidence interval, 82% to 99%) and 91% (95% confidence interval, 83% to 95%), respectively.

Conclusions Fractional excretion of sodium has a limited role for AKI differentiation in patients with a history of CKD or those on diuretic therapy. It is most valuable when oliguria is present.

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Introduction

AKI is defined as an abrupt decline in kidney function. Multiple criteria are used to define and stage AKI (1–3); it has multiple etiologies, commonly classified into prerenal, intrinsic renal, and postrenal. Prerenal AKI and intrinsic renal AKI are commonly regarded as transient and persistent AKI, respectively (4).

Identifying the cause of AKI is essential in guiding the required therapy, which highly influences the outcome of patients with AKI (5); unfortunately, there is no definitive way to differentiate intrinsic from prerenal AKI early in the disease.

Espinel (6) first introduced fractional excretion of sodium (FENa) in 1976. He showed FENa to be beneficial in differentiating prerenal and intrinsic AKI in the early course of AKI, especially in oliguric patients (7). However, FENa performance in the diagnosis of AKI has been inconsistent in the literature due to multiple reported confounders—the concurrent use of diuretics and having a history of CKD being the most important (8–11).

Given the invasive nature of kidney biopsy and the inconsistency of the literature regarding FENa usefulness, we performed a systematic review and meta-analysis encompassing different subgroups to evaluate the diagnostic performance of FENa in patients with AKI.

Materials and Methods

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies statement (12). The study protocol was not registered.

Eligibility Criteria

We included all studies that evaluated the diagnostic accuracy of the FENa for differentiating prerenal and intrinsic renal AKI. We included studies that provided information on the index test and reference standards irrespective of publication status or whether the data were collected prospectively or retrospectively. However, we excluded narrative reviews, letters, editorials, case reports, guidelines, consensus statements, trial registries, and animal studies. We also excluded studies that did not provide sufficient data to extract diagnostic test accuracy measures (*i.e.*, true positives, false positives, false negatives, and true negatives).

The included patients were either hospitalized patients or outpatients aged ≥18 years diagnosed with AKI using any recognized criteria or equivalent. The included studies were required to categorize the patients into prerenal or intrinsic renal AKI using at least one of the following reference standards with or without urine microscopy: (*1*) responsiveness to volume expansion and (2) kidney biopsy. Additionally, we considered hepatorenal syndrome (HRS) and cardiorenal syndrome prerenal AKI causes. We included studies that enrolled patients with HRS if the diagnosis was consistent with recognized criteria proposed by expert panels (13–16). Moreover, for studies that comprised patients with cardiorenal syndrome, the diagnosis was to be compatible with the scientific statement from the American Heart Association (17).

Search Strategy

The search strategy was designed and conducted by an experienced librarian with input from the study's authors for the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, The Cochrane Library (Cochrane Database of Systematic Reviews), and Scopus; all potential records published in English until December 31, 2021 were exported. Furthermore, we searched the included studies' reference lists and any related review articles identified during the search. The actual strategy is provided in Supplemental Table 1.

Study Selection

DistillerSR was used to record the included studies. Two independent reviewers evaluated the title and abstract of each study identified from the search. We obtained the full text for references included by at least one of the two reviewers. The full-text screening was then independently carried out by two independent reviewers. A group discussion resolved disagreements.

Data Extraction

Two reviewers independently extracted the following data from each included study using a prepiloted data extraction form: first author; year of publication; publication status (abstract or full text); setting (hospitalized, outpatient, patients in the emergency room); inclusion and exclusion criteria for individual studies; the number of patients with prerenal and intrinsic renal AKI; the percentage of women; the average age of each group of study patients; comorbidities in each group of study patients; the proportion of oliguric patients in each group; the percentage of patients receiving diuretics ≤24 hours before the FENa test; mean serum creatinine of each group; the cutoff point used for the index test; reference standard; and the number of true positives, false positives, false negatives, and true negatives (*i.e.*, 2×2 table) at each reported threshold. Any differences were resolved by discussion.

Quality Assessment

Two independent reviewers assessed the quality of the studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (18). We examined the bias and applicability of each study concerning four separate domains: patient selection, index test, reference standard, and the flow and timing of patients through the study. The criteria used for quality assessment were pre-established between the authors and provided in Supplemental Table 2. Any disagreement was resolved by discussion.

Statistical Analyses and Data Synthesis

We investigated how using FENa above the cutoff point performed at differentiating intrinsic AKI from prerenal AKI. We considered patients with FENa above the cutoff point who were diagnosed with intrinsic AKI true positives, and those who were diagnosed with prerenal AKI were considered false positives. We categorized patients with FENa results below the cutoff point who were diagnosed with prerenal AKI true negatives, and those diagnosed with intrinsic AKI were considered false negatives. Data from all articles were entered into Review Manager (RevMan; Version 5.4; The Cochrane Collaboration), which calculated the sensitivity, specificity, and 95% confidence interval (95% CI) for each study. For studies that applied over one cutoff point on their patients, we used 1% if it was applied, as it is the most clinically relevant. We then plotted the estimates of the perceived sensitivities and specificities together with their 95% CIs in the forest plot.

Only studies that used a cutoff of 1% were included in the quantitative analysis. To estimate the summary sensitivity and specificity and their corresponding 95% CIs for the included articles that used the 1% cutoff, we performed a meta-analysis using the bivariate random effects model on R 4.1.1 (R Core Team); we also computed the positive and negative likelihood ratios from the pooled estimates of sensitivity and specificity, as well as the diagnostic odds ratios with their corresponding 95% CIs. We also used the bivariate random effects model for the meta-analysis of the positive predictive value and the negative predictive value (19).

We identified the summary operating point and estimated average sensitivities and specificities with the 95% confidence and prediction regions on the summary receiver operating characteristics (SROC) plot. We assessed heterogeneity initially by visually inspecting the forest plot and the receiver operating characteristic space.

Finally, we performed subgroup analyses for the following: (*1*) patients who did not receive diuretics ≤24 hours before the FENa test; (*2*) patients who received diuretics; (*3*) studies that excluded patients with CKD; (*4*) studies that excluded patients with CKD and those receiving diuretics; (*5*) oliguric patients with AKI; (*6*) after combining the previously mentioned categorizations, oliguric patients with AKI who were not receiving diuretics and had no history of CKD; (*7*) studies that included patients with CKD or patients on diuretics; (*8*) studies published before 2000; and (*9*) studies published after 2000. Moreover, we compared subgroups when the data are independent (*i.e.*, the participants should be part of one comparator only). We undertook comparisons of FENa accuracy between the diuretics and nondiuretics subgroups and also between the older and newer studies subgroups using meta-regression, with the subgroup added as a covariate to the bivariate model. We obtained the *P* value using the likelihood ratio test (Wald test).

Results

Study Selection and General Information

The literature search identified 2607 references. An additional two references were retrieved by checking the reference lists of the related articles. After duplicate removal and title and abstract screening, we excluded 2325 references and obtained the full text of 232 studies. Nineteen studies (1287 participants) met our inclusion criteria, of which we included 15 (872 participants) in the quantitative analysis. We present the study selection process in Figure 1. Table 1 shows the details of the 19 included studies. All of the included studies were full-text articles conducted prospectively except for one study, which was the only retrospective study (20). The majority of the intrinsic AKI in the included studies was in patients with acute tubular necrosis (ATN). All studies included hospitalized patients or patients in the intensive care unit, except for one study that did not report patients' settings (6) and one study that enrolled patients in the emergency room (18). All but five studies (18,21–24) used the 1% threshold. In addition, we obtained the necessary data to apply the 1% threshold in one study (22). All of the studies used the clinical responsiveness to fluids as a reference standard, and two of them included patients with HRS and AKI (19,24,25). Additionally, four studies (6,7,21,26) used histopathologic examination other than response to fluid expansion, whereas nine studies (4,9,20,22–24,27–30) supported their findings using microscopic urine analysis.

Risk of Bias and Applicability

Nine studies (45%) have at least one high-risk judgment in one of the four domains. Six studies (30%) were judged to be at a high risk of bias for the patients' selection domain. Moreover, for the reference standard domain, only two studies (10%) were considered to have a low risk of bias. We considered 12 studies (60%) at low risk of applicability concerns in all three domains. Additionally, we judged all included studies to have a low-risk applicability concern in the reference standard domain. We present the QUADAS-2 results in Table 2 (Supplemental Figure 1 shows RevMan output).

Synthesis of Results

The forest plot in Figure 2 shows the true positives, false positives, false negatives, true negatives, sensitivity, and specificity of the FENa for each of the 19 studies included in the review at the principal reported threshold, with the corresponding 95% CIs. In 15 (79%) of the included studies, we extracted the data at a 1% threshold, in which the overall intrinsic AKI percentage was 48%. The overall sensitivity ranged from 48% to 100%, whereas the specificity was between 39% and 100%. The pooled sensitivity, specificity, diagnostic odds ratio, positive and negative likelihood ratios, and positive and negative predictive values of the FENa at the 1% cutoff point were 90% (95% CI, 81% to 95%), I^2=85%; 82% (95% CI, 70% to 90%), I^2=82%; 39 (95% CI, 13 to 122), I^2=79%; 4.98 (95% CI, 2.82 to 8.78), I^2=84%; 0.13 (95% CI, 0.06 to 0.26), I^2=85%; 85% (95% CI, 71% to 93%), I^2=90%; and 89% (95% CI, 78% to 95%), I^2=87%, respectively. For the 15 studies included in the meta-analysis, we presented the summary operating point (summary sensitivity and specificity) and 95% confidence and prediction regions in the SROC plot (Figure 3).

Subgroup Analyses

We conducted subgroup analyses to investigate sources of heterogeneity other than exploring the effect of the known confounders influencing FENa accuracy. We provided the results of the subgroup analysis in Table 3; forest plots and SROC plots are provided in Supplemental Figures 2 and 3, respectively. In six studies with 511 patients that included patients with CKD or patients on diuretics, the overall intrinsic AKI percentage was 38%. The pooled sensitivity, specificity, and positive and negative predictive values were 83% (95% CI, 64% to 93%), 66% (95% CI, 51% to 78%), 56% (95% CI, 43% to 69%), and 88% (95% CI, 66% to 97%), respectively. The accuracy of the FENa test was significantly higher in the nondiuretics group than in the diuretics (relative diagnostic odds ratio, 14.02; 95% CI, 2.53 to 77.74; P=0.005). The pooled sensitivity was higher in the nondiuretics group (92%; 95% CI, 85% to 96%) compared with the diuretics (80%; 95% CI, 69% to 87%) but statistically was not significant (P=0.08). Still, the pooled specificity was significantly higher in the nondiuretics group (88%; 95% CI, 83% to 92%; P<0.001) than the diuretics group (54%; 95% CI, 31% to 75%). Moreover, we were able to conduct a subgroup analysis for 264 oliguric patients with no history of CKD or diuretic therapy from eight studies. Altogether, intrinsic AKI percentage was 49%; the pooled sensitivity, specificity, and positive and negative predictive values were 95% (95% CI, 82% to 99%), 91% (95% CI, 83% to 95%), 92% (95% CI, 81% to 97%), and 96% (95% CI, 81% to 99%), respectively. The accuracy of FENa was significantly lower in studies published after 2000 than the earlier studies (relative diagnostic odds ratio, 0.06; 95% CI, 0.01 to 0.32; P=0.003), although the specificity but not the sensitivity was significantly lower in the newer studies (P<0.001).

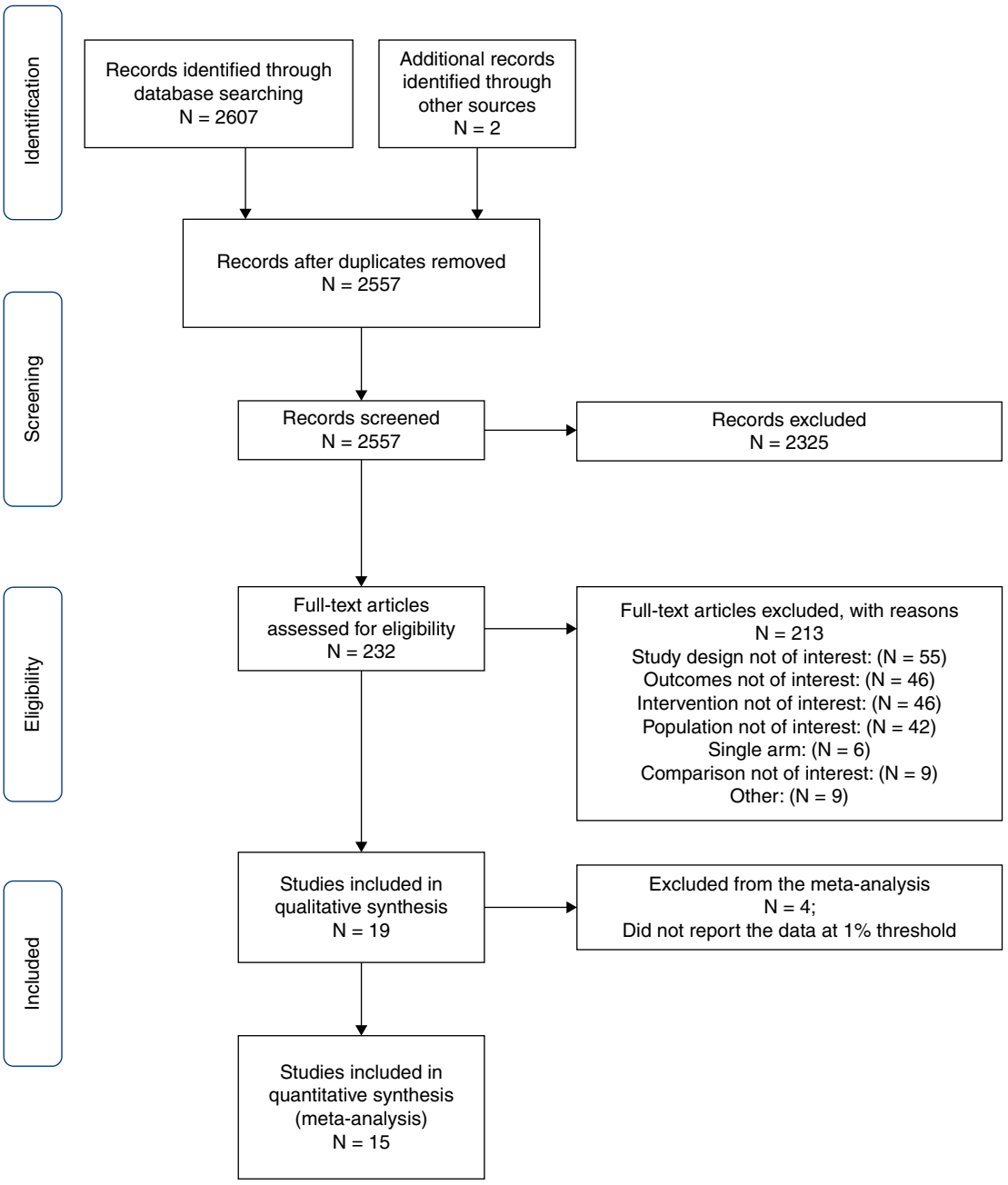

Figure 1. | **Flow chart of literature search and selection.**

Discussion

We conducted the first systematic review and meta-analysis to evaluate the performance of FENa in differentiating intrinsic AKI (mainly ATN) from prerenal AKI in adult patients, including controlling for the pertinent confounders. Our results showed that FENa is a good tool for differentiating intrinsic AKI from prerenal AKI in oliguric patients but performed less favorably in patients who have CKD and those on diuretics. When FENa was first introduced by Espinel (6) and examined in multiple studies later (7,27), the targeted population was patients with AKI not on diuretics, without a history of CKD, and had oliguria, in whom FENa showed robust performance. Although our findings showed a notably good performance for FENa in this subgroup of patients (Table 3, subgroup 6), considerable within-study uncertainty was observed through the 95% CI in the receiver operating characteristic plot (Supplemental Figure 3E). Additionally, the number of included studies and the number of involved patients in each study are small, which may concern the applicability of the results.

CKD and diuretics cannot be ignored when evaluating the performance of FENa; for instance, 30% and nearly 50% of patients in the intensive care unit had preadmission CKD and diuretics use, respectively (31,32). Diuretics alter urinary electrolyte concentrations; they increase the urinary sodium concentration and thus can falsely elevate the

Table 1. Studies that examined the performance of the fractional excretion of sodium in AKI

Study, Year	Design, Settings	Intrinsic AKI, *n*; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl	Prerenal AKI, *n*; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl	Inclusion Criteria	Exclusion Criteria	Reference Standard	Fractional Excretion of Sodium Cutoff(s), %	Intrinsic AKI: Oliguric, %; Receiving Diuretics, %	Prerenal AKI: Oliguric, %; Receiving Diuretics, %	Intrinsic AKI: CKD, %; Sepsis, %	Prerenal AKI: CKD, %; Sepsis, %
Espinel (6), 1976	P, N/R	9; N/R; N/R; 9.2±0.7	8; N/R; N/R; 8.3±1.1	Acute onset of oliguria (urinary output below 20 ml/hr)	CKD, patients on diuretics, acute glomerular disease, or urinary tract obstruction	Responsiveness to fluids. ATN cases were also confirmed by histologic findings	<1 and >3; 1	100; 0	100; 0	0; N/R	0; N/R
Miller *et al.* (27), 1978	P, hospitalized	55; 58.1±3.5; 20; 3.9±0.26	30; 62±3; 34; 3±0.3	Acute elevation of serum creatinine from normal levels (<1.4 mg/dl) to >2.0 mg/dl	CKD, patients on diuretics	Responsiveness to fluids, urine microscopy findings	1	44; 0	N/R; 0	0; N/R	0; N/R
Espinel and Gregory (7), 1980	P, hospitalized	65; N/R; N/R; 5.2±1.5	8; N/R; N/R; 5.4±0.8	Acute increase in creatinine level above 2 mg/dl	CKD, patients on diuretics	Response to fluids, urine microscopy, histopathology in some cases	1	56; 0	100; 0	0; N/R	0; N/R
Zager *et al.* (28), 1980	P, hospitalized	22; N/R; N/R; N/R	5; N/R; N/R; N/R	Patients with AKI, defining criteria are not reported	N/R	Response to fluids, urine microscopy	1	59; N/R	100; N/R	0; 0	0; 0
Chugh *et al.* (21), 1981	P, hospitalized	40; N/R; N/R; N/R	21; N/R; N/R; N/R	Oliguric AKI, defining criteria are not reported	CKD, acute GN, obstructive uropathy, diabetes mellitus, and cirrhosis	Response to fluids and pathologic findings	<1 and >3	100; 0	100; 0	0; N/R	0; N/R
Brown *et al.* (29), 1983	P, hospitalized	10; N/R; N/R; N/R	7; N/R; N/R; N/R	AKI defined by an acute rise in blood urea	CKD, patients on diuretics	Response to fluids, urine microscopy	1	80; 0	100; 0	0; N/R	0; N/R
Anderson *et al.* (30), 1984	P, hospitalized	41; N/R; N/R; 4.4±0.5	21; N/R; N/R; 2.6±0.2	Acute rise in creatinine from <1.4 to >2.0 mg/dl	N/R; patients with CKD were studied separately	Responsiveness to fluids, urine microscopy findings	1	53; N/R	100; 0	0;[a] 0	0; 0
Tankhiwale and Ungratwar (26), 1987	P, hospitalized	22; N/R; N/R; N/R	20; N/R; N/R; N/R	Patients with AKI, although the defining criteria are not reported	Patients with CKD	Responsiveness to fluid expansion; histopathologic findings	1	100; N/R	100; N/R	0; N/R	0; N/R
Fushimi *et al.* (40), 1990	P, hospitalized	6; 52±16; 33; 5.2±1.3	8; 66.4±23; 50; 2.8±0.4	Acute elevation of serum creatinine to >1.5 mg/dl, with a decrease in creatinine clearance	CKD, acute GN, and patients receiving diuretics	Responsiveness to fluids, urine microscopy findings	1	N/R; 0	100; 0	0; 0	0; 0
Steinhäuslin *et al.* (18), 1994	P, ICU and ER	18; 39 (10th [21] to 90th [76] percentile); 64; 5.6 (10th [3.6] to 90th [9.5] percentile)	28; 65.5 (10th [18] to 90th [88] percentile); 65; 1.8 (10th [1.2] to 90th [3.5] percentile)	A recent increase in plasma creatinine of >20% or plasma creatinine concentration above 200 μmol/L at the time of referral	Presence of acute GN, acute interstitial nephritis, and obstructive uropathy	Responsiveness to fluids, urine microscopy findings	<1.3 and >3.5	N/R; 50	N/R; 39	0; 0	0; 0
Carvounis *et al.* (9), 2002	P, hospitalized (mostly ICU)	25; 47±3; 48; 5.9±0.5	77; 51±3; 51; 1.7±0.25	Rapidly increasing BUN and creatinine (BUN >30 mg/dl and creatinine >1.5 mg/dl) with or without oliguria or serum creatinine increase in excess of 0.5 mg/dl in the preceding 2 d	Patients with acute interstitial nephritis, acute GN, and obstructive uropathy	Responsiveness to fluids, urinalysis findings	1; 0.60; 0.80; 1.20; 1.50; 2; 3	N/R; 0	N/R; 35	0; 1	0; 32

Table 1. (Continued)

Study, Year	Design, Settings	Intrinsic AKI, *n*; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl	Prerenal AKI, *n*; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl	Inclusion Criteria	Exclusion Criteria	Reference Standard	Fractional Excretion of Sodium Cutoff(s), %	Intrinsic AKI: Oliguric, %; Receiving Diuretics, %	Prerenal AKI: Oliguric, %; Receiving Diuretics, %	Intrinsic AKI: CKD, %; Sepsis, %	Prerenal AKI: CKD, %; Sepsis, %
du Cheyron *et al.* (39), 2003	P, ICU	19; N/R; N/R; 3.3±1.6	17; N/R; N/R; 2.1 ± 0.5	Sudden increase in serum creatinine level to ≥2 mg/dl or a value 50% greater than the basal concentration when CKD already existed	Patients with hepatorenal syndrome, cirrhosis	Responsiveness to fluids	1	N/R; N/R	N/R; N/R	0; 0	0; 6
Pépin *et al.* (4), 2007	P, hospitalized	33; 66.3; 55; 3.8±1.6	66; 66.8; 47; 2.5±1.3	An increase in serum creatinine level of 30% or higher over the baseline with an abrupt onset (<1 wk)	Contrast examination <48 h before the onset of AKI, rhabdomyolysis, obstructive uropathy, acute GN, drug nephrotoxicity, and kidney failure	Responsiveness to fluids, urine microscopy findings	1	36; 64	24; 65	45; 42	36; 24
Diskin *et al.* (22), 2010	P, hospitalized	20; 67.5±12.7; 56; N/R	80; 66.8±12.3; 49; N/R	AKI patients with oliguria; defined as urine output <600 ml/24 h and abrupt sustained rise in creatinine >1.9 mg/dl	All patients with possible creatinine assay–interfering drugs/conditions	Responsiveness to fluids	<1 and >3	100; 55	100; 71	28; 0	0; 7
Darmon *et al.* (25), 2011	P, ICU	82; 66 (IQR, 56–74); 32; 2.5 (IQR, 1.6–4.1)	54; 71 (IQR, 49–76); 41; 1.4 (IQR, 1.1–1.9)	AKI defined according to the AKIN or MDRD formula	Patients on dialysis, obstructive uropathy	Responsiveness to fluids	1; 0.58	N/R; 39	N/R; 33	28; 74	6; 61
Dewitte *et al.* (41), 2012	P, ICU	24; 69 (IQR, 54–73); 8; N/R	23; 64 (IQR, 43–75); 35; N/R	AKI according to the consensus definition from the Acute Dialysis Quality Initiative group	Patients with CKD, obstructive uropathy	Responsiveness to fluids	1	75; 58	74; 61	0; 29	0; 39
Yassin *et al.* (23), 2013	P, ICU	14; 56.29±19.5; 42; 5.5±2.1	26; 60±15.15; 62; 2.2±0.6	Patients with AKI with circulatory shock; circulatory shock was diagnosed according to the empirical criteria, AKI according to the RIFLE criteria in oliguric patients	CKD, obstructive uropathy, and patients on osmotic diuresis	Response to fluids, urinalysis	1	100; 57	100; 46	0; N/R	0; N/R
Patidar *et al.* (20), 2017	R, hospitalized	12; N/R; N/R; N/R	21; N/R; N/R; N/R	Cirrhotic patients who were admitted for AKI, the defining criteria of AKI are not reported; HRS AKI was diagnosed on the basis of the International Club of Ascites definition	Patients with ascites, patients not on diuretics, advanced kidney failure	Clinical course decided by a nephrologist	1	N/R; 100	N/R; 100	0; 0	0; 0

Table 1. (Continued)

Study, Year	Design, Settings	Intrinsic AKI, *n*; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl	Prerenal AKI, *n*; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl	Inclusion Criteria	Exclusion Criteria	Reference Standard	Fractional Excretion of Sodium Cutoff(s), %	Intrinsic AKI: Oliguric, %; Receiving Diuretics, %	Prerenal AKI: Oliguric, %; Receiving Diuretics, %	Intrinsic AKI: CKD, %; Sepsis, %	Prerenal AKI: CKD, %; Sepsis, %
Gowda *et al.* (D) (24), 2021	P, hospitalized	57; 48.47±10.8; 5; 3.2±1.78	143; 50.42±12.26; 6; 2.5±1.08	Cirrhotic patients who were screened for AKI as per revised International Club of Ascites definitions at admission	CKD, history of KRT, diuretic use, exposure to potential nephrotoxic drugs, cardiovascular disease	Responsiveness to fluids; ATN AKI was diagnosed if abnormal kidney finding is present on ultrasound, proteinuria >500 mg/d, microhematuria (>50 red blood cells per high-power field), or presence of active urinary sediments; HRS AKI was diagnosed on the basis of the International Club of Ascites definition	0.57	N/R; 0	N/R; 0	0; 0	0; 0
Gowda *et al.* (V) (24), 2021	P, hospitalized	17; 49.24±9.5; 0; 2.5±1.11	33; 51.24±12.7; 15; 2.5±1.08	Cirrhotic patients who were screened for AKI as per revised International Club of Ascites definitions at admission	CKD, history of KRT, diuretic use, exposure to potential nephrotoxic drugs, cardiovascular disease	Responsiveness to fluids; ATN AKI was diagnosed if abnormal kidney finding is present on ultrasound, proteinuria >500 mg/d, microhematuria (>50 red blood cells per high-power field), or presence of active urinary sediments; HRS AKI was diagnosed on the basis of the International Club of Ascites definition	0.57	N/R; 0	N/R; 0	0; 0	0; 0

P, prospective; N/R, not reported; ATN, acute tubular necrosis; ICU, intensive care unit; ER, emergency room; IQR, interquartile range; AKIN, Acute Kidney Injury Network; MDRD, Modification of Diet in Renal Disease; R, retrospective; HRS, hepatorenal syndrome; D, derivation cohort; V, validation cohort.

[a]This study included patients with CKD, but their data were not available.

Table 2. Risk of bias and applicability concerns results

Study Identification	Could the Selection of Patients Have Introduced Bias?	Are There Concerns that the Included Patients and Setting Do Not Match the Review Question?	Could the Conduct or Interpretation of the Index Test Have Introduced Bias?	Are There Concerns that the Index Test, Its Conduct, or Interpretation Differ from the Review Question?	Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?	Are There Concerns that the Target Condition as Defined by the Reference Standard Does Not Match the Question?	Could the Patient Flow Have Introduced Bias?
Espinel (6), 1976	Low risk	Unclear concern	Low risk	Low concern	Unclear risk	Low concern	Low risk
Miller *et al.* (27), 1978	High risk	Low concern	Low risk	Low concern	Unclear risk	Low concern	Low risk
Espinel and Gregory (7), 1980	Low risk	Low concern	Low risk	Low concern	Low risk	Low concern	Low risk
Zager *et al.* (28), 1980	Low risk	Low concern	Low risk	Low concern	Unclear risk	Low concern	High risk
Chugh *et al.* (21), 1981	Low risk	Low concern	Unclear risk	High concern	Unclear risk	Low concern	Unclear risk
Brown *et al.* (29), 1983	Low risk	Low concern	Unclear risk	Low concern	Unclear risk	Low concern	Unclear risk
Anderson *et al.* (30), 1984	Low risk	Low concern	Low risk	Low concern	Unclear risk	Low concern	Low risk
Tankhiwale and Ungratwar (26), 1987	Low risk	Low concern	Unclear risk	Low concern	Unclear risk	Low concern	Unclear risk
Fushimi *et al.* (40), 1990	Low risk	Low concern	Unclear risk	Low concern	Unclear risk	Low concern	Low risk
Steinhäuslin *et al.* (18), 1994	High risk	Low concern	High risk	High concern	Unclear risk	Low concern	Low risk
Carvounis *et al.* (9), 2002	Low risk	Low concern	Unclear risk	Low concern	High risk	Low concern	Unclear risk
du Cheyron *et al.* (39), 2003	High risk	Low concern	Unclear risk	Low concern	High risk	Low concern	Low risk
Pépin *et al.* (4), 2007	High risk	Low concern	Low risk	Low concern	Low risk	Low concern	Low risk
Diskin *et al.* (22), 2010	Low risk	Low concern	Low risk	Low concern	Unclear risk	Low concern	Low risk
Darmon *et al.* (25), 2011	Low risk	Low concern	Low risk	Low concern	Unclear risk	Low concern	Low risk
Dewitte *et al.* (41), 2012	Low risk	Low concern	Low risk	Low concern	Unclear risk	Low concern	Low risk
Yassin *et al.* (23), 2013	Low risk	Low concern	Unclear risk	Unclear concern	Unclear risk	Low concern	Unclear risk
Patidar *et al.* (20), 2017	Low risk	Low concern	High risk	Unclear concern	Unclear risk	Low concern	Low risk
Gowda *et al.* (D) (24), 2021	High risk	High concern	High risk	High concern	Unclear risk	Low concern	Low risk
Gowda *et al.* (V) (24), 2021	High risk	High concern	Low risk	High concern	Unclear risk	Low concern	Low risk

D, derivation cohort; V, validation cohort.

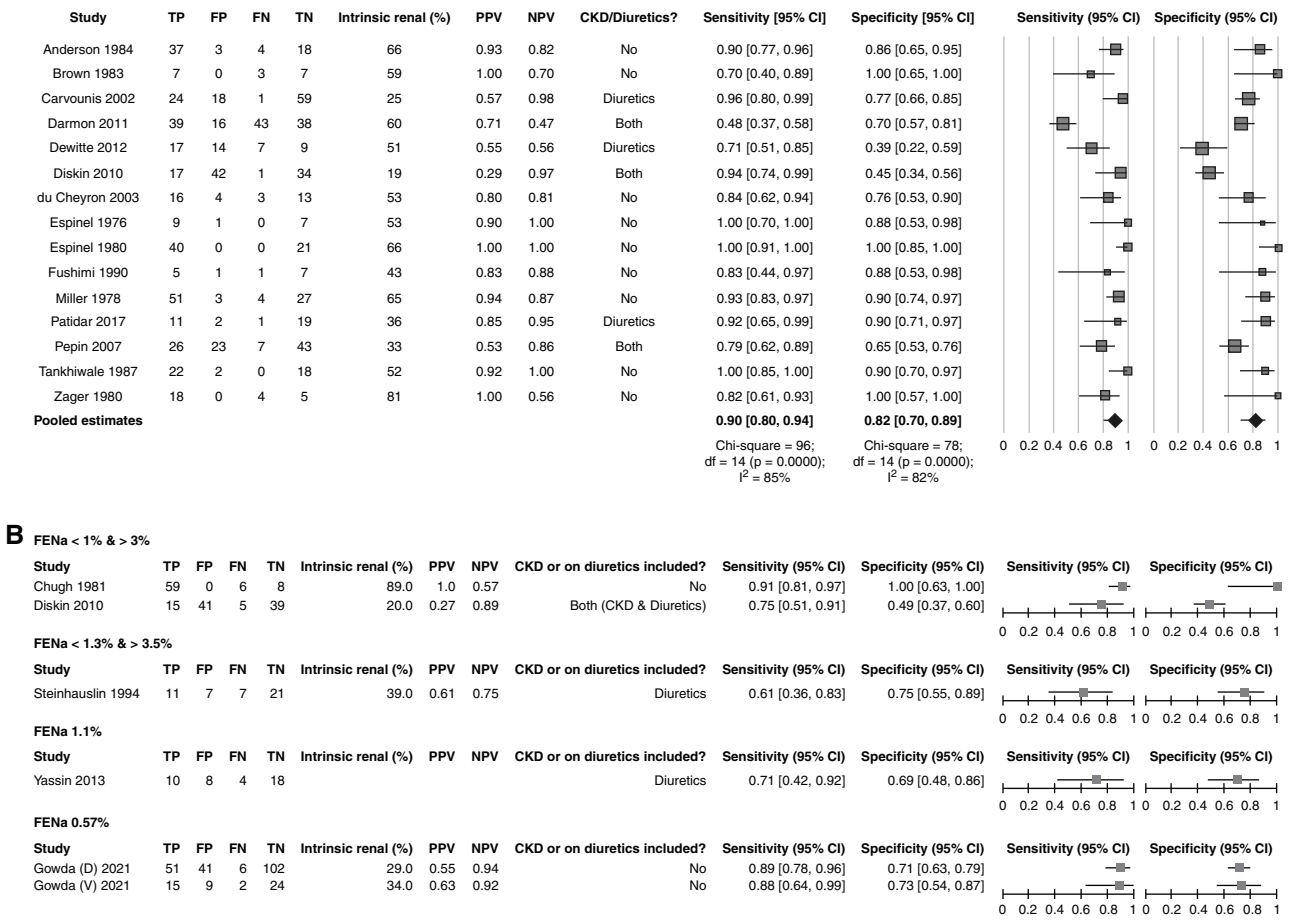

Figure 2. | Forest plots for the included studies at the reported threshold of the fractional excretion of sodium (FENa) for intrinsic AKI versus prerenal AKI. (A) The forest plot for the 15 studies uses a 1% cutoff, including a quantitative meta-analysis of the sensitivity and specificity. The size of the square is proportional to the size of the population. The diamonds represent the pooled estimates. (B) The forest plot for studies that did not use a 1% threshold: FENa <1% and >3%, FENa <1% and >4%, FENa=1%, and FENa 0.57%. Output was from Review Manager (computer program). 95% CI, 95% confidence interval; D, derivation cohort; df, degrees of freedom; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive; V, validation cohort.

FENa in prerenal patients with AKI (*i.e.*, higher false-positive rate) (30,33). Patients with CKD may not conserve their sodium in response to AKI because of prekidney disease or with a decrease in dietary sodium intake (11), leading to a higher false-positive rate. Also, this is consistent with our findings in the diuretics and CKD/diuretics subgroups. The accuracy of the FENa test, especially the specificity, is substantially reduced among this group of patients. Our results demonstrated better FENa performance when used in the patients not on diuretics compared with patients on diuretics, and this was particularly true for test specificity ($P<0.001$). This finding is concurrent with the effect of diuretics on sodium reabsorption (30,33). Moreover, excluding patients on diuretics and patients with CKD provided a prominently high pooled sensitivity and specificity (Table 3, subgroup 4) and explained much of the observed heterogeneity in Figure 3 (Supplemental Figure 3C).

FENa can have higher false negatives when used in nonoliguric patients with AKI; nonoliguric ATN can falsely decrease the result of FENa below 1%. The large volume of solvent in nonoliguric ATN may lower the concentration of sodium in the urine when there is neither salt nor water conservation (34). However, we could not extract the nonoliguric subgroup to test the accuracy of FENa in patients with AKI with no oliguria. Most of the studies were not clear about the urine output state or did not provide enough data to extract the required 2×2 table. Nevertheless, we were able to perform a subgroup analysis for oliguric patients (Table 3, subgroup 5). Additionally, we observed a higher performance for the FENa test in most of the earlier studies (before 2000) compared with more recent studies, and this was statistically significant for specificity ($P<0.001$) but not for sensitivity ($P=0.12$). However, this variation can be explained by including patients with CKD or patients on diuretics in most of the recent studies (Supplemental Figure 3F).

Perazella *et al.* (35) recently reported on using urine microscopy as an estimable diagnostic tool for enhancing

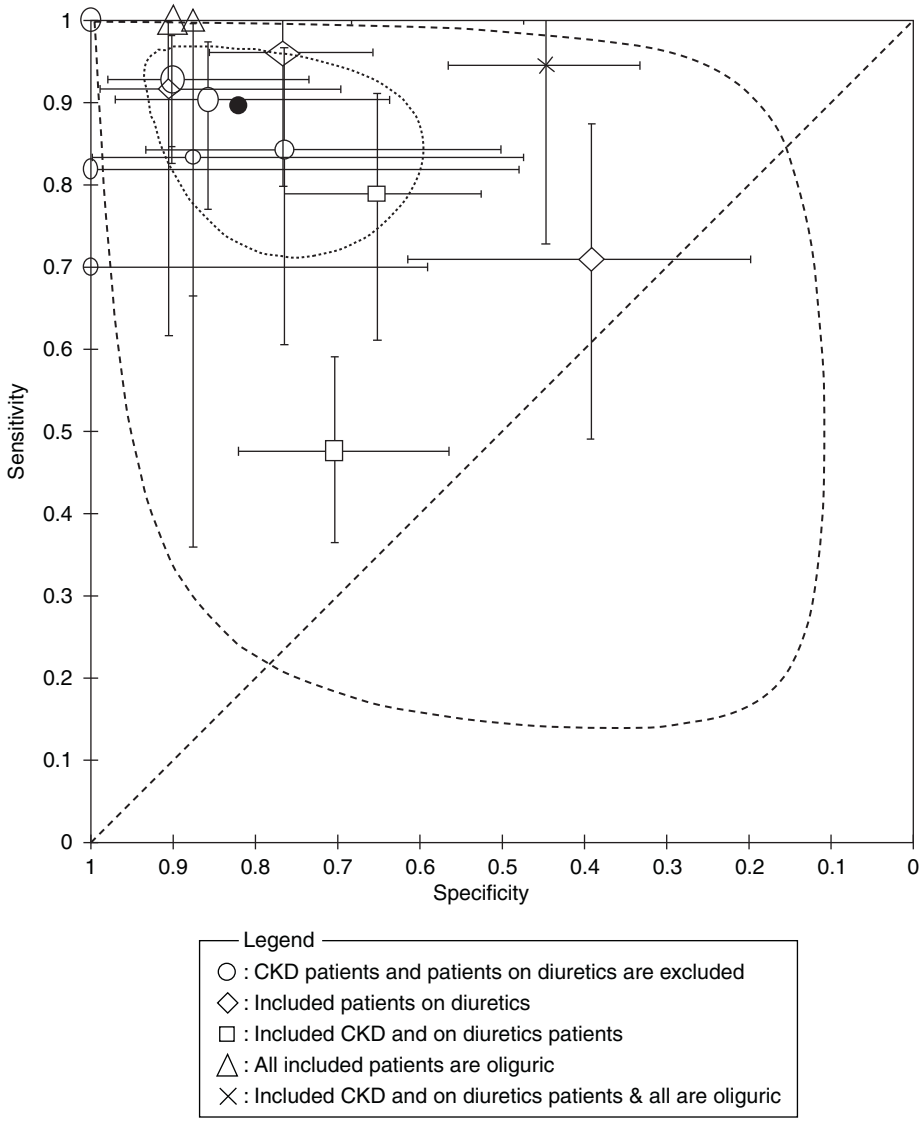

Figure 3. | **Summary receiver operating characteristic plot for the 15 studies used for FENa at the 1% threshold.** The summary operating point (filled circle) for the 15 studies included in the meta-analysis is shown with the 95% confidence interval (dotted curve) and the 95% prediction region (dashed curve). The different legends represent the characteristics of each study population. The sizes of the ellipsoids, diamonds, squares, triangles, and crosses are proportional to the sample sizes for each study. Output was from Review Manager (computer program).

ATN diagnosis. They showed that it strongly supports the differentiation between the etiologies of AKI. They developed a scoring system that solely relies on the number of granular casts and renal tubular epithelial cells in the microscopic analysis of urine. Their approach provided a sensitivity of 76% and a specificity of 86% in distinguishing ATN from prerenal AKI (35). Still, when clinical suspicion contradicts urine microscopy, FENa would be beneficial to support the diagnosis, especially in oliguric patients without CKD and not on diuretics. A scoring system that combines urine microscopy and FENa would be of interest but has not been developed. Given the findings in our review, future studies combining the FENa and urine microscopy could improve the sensitivity and specificity of the scoring system. Additionally, Carvounis *et al.* (9) introduced fractional excretion of urea (FEUrea) for distinguishing prerenal and intrinsic AKI and showed that it has better accuracy in patients with AKI using diuretics. Their results revealed that 48% of prerenal patients on diuretics had FENa <1%. By contrast, 89% had FEUrea <35% (9). Moreover, their findings were confirmed by Diskin *et al.* (22) as 96% of prerenal patients receiving diuretics had FEUrea <40%, whereas 29% of them had FENa <1%. Yet, FENa was reported to be superior in patients not on diuretics (4).

Ultimately, there are multiple known causes of intrinsic AKI with FENa below 1%. Early in the course of sepsis-induced ATN (36), in patients with chronic prekidney disease overlays by ATN, such as liver cirrhosis and heart failure (37), and patients with less severe early assessed ischemic ATN, as these patients might be in the transition state from prekidney disease to postischemic ATN (38).

Table 3. Results of subgroup analysis

Subgroup No.	Subgroup	No. of Studies	No. of Participants	Intrinsic AKI, *N* (%)	Pooled Sensitivity [95% Confidence Interval]; I^2	Pooled Specificity [95% Confidence Interval]; I^2	Diagnostic Odds Ratio [95% Confidence Interval]; I^2	Positive Likelihood Ratio [95% Confidence Interval]; I^2	Negative Likelihood Ratio [95% Confidence Interval]; I^2	Positive Predictive Value [95% Confidence Interval]; I^2	Negative Predictive Value [95% Confidence Interval]; I^2
1	Patients not on diuretics	12	502	270 (54)	92% [85% to 96%]; 57%	88% [83% to 92%]; 20%	88 [34 to 226]; 24%	7.83 [5.10 to 12.01]; 0%	0.09 [0.05 to 0.17]; 47%	91% [83% to 95%]; 62%	92% [82% to 96%]; 65%
2	Patients on diuretics	5	238	88 (37)	80% [69% to 87%]; 0%	54% [31% to 75%]; 86%	5 [1 to 16]; 59%	1.71 [0.97 to 3.02]; 77%	0.38 [0.18 to 0.80]; 27%	54% [31% to 75%]; 89%	82% [61% to 93%]; 76%
3	Without patients with CKD	13	632	294 (47)	92% [87% to 96%]; 50%	85% [73% to 93%]; 84%	69 [25 to 191]; 36%	6.22 [3.21 to 12.02]; 88%	0.09 [0.05 to 0.16]; 38%	89% [73% to 96%]; 92%	92% [84% to 96%]; 69%
4	Patients without CKD and not on diuretics	11	464	225 (49)	93% [86% to 96%]; 54%	89% [84% to 93%]; 14%	107 [41 to 279]; 0%	8.60 [5.53 to 13.38]; 0%	0.08 [0.04 to 0.16]; 46%	92% [85% to 96%]; 58%	92% [82% to 97%]; 68%
5	Oliguric patients	9	355	154 (43)	93% [82% to 97%]; 62%	88% [71% to 96%]; 87%	97 [20 to 471]; 46%	7.84 [2.91 to 21.10]; 90%	0.08 [0.03 to 0.22]; 62%	90% [70% to 97%]; 92%	93% [82% to 98%]; 60%
6	Oliguric patients without CKD and not on diuretics	8	264	130 (49)	95% [82% to 99%]; 62%	91% [83% to 95%]; 20%	197 [38 to 1017]; 0%	10.07 [5.58 to 18.15]; 0%	0.05 [0.01 to 0.22]; 65%	92% [81% to 97%]; 51%	96% [81% to 99%]; 57%
7	Studies including patients with CKD or on diuretics	6	511	194 (38)	83% [64% to 93%]; 88%	66% [51% to 78%]; 84%	10 [3 to 34.0]; 78%	2.42 [1.52 to 3.87]; 82%	0.26 [0.10 to 0.63]; 85%	56% [43% to 69%]; 82%	88% [66% to 97%]; 94%
8	Studies published before 2000	7	325	205 (63)	93% [84% to 97%]; 63%	92% [85% to 95%]; 1%	148 [43 to 508]; 0%	10.93 [5.89 to 20.30]; 0%	0.07 [0.03 to 0.18]; 55%	95% [91% to 97%]; 36%	90% [75% to 96%]; 55%
9	Studies published after 2000	8	547	213 (39)	83% [67% to 92%]; 86%	67% [53% to 78%]; 82%	10 [3 to 30]; 76%	2.52 [1.64 to 3.86]; 80%	0.25 [0.12 to 0.55]; 84%	60% [46% to 72%]; 82%	87% [68% to 96%]; 93%

This study has some limitations. Some variations are present in defining AKI in the included studies, as many were conducted before the introduction of the recent definitions of AKI (1–3). Although we are reasonably confident that the reference standard used in our review is robust and clinically appropriate, it should be mentioned that in two (9,39) of the included studies, the reference standard was carried out with the knowledge of the index test results; only two studies (4,7) of the remaining 17 were clear about interpreting the reference standard apart from the index test. This may overestimate the accuracy of the index test. Although the FENa test should be done early in the disease before the final diagnosis, six studies (21,23,26,29,39,40) were unclear if the index test was interpreted separately from the reference standard. In five (9,21,23,26,29) of the included studies, we were uncertain whether the interval between the index test and the reference standard was appropriate. Finally, most of the studies' patients were hospitalized, which may affect the external validity of our findings.

FENa can be used to distinguish intrinsic from prerenal AKI in oliguric patients, where we found it to perform the best. Its ability to distinguish intrinsic from prerenal AKI and, hence, its clinical utility are significantly diminished in patients with CKD and those receiving diuretics. On the basis of the results of this meta-analysis, obtaining an FENa value for every patient with AKI, as commonly practiced, should be discouraged, and a thorough clinical review of existing comorbidities, including the presence of CKD and current use of diuretics, is needed to help guide its clinical use and interpretation. A large prospective study that considers patients' history, comorbidities, medications, and urine output is much needed to further define the clinical role of FENa in the diagnosis of AKI.

Disclosures

All authors have nothing to disclose.

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Author Contributions

M. Abdelhafez, O. AbuShamma, A. Atieh, B. Babaa, M. Baniowda, K. Gharaibeh, and A. Hamadah conceptualized the study; M. Abdelhafez, O. AbuShamma, A. Atieh, B. Babaa, M. Baniowda, K. Gharaibeh, A. Hamadah, B. Hasan, A. Hrizat, and T. Nayfeh were responsible for data curation; M. Abdelhafez, O. AbuShamma, A. Atieh, B. Babaa, M. Baniowda, K. Gharaibeh, A. Hamadah, B. Hasan, A. Hrizat, and T. Nayfeh were responsible for investigation; M. Abdelhafez and T. Nayfeh were responsible for formal analysis; M. Abdelhafez, O. AbuShamma, A. Atieh, B. Babaa, M. Baniowda, K. Gharaibeh, A. Hamadah, B. Hasan, A. Hrizat, and T. Nayfeh were responsible for methodology; M. Abdelhafez, K. Gharaibeh, A. Hamadah, B. Hasan, and T. Nayfeh were responsible for project administration; B. Hasan, L. Hassett, and T. Nayfeh were responsible for resources; M. Abdelhafez, O. AbuShamma, A. Atieh, and T. Nayfeh were responsible for software; K. Gharaibeh, A. Hamadah, B. Hasan, and T. Nayfeh were responsible for validation; M. Abdelhafez, K. Gharaibeh, A. Hamadah, and B. Hasan were responsible for visualization; K. Gharaibeh, A. Hamadah, B. Hasan, and T. Nayfeh provided supervision; M. Abdelhafez wrote the original draft; and M. Abdelhafez, O. AbuShamma, A. Atieh, K. Gharaibeh, A. Hamadah, B. Hasan, A. Hrizat, and T. Nayfeh reviewed and edited the manuscript.

Data Sharing Statement

All data used in this study are available in this article.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14561121/-/DCSupplemental.

Supplemental Figure 1. Risk of bias and applicability concerns.

Supplemental Figure 2. Forest plots for the subgroup analysis.

Supplemental Figure 3. The summary ROC plots for the subgroup analysis.

Supplemental Table 1. Actual search strategies.

Supplemental Table 2. QUADAS-2 classification.

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See related editorial, "Fractional Excretion of Sodium (FENa): An Imperfect Tool for a Flawed Question," on pages 777–778.

Supplemental Material

Table of contents:

Supplemental Table 1: Actual Search Strategies

OVID

Database(s): **Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews - Cochrane Central Register of Controlled Trials** November 2021**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to December 28, 2021**, Embase** 1974 to 2021 December 30

Search Strategy:

#	Searches
1	exp Acute Kidney Injury/ or acute kidney failure/
2	(acute adj2 ("kidney injury" or "kidney failure" or "kidney insufficiency" or "renal injury" or "renal failure" or "renal insufficiency")).ti,ab,hw,kw.
3	1 or 2
4	exp Sodium/
5	((("fractional excretion" or "excreted fraction*") adj5 (sodium or natrium or na)) or ("(fena)" or fena)).ti,ab,hw,kw.
6	4 or 5
7	3 and 6
8	(exp animals/ or exp nonhuman/) not exp humans/
9	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots

	or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.
10	(rat or rats or mice or mouse or murine or pig or pigs or porcine or swine or dog or dogs).ti.
11	or/8-10
12	7 not 11
13	limit 12 to english language [Limit not valid in CDSR; records were retained]
14	limit 12 to no language specified [Limit not valid in CDSR; records were retained]
15	13 or 14
16	remove duplicates from 15

SCOPUS

1	TITLE-ABS-KEY (acute W/2 ("kidney injury" or "kidney failure" or "kidney insufficiency" or "renal injury" or "renal failure" or "renal insufficiency"))
2	TITLE-ABS-KEY ((("fractional excretion" or "excreted fraction*") W/5 (sodium or natrium or na)) or ("(fena)" or fena))
3	1 and 2
4	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
5	3 not 4
6	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
7	5 not 6
8	LANGUAGE(english)
9	7 and 8
10	(TITLE-ABS-KEY ((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR

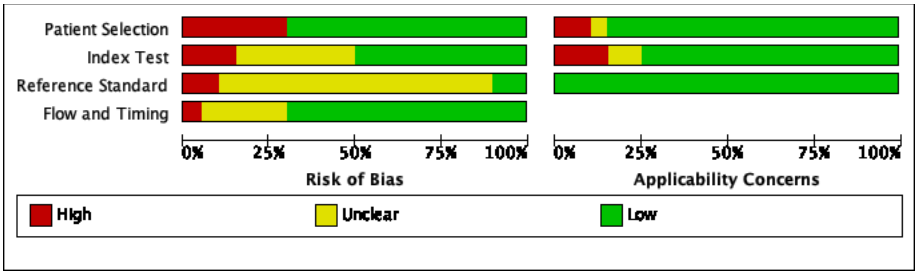
	baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans OR patient OR patients)))
11	9 not 10

Supplemental Table 2: QUADAS-2 classification

Domain 1: Patient selection	**Patient sampling**	Patients who developed AKI, defined by any known criteria or equivalent, and have had a FENa test.
	Was a consecutive or random sample of patients enrolled?	Yes: if a consecutive or random sample of participants were enrolled. No: if a consecutive or random sample of participants were not enrolled. Unclear: if the study does not describe the method of participants enrolment.
	Was a case-control design avoided?	Yes: if the study has not used a case-control design. No: if the study has used a case-control design. Unclear: if the study does not report enough information to fulfill whether a case-control design was used.
	Did the study avoid inappropriate exclusions?	Yes: if the study has included the results of all patients in the study irrespective of their comorbidities or characteristics. No: if the study has excluded patients from the analysis based on having factors that may affect the test result Unclear: if the study does not report enough information.
	Could the selection of patients have introduced bias?	Low risk of bias: if 'yes' was the answer for all of the above 3 questions. High risk of bias: if 'no' was the answer for any of the above 3 questions. Unclear risk of bias: if 'unclear' was the answer for any of the above 3 questions but without a 'no' answer for any of the above 3 questions.
	Patient characteristics and setting	Patients' settings for each study will be listed under "Patient characteristics and setting" in the table of "Characteristics of included studies".
	Are there concerns that the included patients and setting do not match the review question?	Low, high, or unclear concern were returned for the applicability based on the answer for the third signaling question above and on balancing how closely the sample meets the target population of interest.
Domain 2: Index tests	**Index test**	Fractional Excretion of Sodium (FENa)
	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes: if the report stated that the person undertaking the index test did not know the results of the reference tests or if the index test appeared to be carried out before the reference standard. No: if the report stated that the same person conducted both tests or that the results of the index test were known to the person undertaking the reference tests. Unclear: if insufficient information is provided.
	If a threshold was used, was it pre-specified?	Yes: if prespecified No: if the authors selected the best non-prespecified cut-off value based on the results of the study. Unclear: if there is doubt which cut-off has been used.
	Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias: if 'yes' was the answer for both of the above questions. High risk of bias: if 'no' was the answer for any of the above 2 questions. Unclear risk of bias: if 'unclear' was the answer for any of the above 2 questions but without a 'no' answer for any of the above 2 questions.
	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	An answer of low, high, or unclear concern about applicability will be made based on a balanced assessment of the information reported under domain 2 'Index test'
Domain 3: Target condition and reference standard	**Target condition and reference standard(s)**	Target condition: AKI defined by any known criteria or their equivalent. The information for the reference standard is reported under 'Reference standard(s)' in the 'Characteristics of included studies

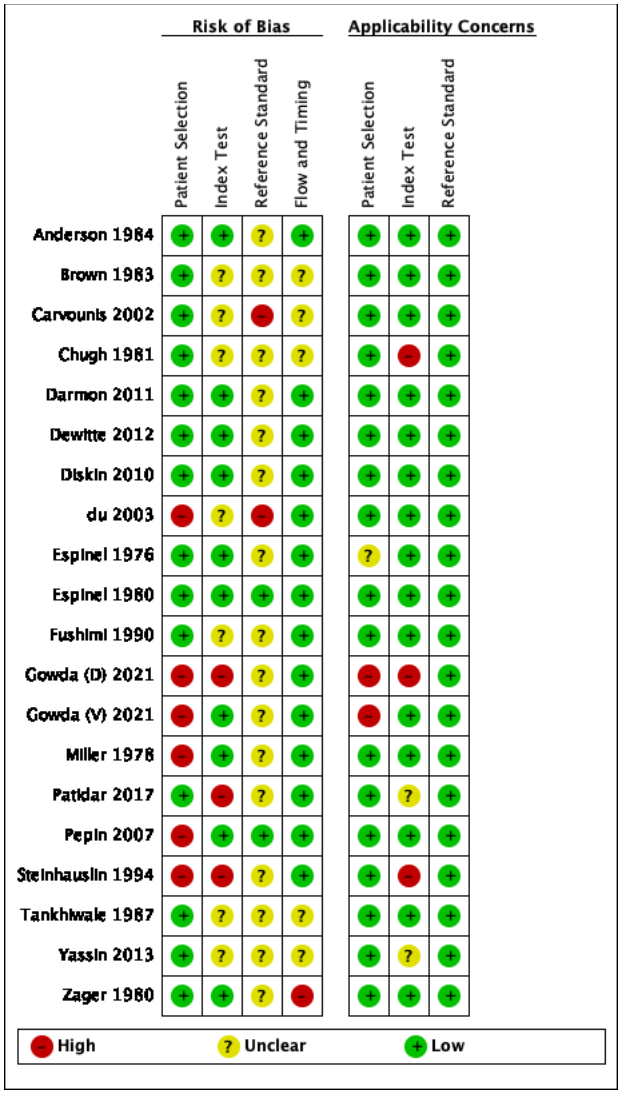
	Are the reference standards likely to correctly classify the target condition?	Yes: if reference standard is one of the following: (1) responsiveness to volume expansion; (2) kidney biopsy, with or without microscopic analysis of the urine No: if the reference standard was none of the above Unclear: if the information is insufficient.
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes: if the reference standard was interpreted without the knowledge of the results of the index test. No: if the reference standard was interpreted with the knowledge of the results of the index test. Unclear: it is not clear whether the reference standard was interpreted without the knowledge of the results of the index test.
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias: if 'yes' was the answer for both of the above 2 questions. High risk of bias: if 'no' was the answer for any of the above 2 questions. Unclear risk of bias: if 'unclear' was the answer for any of the above 2 questions but without a 'no' answer for any of the above 2 questions.
	Are there concerns that the target condition as defined by the reference standard does not match the question?	The answer to this question will always be "No concern" because if they did not match, the study will be excluded.
Domain 4: Flow and timing	**Flow and timing**	Patients may have progression of the disease from prerenal into intrinsic renal AKI, or they may spontaneously recover. The reference standards should be carried within 2 to 3 days.
	Was there an appropriate interval between index test and reference standard?	Yes: if the time interval between the index test and the reference standard was less than 3 days. No: if the time interval between the index test and the reference standard was more than 3 days. Unclear: if the time interval between the index test and the reference standard was unclear.
	Did all patients receive the same reference standard?	Yes: if all the patients received the same reference standard. No: if different patients received different reference standards. Unclear: if it was not clear whether the patients received the same reference standard or did not.
	Could the patient flow have introduced bias?	Low risk of bias: if 'yes' was the answer for both of the above 2 questions. High risk of bias: if 'no' was the answer for any of the above 2 questions. Unclear risk of bias: if 'unclear' was the answer for any of the above 2 questions but without a 'no' answer for any of the above 2 questions.

Supplemental figure 1-a: Risk of bias and applicability concerns graph



Description: Review authors' judgements about each domain presented as percentages across included studies. ***(Output from Review Manager (RevMan) [Computer program]).***

Supplemental figure 1-b: Risk of bias and applicability concerns summary

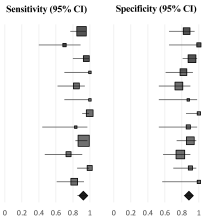


Description: Review authors' judgements about each domain for each included study. ***(Output from Review Manager (RevMan) [Computer program])***

Supplemental figure 2: Forest plots for the subgroup analysis

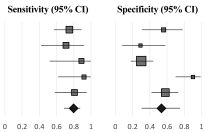
1- FENa 1% (Patients not on diuretics)

Study	TP	FP	FN	TN	Intrinsic renal (%)	PPV	NPV	Sensitivity [95% CI]	Specificity [95% CI]
Anderson 1984	37	3	4	18	66	0.93	0.82	0.90 [0.77, 0.96]	0.86 [0.65, 0.95]
Brown 1983	7	0	3	7	59	1.00	0.70	0.70 [0.40, 0.89]	1.00 [0.65, 1.00]
Carvounis 2002	24	11	1	39	33	0.86	0.98	0.96 [0.80, 0.99]	0.92 [0.81, 0.98]
Diskin 2010	9	4	0	18	29	0.69	1.00	1.00 [0.70, 1.00]	0.82 [0.61, 0.93]
du 2003	16	4	3	13	53	0.80	0.81	0.84 [0.62, 0.94]	0.76 [0.53, 0.90]
Espinel 1976	9	1	0	7	53	0.90	1.00	1.00 [0.70, 1.00]	0.88 [0.53, 0.98]
Espinel 1980	40	0	0	21	66	1.00	1.00	1.00 [0.91, 1.00]	1.00 [0.85, 1.00]
Fushimi 1990	5	1	1	7	43	0.83	0.88	0.83 [0.44, 0.97]	0.88 [0.53, 0.98]
Miller 1978	51	3	4	27	65	0.94	0.87	0.93 [0.83, 0.97]	0.90 [0.74, 0.97]
Pepin 2007	9	5	3	18	34	0.64	0.86	0.75 [0.47, 0.91]	0.78 [0.58, 0.90]
Tankhiwale 1987	22	2	0	18	52	0.92	1.00	1.00 [0.85, 1.00]	0.90 [0.70, 0.97]
Zager 1980	18	0	4	5	81	1.00	0.56	0.82 [0.61, 0.93]	1.00 [0.57, 1.00]
Pooled estimates								**0.92 [0.85, 0.96]**	**0.88 [0.83, 0.96]**
								Chi-square = 25; df = 11 (p = 0.0079); I^2 = 57%	Chi-square = 14; df = 11 (p = 0.2493); I^2 = 20%



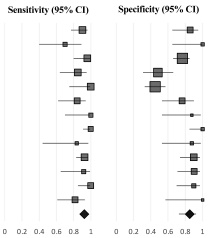
2- FENa 1% (Patients on diuretics)

Study	TP	FP	FN	TN	Intrinsic renal (%)	PPV	NPV	Sensitivity [95% CI]	Specificity [95% CI]
Darmon 2011	24	8	8	10	64	0.75	0.56	0.75 [0.57, 0.89]	0.56 [0.31, 0.78]
Dewitte 2012	10	10	4	4	50	0.50	0.50	0.71 [0.42, 0.92]	0.29 [0.08, 0.58]
Diskin 2010	8	38	1	16	14	0.17	0.94	0.89 [0.52, 1.00]	0.30 [0.18, 0.44]
Patidar 2017	11	2	1	19	36	0.85	0.95	0.92 [0.62, 1.00]	0.90 [0.70, 0.99]
Pepin 2007	17	18	4	25	33	0.49	0.86	0.81 [0.58, 0.95]	0.58 [0.42, 0.73]
Pooled estimates								**0.80 [0.69, 0.87]**	**0.54 [0.31, 0.75]**
								Chi-square = 3; df = 4 (p = 0.5894); I^2 = 0%	Chi-square = 29; df = 4 (p = 0.0000); I^2 = 86%



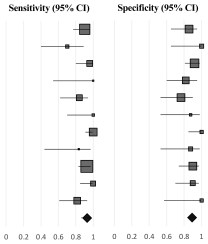
3- FENa 1% (Without CKD patients)

Study	TP	FP	FN	TN	Intrinsic renal (%)	PPV	NPV	Sensitivity [95% CI]	Specificity [95% CI]
Anderson 1984	37	3	4	18	66	0.93	0.82	0.90 [0.77, 0.96]	0.86 [0.65, 0.95]
Brown 1983	7	0	3	7	59	1.00	0.70	0.70 [0.40, 0.89]	1.00 [0.65, 1.00]
Carvounis 2002	24	18	1	59	25	0.57	0.98	0.96 [0.80, 0.99]	0.77 [0.66, 0.85]
Dewitte 2012	17	14	3	13	43	0.55	0.81	0.85 [0.64, 0.95]	0.48 [0.31, 0.66]
Diskin 2010	13	42	0	34	15	0.24	1.00	1.00 [0.70, 1.00]	0.45 [0.33, 0.57]
du 2003	16	4	3	13	53	0.80	0.81	0.84 [0.62, 0.94]	0.76 [0.53, 0.90]
Espinel 1976	9	1	0	7	53	0.90	1.00	1.00 [0.70, 1.00]	0.88 [0.53, 0.98]
Espinel 1980	40	0	0	21	66	1.00	1.00	1.00 [0.91, 1.00]	1.00 [0.85, 1.00]
Fushimi 1990	5	1	1	7	43	0.83	0.88	0.83 [0.44, 0.97]	0.88 [0.53, 0.98]
Miller 1978	51	3	4	27	65	0.94	0.87	0.93 [0.83, 0.97]	0.90 [0.74, 0.97]
Patidar 2017	11	2	1	19	36	0.85	0.95	0.92 [0.65, 0.99]	0.90 [0.71, 0.97]
Tankhiwale 1987	22	2	0	18	52	0.92	1.00	1.00 [0.85, 1.00]	0.90 [0.70, 0.97]
Zager 1980	18	0	4	5	81	1.00	0.56	0.82 [0.61, 0.93]	1.00 [0.57, 1.00]
Pooled estimates								**0.92 [0.87, 0.96]**	**0.85 [0.73, 0.93]**
								Chi-square = 24; df = 12 (p = 0.0071); I^2 = 50%	Chi-square = 73; df = 12 (p = 0.0000); I^2 = 84%



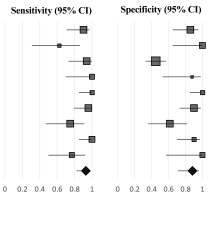
4- FENa 1% (Patients without CKD and not on diuretics)

Study	TP	FP	FN	TN	Intrinsic renal (%)	PPV	NPV	Sensitivity [95% CI]	Specificity [95% CI]
Anderson 1984	37	3	4	18	66	0.93	0.82	0.90 [0.77, 0.97]	0.86 [0.64, 0.97]
Brown 1983	7	0	3	7	59	1.00	0.70	0.70 [0.35, 0.93]	1.00 [0.59, 1.00]
Carvounis 2002	24	11	1	39	33	0.86	0.98	0.96 [0.80, 1.00]	0.92 [0.81, 0.98]
Diskin 2010	6	4	0	18	21	0.60	1.00	1.00 [0.54, 1.00]	0.82 [0.60, 0.95]
du 2003	16	4	3	13	53	0.80	0.81	0.84 [0.60, 0.97]	0.76 [0.50, 0.93]
Espinel 1976	9	1	0	7	53	0.90	1.00	1.00 [0.66, 1.00]	0.88 [0.47, 1.00]
Espinel 1980	40	0	0	21	66	1.00	1.00	1.00 [0.91, 1.00]	1.00 [0.84, 1.00]
Fushimi 1990	5	1	1	7	43	0.83	0.88	0.83 [0.36, 1.00]	0.88 [0.47, 1.00]
Miller 1978	51	3	4	27	65	0.94	0.87	0.93 [0.82, 0.98]	0.90 [0.73, 0.98]
Tankhiwale 1987	22	2	0	18	52	0.92	1.00	1.00 [0.85, 1.00]	0.90 [0.68, 0.99]
Zager 1980	18	0	4	5	81	1.00	0.56	0.82 [0.60, 0.95]	1.00 [0.48, 1.00]
Pooled estimates								**0.93 [0.86, 0.96]**	**0.89 [0.84, 0.93]**
								Chi-square = 22; df = 10 (p = 0.0158); I^2 = 54%	Chi-square = 12; df = 10 (p = 0.3144); I^2 = 14%



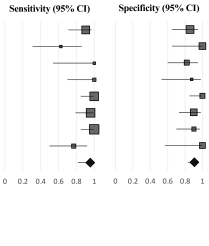
5- FENa 1% (Oliguric patients)

Study	TP	FP	FN	TN	Intrinsic renal (%)	PPV	NPV	Sensitivity [95% CI]	Specificity [95% CI]
Anderson 1984	19	3	2	18	50	0.86	0.90	0.90 [0.70, 0.99]	0.86 [0.64, 0.97]
Brown 1983	5	0	3	7	53	1.00	0.70	0.63 [0.24, 0.91]	1.00 [0.59, 1.00]
Diskin 2010	17	42	1	34	19	0.29	0.97	0.94 [0.73, 1.00]	0.45 [0.33, 0.57]
Espinel 1976	9	1	0	7	53	0.90	1.00	1.00 [0.66, 1.00]	0.88 [0.47, 1.00]
Espinel 1980	22	0	0	21	51	1.00	1.00	1.00 [0.85, 1.00]	1.00 [0.84, 1.00]
Miller 1978	23	3	1	27	44	0.88	0.96	0.96 [0.79, 1.00]	0.90 [0.73, 0.98]
Pepin 2007	9	5	3	8	48	0.64	0.73	0.75 [0.43, 0.95]	0.62 [0.32, 0.86]
Tankhiwale 1987	22	2	0	18	52	0.92	1.00	1.00 [0.85, 1.00]	0.90 [0.68, 0.99]
Zager 1980	10	0	3	5	72	1.00	0.63	0.77 [0.46, 0.95]	1.00 [0.48, 1.00]
Pooled estimates								**0.93 [0.82, 0.97]**	**0.88 [0.71, 0.96]**
								Chi-square = 21; df = 8 (p = 0.0075); I^2 = 62%	Chi-square = 60; df = 8 (p = 0.0000); I^2 = 87%



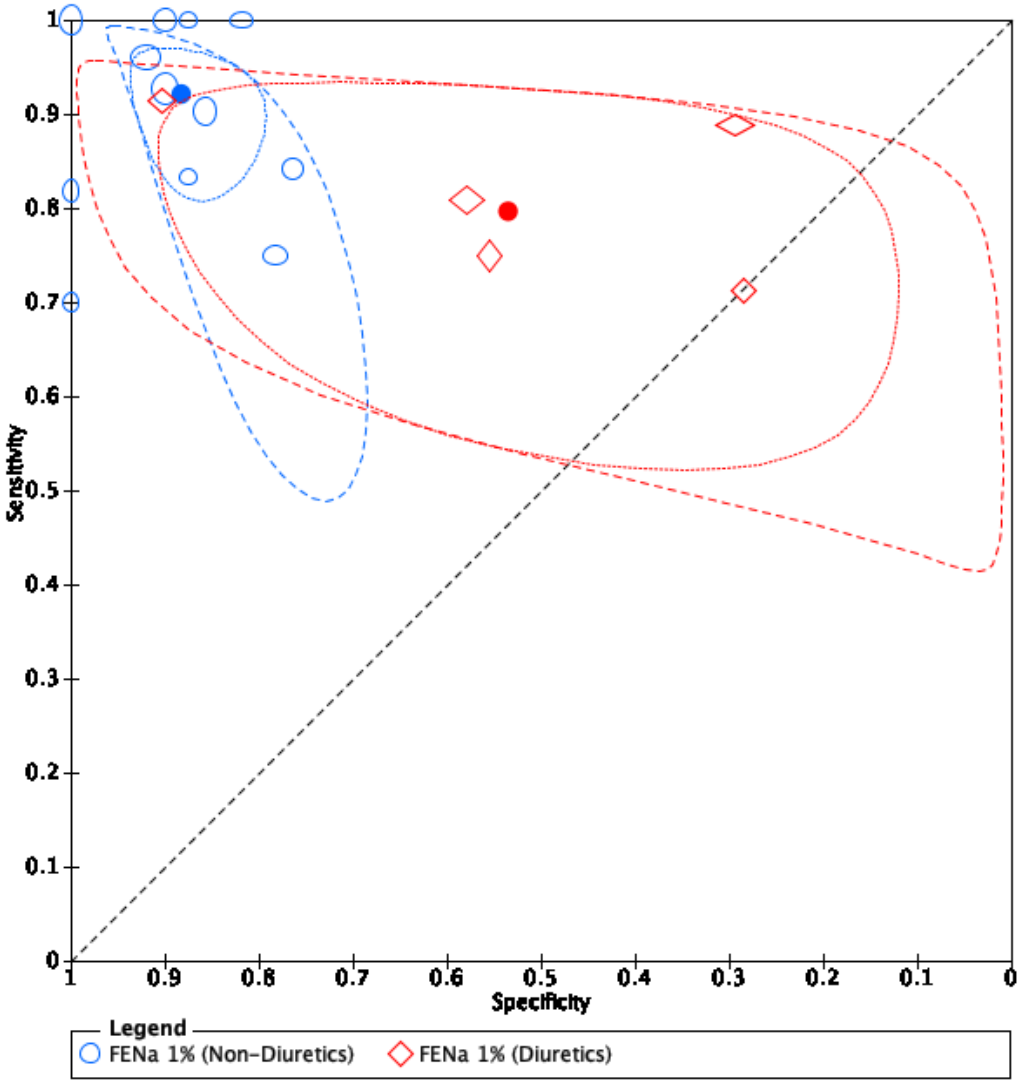
6- FENa 1% (Oliguric patients without CKD and not on diuretics)

Study	TP	FP	FN	TN	Intrinsic renal (%)	PPV	NPV	Sensitivity [95% CI]	Specificity [95% CI]
Anderson 1984	19	3	2	18	50	0.86	0.90	0.90 [0.70, 0.99]	0.86 [0.64, 0.97]
Brown 1983	5	0	3	7	53	1.00	0.70	0.63 [0.24, 0.91]	1.00 [0.59, 1.00]
Diskin 2010	6	4	0	18	21	0.60	1.00	1.00 [0.54, 1.00]	0.82 [0.60, 0.95]
Espinel 1976	9	1	0	7	53	0.90	1.00	1.00 [0.66, 1.00]	0.88 [0.47, 1.00]
Espinel 1980	22	0	0	21	51	1.00	1.00	1.00 [0.85, 1.00]	1.00 [0.84, 1.00]
Miller 1978	23	3	1	27	44	0.88	0.96	0.96 [0.79, 1.00]	0.90 [0.73, 0.98]
Tankhiwale 1987	22	2	0	18	52	0.92	1.00	1.00 [0.85, 1.00]	0.90 [0.68, 0.99]
Zager 1980	10	0	3	5	72	1.00	0.63	0.77 [0.46, 0.95]	1.00 [0.48, 1.00]
Pooled estimates								**0.95 [0.82, 0.99]**	**0.91 [0.83, 0.95]**
								Chi-square = 19; df = 7 (p = 0.0097); I^2 = 62%	Chi-square = 9; df = 7 (p = 0.2728); I^2 = 20%



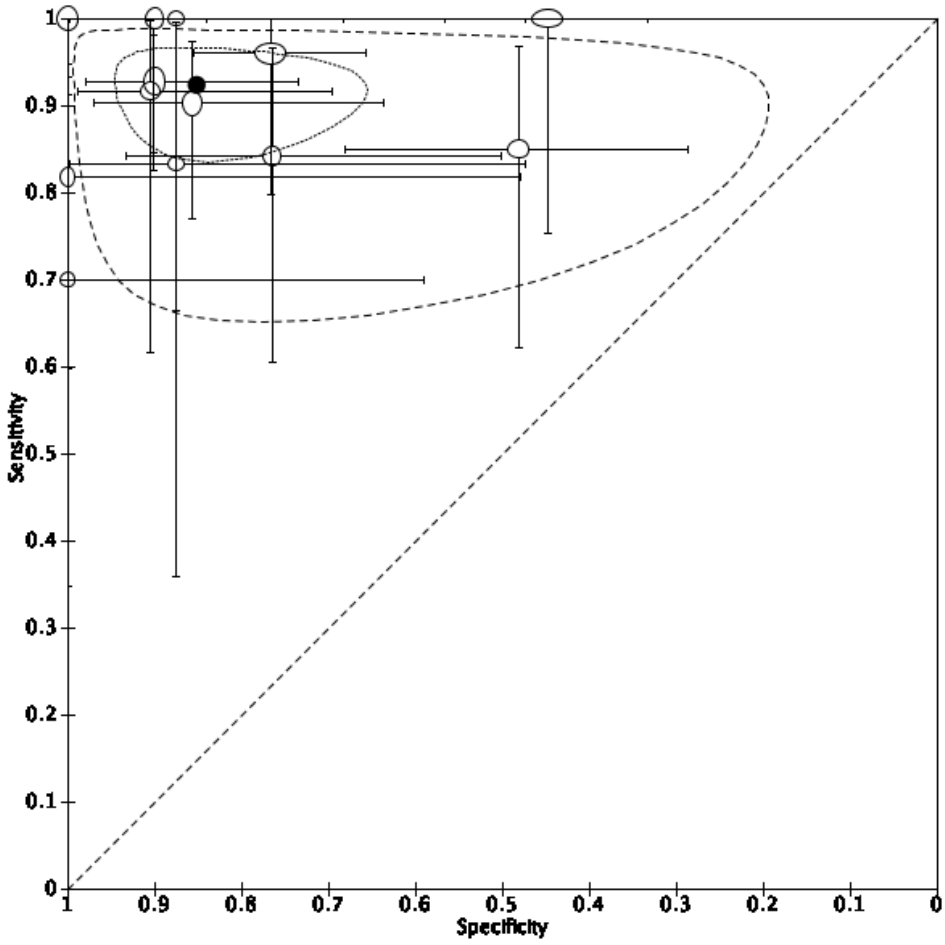
Description: The size of the square is proportional to the size of the population. The diamond represents the pooled estimates. TP: True Positive, FP: False Positive, FN: False Negative, TN: True Negative, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

Supplemental figure 3-a: Summary receiver operating characteristic plot for the non-diuretics and diuretics subgroups



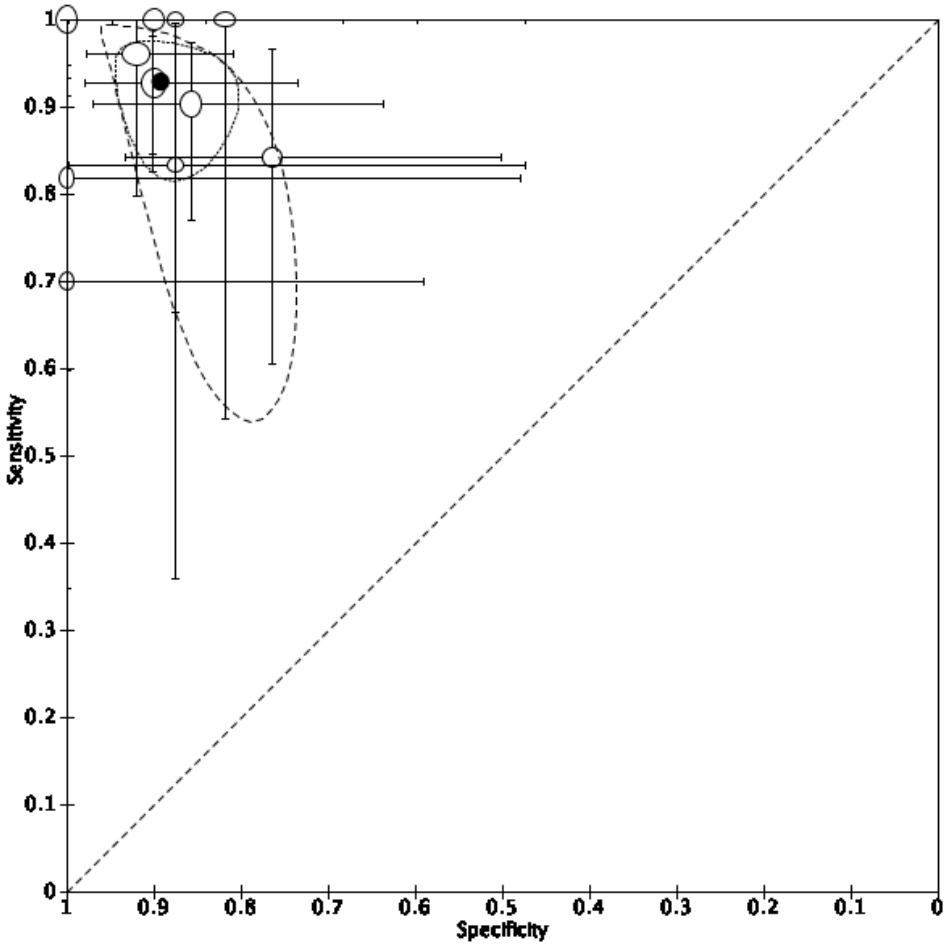
Description: The summary operating point (the filled circles) with the estimated average sensitivities and specificities with their 95% confidence (dotted curve) and prediction regions (dashed curve) for the non-diuretics subgroup (blue) compared to the diuretics subgroup (red). The size of the ellipsoid and diamond are proportional to the sample size for each study. ***(Output from Review Manager (RevMan) [Computer program])***

Supplemental figure 3-b: Summary receiver operating characteristic plot for the 13 studies that excluded chronic kidney disease patients



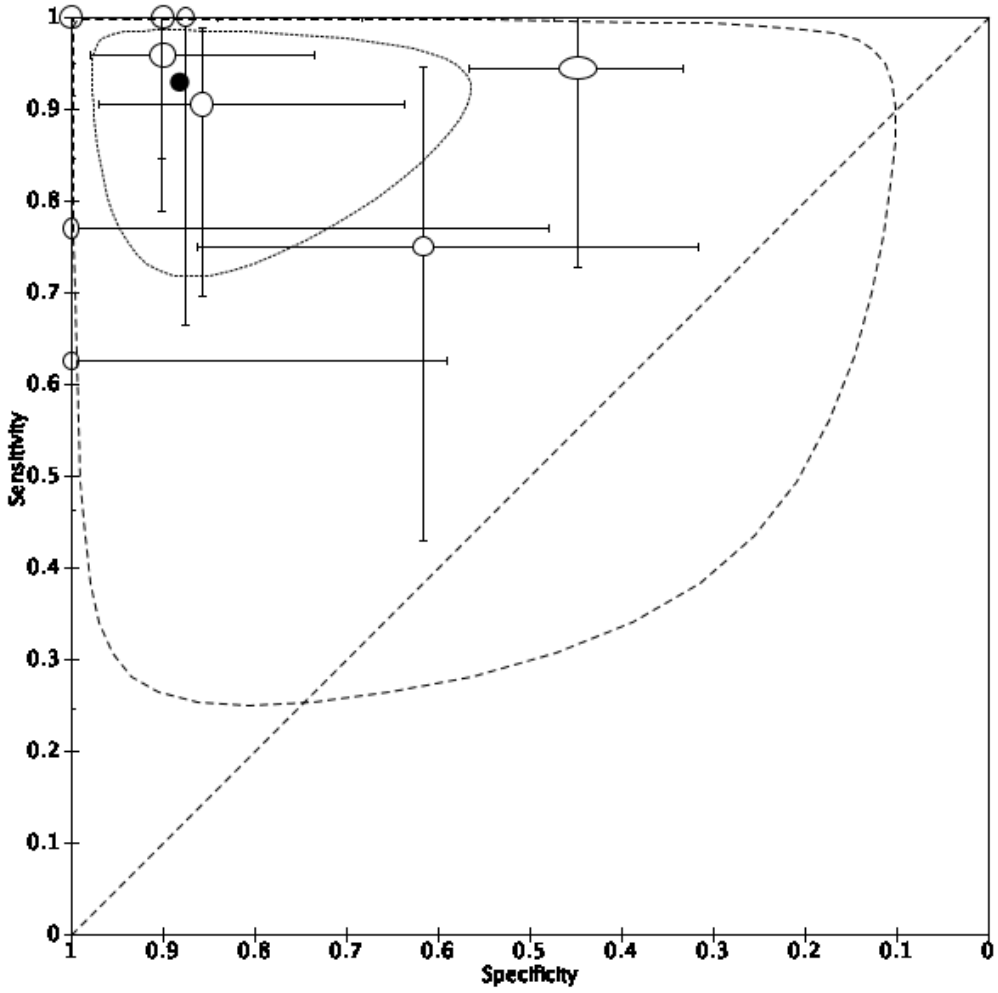
Description: The summary operating point (the filled circle) with the estimated average sensitivities and specificities with their 95% confidence (dotted curve) and prediction regions (dashed curve) for the 13 studies that excluded CKD patients. The size of the ellipsoid is proportional to the sample size for each study. ***(Output from Review Manager (RevMan) [Computer program])***

Supplemental figure 3-c: Summary receiver operating characteristic plot for the 11 studies that excluded chronic kidney disease and diuretics patients



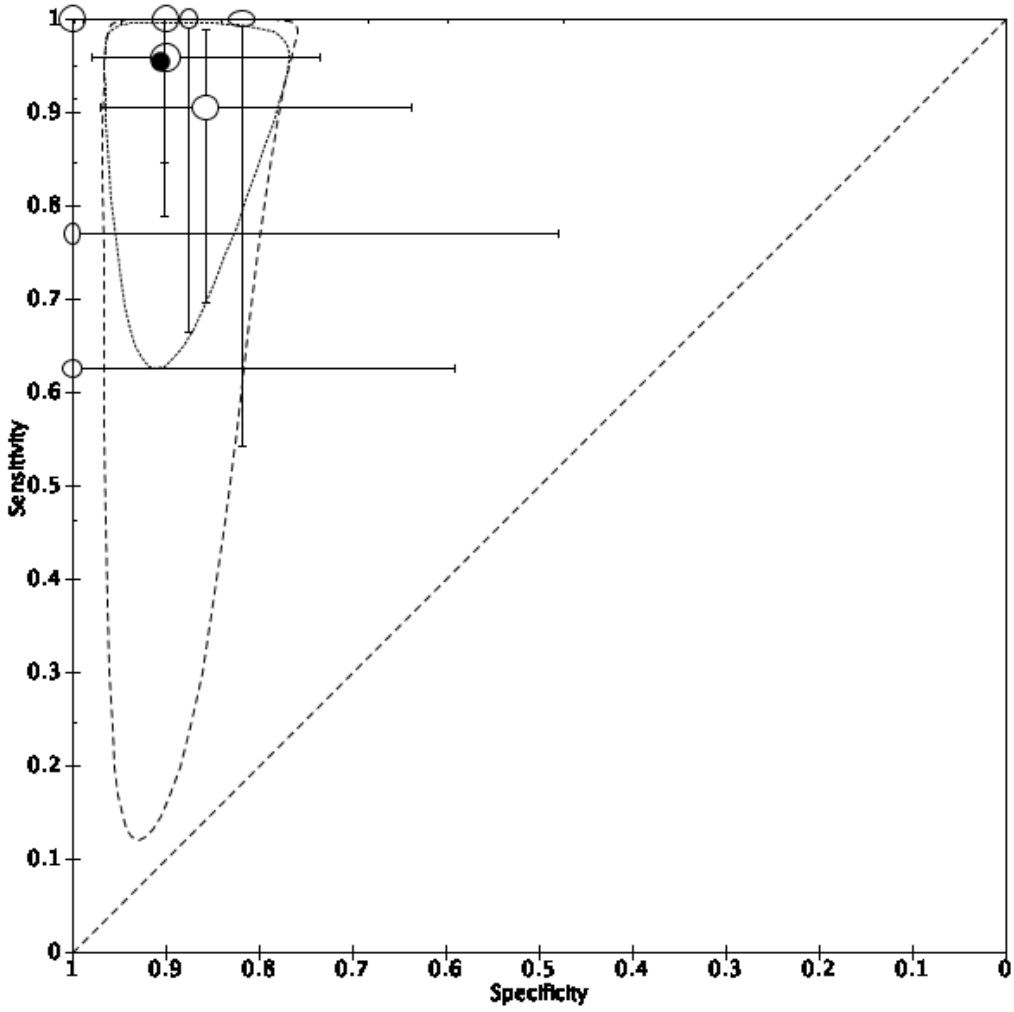
Description: The summary operating point (the filled circle) with the estimated average sensitivities and specificities with their 95% confidence (dotted curve) and prediction regions (dashed curve) for the 11 studies that excluded CKD and diuretics patients. The size of the ellipsoid is proportional to the sample size for each study. ***(Output from Review Manager (RevMan) [Computer program])***

Supplemental figure 3-d: Summary receiver operating characteristic plot for the 9 studies included in the oliguric subgroup analysis



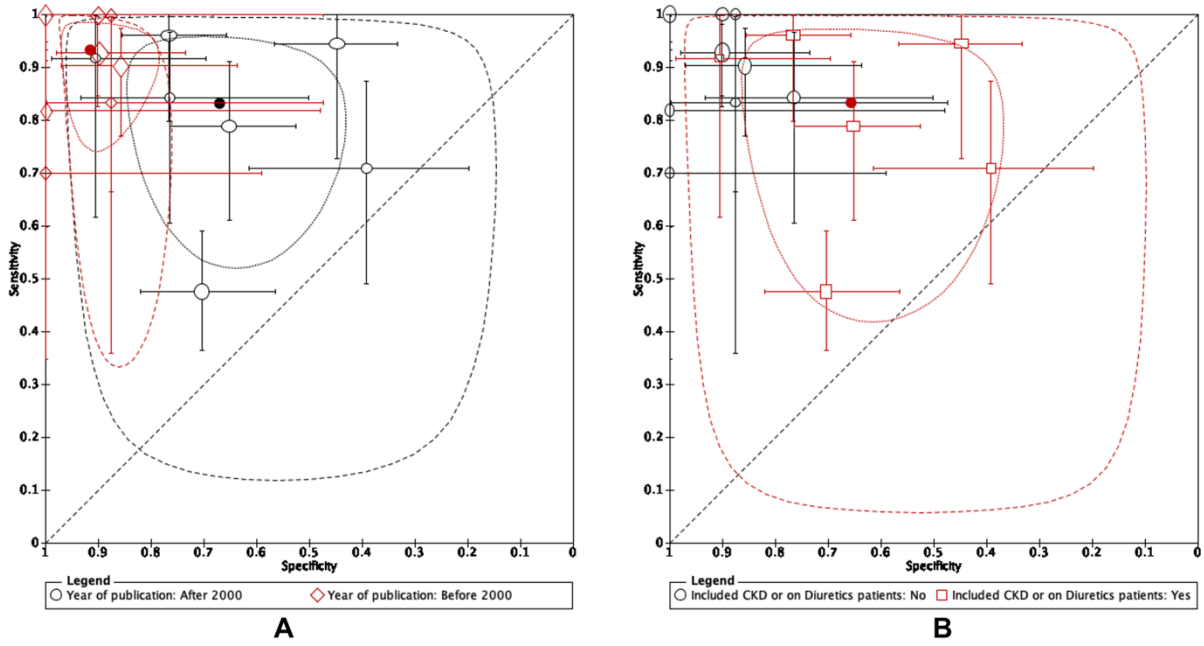
Description: The summary operating point (the filled circle) with the estimated average sensitivities and specificities with their 95% confidence (dotted curve) and prediction regions (dashed curve) for the 9 studies included in the oliguric subgroup analysis. The size of the ellipsoid is proportional to the sample size for each study. ***(Output from Review Manager (RevMan) [Computer program])***

Supplemental figure 3-e: Summary receiver operating characteristic plot for the 7 studies that included oliguric patients with no history of CKD or diuretics intake.



Description: The summary operating point (the filled circle) with the estimated average sensitivities and specificities with their 95% confidence (dotted curve) and prediction regions (dashed curve) for the 7 studies that included oliguric patients with no history of CKD or diuretics intake. The size of the ellipsoid is proportional to the sample size for each study. ***(Output from Review Manager (RevMan) [Computer program])***

Supplemental figure 3-f: Summary receiver operating characteristic plot for the 15 studies used fractional excretion of sodium at 1% threshold



Description: The summary operating point (the filled circles) with the estimated average sensitivities and specificities with their 95% confidence (dotted curve) and prediction regions (dashed curve) for A: comparison between the recent (black) and the older (red) studies subgroups, B (red): studies that included CKD or diuretics patients. ***(Output from Review Manager (RevMan) [Computer program])***