Diagnostic Performance of Fractional Excretion of Sodium for the Differential Diagnosis of Acute Kidney Injury: A Systematic Review and Meta-Analysis

Mohammad Abdelhaleem, Tarek Nayfeh, Anwar Atieh, Omar AbuShamma, Basheer Babaa, Alaa Hrizat, Bashar Hasan, Leslie Hassett, Abdurrahman Hamadah, and Kamel Gharaibeh

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 12 studies (1287 participants) 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 85% (95% CI, 82% to 88%), 95% (95% CI, 82% to 98%), and 85% (95% CI, 82% to 98%), respectively. The accuracy of the FENa test was significantly higher in the nondiuretics group than in the diuretics group (relative diagnostic odds ratio, 14.02; 95% CI, 2.53 to 77.74; \( P = 0.005 \)). The pooled specificity 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 90% (95% CI, 81% to 95%), 79% (95% CI, 70% to 90%), 82% (95% CI, 82% to 85%), 95% (95% CI, 71% to 93%), 90% (95% CI, 78% to 95%), and 87% (95% CI, 66% to 97%), 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).

#### 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%), 79% (95% CI, 70% to 90%), 82% (95% CI, 70% to 90%), 85% (95% CI, 71% to 93%), 90% (95% CI, 78% to 95%), and 87% (95% CI, 66% to 97%), 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 (Supplemental Figure 1).
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 Espinéel (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

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Design, Settings</th>
<th>Intrinsic AKI: n; Age, yr; Women, %; Creatinine, Mean, mg/dl</th>
<th>Preternal AKI: n; Age, yr; Women, %; Creatinine, Mean, mg/dl</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Reference Standard</th>
<th>Fractional Excretion of Sodium Cutoff(s), %</th>
<th>Intrinsic AKI: Oliguric, %; Receiving Diuretics, %</th>
<th>Preter nal AKI: Oliguric, %; Receiving Diuretics, %</th>
<th>Intrinsic AKI: CKD, %</th>
<th>Preter nal AKI: CKD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Espinel (6), 1976</td>
<td>P, N/R</td>
<td>9; N/R; N/R; 9.2±0.7</td>
<td>8; N/R; N/R; 8.3±1.1</td>
<td>Acute onset of oliguria (urinary output below 20 ml/hr)</td>
<td>CKD, patients on diuretics, acute glomerular disease, or urinary tract obstruction</td>
<td>Responsiveness to fluids. ATN cases were also confirmed by histologic findings</td>
<td>&lt;1 and &gt;3; 1</td>
<td>100; 0 100; 0</td>
<td>0; N/R 0; N/R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al. (27), 1978</td>
<td>P, hospitalized</td>
<td>55; 58.1±3.5; 20; 3.9±0.26</td>
<td>30; 62±3; 34; 3±5.3</td>
<td>Acute elevation of serum creatinine from normal levels (&lt;1.4 mg/dl) to &gt;2.0 mg/dl</td>
<td>CKD, patients on diuretics</td>
<td>Responsiveness to fluids, urine microscopy findings</td>
<td>1</td>
<td>44; 0</td>
<td>N/R 0; N/R 0; N/R 0; N/R</td>
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<tr>
<td>Espinel and Gregory (7), 1980</td>
<td>P, hospitalized</td>
<td>65; N/R; N/R; 5±2.15</td>
<td>8; N/R; N/R; 5±2.0</td>
<td>Acute increase in creatinine level above 2 mg/dl</td>
<td>CKD, patients on diuretics</td>
<td>Response to fluids, urine microscopy, histopathology in some cases</td>
<td>1</td>
<td>56; 0</td>
<td>100; 0 0; N/R 0; N/R</td>
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<tr>
<td>Zager et al. (26), 1980</td>
<td>P, hospitalized</td>
<td>22; N/R; N/R; N/R</td>
<td>5; N/R; N/R; N/R</td>
<td>Patients with AKI, although the defining criteria are not reported</td>
<td>N/R</td>
<td>Response to fluids, urine microscopy</td>
<td>1</td>
<td>59; N/R</td>
<td>100; N/R 0; 0 0; 0 0; 0</td>
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<tr>
<td>Chugh et al. (21), 1981</td>
<td>P, hospitalized</td>
<td>40; N/R; N/R; N/R</td>
<td>21; N/R; N/R; N/R</td>
<td>Oliguric AKI, defining criteria are not reported</td>
<td>CKD, acute GN, obstructive uropathy, diabetes mellitus, and cirrhosis</td>
<td>Responsiveness to fluids and pathologic findings</td>
<td>&lt;1 and &gt;3</td>
<td>100; 0 100; 0</td>
<td>0; N/R 0; N/R 0; N/R</td>
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<tr>
<td>Brown et al. (29), 1983</td>
<td>P, hospitalized</td>
<td>10; N/R; N/R; N/R</td>
<td>7; N/R; N/R; N/R</td>
<td>AKI defined by an acute rise in blood urea nitrogen</td>
<td>CKD, patients on diuretics</td>
<td>Response to fluids, urine microscopy</td>
<td>1</td>
<td>80; 0</td>
<td>100; 0 0; N/R 0; N/R</td>
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<tr>
<td>Anderson et al. (30), 1984</td>
<td>P, hospitalized</td>
<td>47; N/R; N/R; N/R</td>
<td>23; N/R; N/R; N/R</td>
<td>Acute rise in creatinine from &lt;1.4 to &gt;2.0 mg/dl</td>
<td>N/R; patients with CKD were studied separately</td>
<td>Responsiveness to fluids, urine microscopy</td>
<td>1</td>
<td>53; N/R</td>
<td>100; 0 0; 0 0; 0 0; 0</td>
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<tr>
<td>Tankhiwale and Ungratwar (26), 1987</td>
<td>P, hospitalized</td>
<td>22; N/R; N/R; N/R</td>
<td>20; N/R; N/R; N/R</td>
<td>Patients with AKI, although the defining criteria are not reported</td>
<td>Patients with CKD</td>
<td>Responsiveness to fluid expansion; histopathologic findings</td>
<td>1</td>
<td>100; N/R</td>
<td>100; N/R 0; N/R 0; N/R 0; N/R</td>
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<tr>
<td>Fushimi et al. (40), 1990</td>
<td>P, hospitalized</td>
<td>6; 52±16; 33; 5.2±1.3</td>
<td>8; 66.4±23; 50; 2.8±0.4</td>
<td>Acute elevation of serum creatinine to &gt;1.5 mg/dl, with a decrease in creatinine clearance</td>
<td>CKD, acute GN, and patients receiving diuretics</td>
<td>Responsiveness to fluids, urine microscopy findings</td>
<td>1</td>
<td>N/R 0</td>
<td>100; 0 0; 0 0; 0 0; 0</td>
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<tr>
<td>Steinhauser et al. (18), 1994</td>
<td>P, ICU and ER</td>
<td>18; 39 (10th [21] to 90th [76] percentile); 64; 5.6 (10th [3.6] to 90th [9.5] percentile)</td>
<td>28; 65.5 (10th [18] to 90th [88] percentile); 65; 1.8 (10th [1.2] to 90th [3.5] percentile)</td>
<td>A recent increase in plasma creatinine of &gt;20% or plasma creatinine concentration above 200 m mol/L at the time of referral</td>
<td>Presence of acute GN, acute interstitial nephritis, and obstructive uropathy</td>
<td>Responsiveness to fluids, urine microscopy findings</td>
<td>&lt;1.3 and &gt;3.5</td>
<td>N/R; 50</td>
<td>N/R; 39 0; 0 0; 0 0; 0</td>
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<tr>
<td>Carvounis et al. (9), 2002</td>
<td>P, hospitalized (mostly ICU)</td>
<td>25; 47±3; 48; 5.9±0.5</td>
<td>24; 71±3; 3; 1.7±0.25</td>
<td>Rapidly increasing BUN and creatinine (BUN &gt;30 mg/dl and creatinine &gt;1.5 mg/dl) with or without oliguria or serum creatinine increase in excess of 0.5 mg/dl in the preceding 2 d</td>
<td>Patients with acute interstitial nephritis, acute GN, and obstructive uropathy</td>
<td>Responsiveness to fluids, urinalysis findings</td>
<td>1; 0; 0.60; 0.80; 1.20; 1.50; 2; 3</td>
<td>N/R; 0</td>
<td>N/R; 35 0; 1 0; 32 0; 0 0; 0 0; 0 0; 0</td>
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<tr>
<td>Study, Year</td>
<td>Design, Settings</td>
<td>Intrinsic AKI, n; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl</td>
<td>Preeonal AKI, n; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Reference Standard</td>
<td>Fractional Excretion of Sodium Cutoff(s), %</td>
<td>Intrinsic AKI Oliguric, %; Receiving Diuretics, %</td>
<td>Preeonal AKI Oliguric, %; Receiving Diuretics, %</td>
<td>Intrinsic AKI CKD, %; Sepsis, %</td>
<td>Preeonal AKI CKD, %; Sepsis, %</td>
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<tr>
<td>du Cheyron et al. (39), 2003</td>
<td>P, ICU</td>
<td>19; N/R; N/R; 3.3±1.6</td>
<td>17; N/R; N/R; 2.1±0.5</td>
<td>Sudden increase in serum creatinine level to ≥2 mg/dl or a value 50% greater than the basal concentration when CKD already existed</td>
<td>Patients with hepatorenal syndrome, cirrhosis</td>
<td>Responsiveness to fluids</td>
<td>1</td>
<td>N/R; N/R</td>
<td>N/R; N/R</td>
<td>0; 0</td>
<td>0; 6</td>
</tr>
<tr>
<td>Pépin et al. (4), 2007</td>
<td>P, hospitalized</td>
<td>33; 66.3; 55; 3.8±1.6</td>
<td>66; 66.8; 47; 2.5±1.3</td>
<td>An increase in serum creatinine level of 30% or higher over the baseline with an abrupt onset (&lt;1 wk)</td>
<td>Contrast examination &lt;48 h before the onset of AKI, rhabdomyolysis, obstructive uropathy, acute GN, drug nephrotoxicity, and kidney failure</td>
<td>Responsiveness to fluids, urine microscopy findings</td>
<td>1</td>
<td>36; 64</td>
<td>24; 65</td>
<td>45; 42</td>
<td>36; 24</td>
</tr>
<tr>
<td>Diskin et al. (22), 2010</td>
<td>P, hospitalized</td>
<td>20; 67.5±12.7; 56; N/R</td>
<td>80; 66.8±12.3; 49; N/R</td>
<td>AKI patients with oliguria; defined as urine output &lt;600 ml/24 h and abrupt sustained rise in creatinine &gt;1.9 mg/dl</td>
<td>All patients with possible creatinine assay-interfering drugs/conditions</td>
<td>Responsiveness to fluids &lt;1 and &gt;3</td>
<td>100; 55</td>
<td>100; 71</td>
<td>28; 0</td>
<td>0; 7</td>
<td></td>
</tr>
<tr>
<td>Darmon et al. (25), 2011</td>
<td>P, ICU</td>
<td>82; 66 (IQR, 56–74); 32; 2.5 (IQR, 1.6–4.1)</td>
<td>54; 71 (IQR, 49–76); 41; 1.4 (IQR, 1.1–1.9)</td>
<td>AKI defined according to the AKIN or MDRD formula</td>
<td>Patients on dialysis, obstructive uropathy</td>
<td>Responsiveness to fluids 1; 0.58</td>
<td>N/R; 39</td>
<td>N/R; 33</td>
<td>28; 74</td>
<td>6; 61</td>
<td></td>
</tr>
<tr>
<td>Dewitte et al. (41), 2012</td>
<td>P, ICU</td>
<td>24; 69 (IQR, 54–73); 37; N/R</td>
<td>23; 64 (IQR, 43–75); 35; N/R</td>
<td>AKI according to the consensus definition from the Acute Dialysis Quality Initiative group</td>
<td>Patients with CKD, obstructive uropathy</td>
<td>Responsiveness to fluids 1</td>
<td>75; 58</td>
<td>74; 61</td>
<td>0; 29</td>
<td>0; 39</td>
<td></td>
</tr>
<tr>
<td>Yassin et al. (23), 2013</td>
<td>P, ICU</td>
<td>14; 56.29±19.5; 42; 5.5±2.1</td>
<td>26; 60±15.15; 62; 2.2±0.6</td>
<td>Patients with AKI with circulatory shock; circulatory shock was diagnosed according to the empirical criteria, AKI according to the RIFLE criteria in oliguric patients</td>
<td>CKD, obstructive uropathy, and patients on osmotic diuresis</td>
<td>Response to fluids, urinalysis</td>
<td>1</td>
<td>100; 57</td>
<td>100; 46</td>
<td>0; N/R</td>
<td>0; N/R</td>
</tr>
<tr>
<td>Patidar et al. (20), 2017</td>
<td>R, hospitalized</td>
<td>12; N/R; 21; N/R; N/R</td>
<td>21; N/R; N/R; N/R</td>
<td>Cirrhotic patients who were admitted for AKI, the defining criteria of AKI are not reported; HBS AKI was diagnosed on the basis of the International Club of Ascites definition</td>
<td>Patients with ascites, patients not on diuretics, advanced kidney failure</td>
<td>Clinical course decided by a nephrologist</td>
<td>1</td>
<td>N/R; 100</td>
<td>N/R; 100</td>
<td>0; 0</td>
<td>0; 0</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Design, Settings</th>
<th>Intrinsic AKI, n; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl</th>
<th>Prerenal AKI, n; Age, Mean, yr; Women, %; Creatinine, Mean, mg/dl</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gowda et al. (D) (24), 2021</td>
<td>P, hospitalized</td>
<td>57; 48.47±10.8; 5; 3.2±1.78</td>
<td>143; 50.42±12.26; 6; 2.5±1.08</td>
<td>Cirrhotic patients who were screened for AKI as per revised International Club of Ascites definitions at admission</td>
<td>CKD, history of KRT, diuretic use, exposure to potential nephrotoxic drugs, cardiovascular disease</td>
<td>Responsiveness to fluids; ATN AKI was diagnosed if abnormal kidney finding is present on ultrasound, proteinuria &gt;500 mg/d, microhematuria (&gt;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</td>
</tr>
<tr>
<td>Gowda et al. (V) (24), 2021</td>
<td>P, hospitalized</td>
<td>17; 49.24±9.5; 0; 2.5±1.11</td>
<td>33; 51.24±12.7; 15; 2.5±1.08</td>
<td>Cirrhotic patients who were screened for AKI as per revised International Club of Ascites definitions at admission</td>
<td>CKD, history of KRT, diuretic use, exposure to potential nephrotoxic drugs, cardiovascular disease</td>
<td>Responsiveness to fluids; ATN AKI was diagnosed if abnormal kidney finding is present on ultrasound, proteinuria &gt;500 mg/d, microhematuria (&gt;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</td>
</tr>
</tbody>
</table>

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.

*This study included patients with CKD, but their data were not available.
<table>
<thead>
<tr>
<th>Study Identification</th>
<th>Could the Selection of Patients Have Introduced Bias?</th>
<th>Are There Concerns that the Included Patients and Setting Do Not Match the Review Question?</th>
<th>Could the Conduct or Interpretation of the Index Test Have Introduced Bias?</th>
<th>Are There Concerns that the Index Test, Its Conduct, or Its Interpretation Differ from the Review Question?</th>
<th>Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?</th>
<th>Are There Concerns that the Target Condition as Defined by the Reference Standard Does Not Match the Question?</th>
<th>Could the Patient Flow Have Introduced Bias?</th>
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<td>Espinel (6), 1976</td>
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<td>Unclear concern</td>
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<td>Low concern</td>
<td>Low risk</td>
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<td>Unclear risk</td>
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<td>Chugh et al. (21), 1981</td>
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<td>Fushimi et al. (40), 1990</td>
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<td>Steinhäuslin et al. (18), 1994</td>
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<td>Carvounis et al. (9), 2002</td>
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<td>du Cheyron et al. (39), 2003</td>
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<td>Diskin et al. (22), 2010</td>
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<td>Yassin et al. (23), 2013</td>
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<td>Patidar et al. (20), 2017</td>
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<td>Unclear risk</td>
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<tr>
<td>Gowda et al. (D) (24), 2021</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
<td>High concern</td>
<td>Unclear risk</td>
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<tr>
<td>Gowda et al. (V) (24), 2021</td>
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<td>High risk</td>
<td>Low risk</td>
<td>High concern</td>
<td>Unclear risk</td>
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</tbody>
</table>

D, derivation cohort; 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
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>
<thead>
<tr>
<th>Subgroup No.</th>
<th>Subgroup</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Intrinsic AKI, N (%)</th>
<th>Pooled Sensitivity [%] [95% Confidence Interval]; $I^2$</th>
<th>Pooled Specificity [%] [95% Confidence Interval]; $I^2$</th>
<th>Diagnostic Odds Ratio [95% Confidence Interval]; $I^2$</th>
<th>Positive Likelihood Ratio [95% Confidence Interval]; $I^2$</th>
<th>Negative Likelihood Ratio [95% Confidence Interval]; $I^2$</th>
<th>Positive Predictive Value [95% Confidence Interval]; $I^2$</th>
<th>Negative Predictive Value [95% Confidence Interval]; $I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patients not on diuretics</td>
<td>12</td>
<td>502</td>
<td>270 (54)</td>
<td>92% [85% to 96%]; 88% [83% to 92%]; 88 [34 to 226]; 5.10 to 12.01; 0.09 [0.05 to 0.17]; 91% [83% to 95%]; 92% [82% to 96%]</td>
<td>0% [4%]; 24% [5]; 5 [0.97 to 3.02]; 0.38 [0.18 to 0.80]; 47% [31% to 75%]; 54% [62% to 65%]; 82%</td>
<td></td>
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<tr>
<td>2</td>
<td>Patients on diuretics</td>
<td>5</td>
<td>238</td>
<td>88 (37)</td>
<td>80% [69% to 87%]; 54% [31% to 75%]; 69 [1 to 16]; 6.22 [0.09]; 86% [83% to 92%]; 54% [83% to 92%]; 0% [0.09]; 88% [83% to 95%]; 82% [61% to 93%]; 76%</td>
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<tr>
<td>3</td>
<td>Without patients with CKD</td>
<td>13</td>
<td>632</td>
<td>294 (47)</td>
<td>92% [87% to 96%]; 85% [73% to 93%]; 89 [25 to 191]; 3.21 to 12.02; 6.22 [0.09]; 86% [83% to 92%]; 54% [83% to 92%]; 86% [83% to 92%]; 82% [84% to 96%]; 92%</td>
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<tr>
<td>4</td>
<td>Patients without CKD and not on diuretics</td>
<td>11</td>
<td>464</td>
<td>225 (49)</td>
<td>93% [86% to 96%]; 89% [84% to 93%]; 107 [41 to 279]; 8.60 [0.08]; 84% [90%]; 93% [84% to 96%]; 58% [82% to 97%]; 88%</td>
<td></td>
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<tr>
<td>5</td>
<td>Oliguric patients</td>
<td>9</td>
<td>355</td>
<td>154 (43)</td>
<td>93% [82% to 97%]; 88% [71% to 96%]; 97 [20 to 471]; 7.84 [0.08]; 90% [0.03 to 0.22]; 90% [83% to 95%]; 90% [82% to 98%]; 93%</td>
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<tr>
<td>6</td>
<td>Oliguric patients without CKD and not on diuretics</td>
<td>8</td>
<td>264</td>
<td>130 (49)</td>
<td>95% [82% to 99%]; 91% [83% to 95%]; 197 [38 to 1017]; 8.60 [0.08]; 90% [0.04 to 0.16]; 92% [85% to 96%]; 58% [82% to 97%]; 88%</td>
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<tr>
<td>7</td>
<td>Studies including patients with CKD or on diuretics published before 2000</td>
<td>6</td>
<td>511</td>
<td>194 (38)</td>
<td>83% [64% to 93%]; 66% [51% to 78%]; 10 [3 to 34.0]; 2.42 [0.26]; 56% [0.10 to 0.63]; 56% [43% to 69%]; 88% [83% to 97%]; 88%</td>
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<tr>
<td>8</td>
<td>Studies published before 2000</td>
<td>7</td>
<td>325</td>
<td>205 (63)</td>
<td>93% [84% to 97%]; 92% [85% to 95%]; 148 [43 to 508]; 10.93 [0.07]; 95% [0.03 to 0.18]; 95% [91% to 97%]; 90%</td>
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<tr>
<td>9</td>
<td>Studies published after 2000</td>
<td>8</td>
<td>547</td>
<td>213 (39)</td>
<td>83% [63% to 92%]; 67% [53% to 78%]; 67 [3 to 30]; 2.52 [0.25]; 93% [0.12 to 0.53]; 93% [46% to 72%]; 82% [68% to 96%]; 93%</td>
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</table>
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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None.

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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 investment; 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.

References