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CLINICAL INVESTIGATION

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Fluid balance-adjusted creatinine in diagnosing acute kidney injury in the critically ill

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Abstract

Background: Acute kidney injury (AKI) is often diagnosed based on plasma creatinine (Cr) only. Adjustment of Cr for cumulative fluid balance due to potential dilution of Cr and subsequently missed Cr-based diagnosis of AKI has been suggested, albeit the physiological rationale for these adjustments is questionable. Furthermore, whether these adjustments lead to a different incidence of AKI when used in conjunction with urine output (UO) criteria is unknown.

Methods: This was a post hoc analysis of the Finnish Acute Kidney Injury study. Hourly UO and daily plasma Cr were measured during the first 5 days of intensive care unit admission. Cr values were adjusted following the previously used formula and combined with the UO criteria. Resulting incidences and mortality rates were compared with the results based on unadjusted values.

Results: In total, 2044 critically ill patients were analyzed. The mean difference between the adjusted and unadjusted Cr of all 7279 observations was 5 (±15) μmol/L. Using adjusted Cr in combination with UO and renal replacement therapy criteria resulted in the diagnosis of 19 (1%) additional AKI patients. The absolute difference in the incidence was 0.9% (95% confidence interval [CI]: 0.3%-1.6%). Mortality rates were not significantly different between the reclassified AKI patients using the full set of Kidney Disease: Improving Global Outcomes criteria.

Conclusion: Fluid balance-adjusted Cr resulted in little change in AKI incidence, and only minor differences in mortality between patients who changed category after adjustment and those who did not. Using adjusted Cr values to diagnose AKI does not seem worthwhile in critically ill patients.

Sanna Törnblom and Renske Wiersema contributed equally.

1 | INTRODUCTION

Acute kidney injury (AKI) is common among acutely hospitalized patients and is associated with long term morbidity and mortality.[1] Among critically ill patients, the incidence of AKI is especially high, about 40%–60%.[2,3] Serum or plasma creatinine (Cr) alone is often used to diagnose and stage AKI since urine output (UO) data are frequently not available.[4,5] Accumulation of fluid is common in the critically ill[6] and could influence serum/plasma Cr values.[7] Dilution of Cr may mask or delay diagnosis or result in underestimation of severity of AKI.[8] A secondary analysis of 1000 acute lung injury patients from the Fluid and Catheter Treatment trial (FACTT) found that almost every fifth patient was reclassified after adjusting for fluid balance.[9] Accordingly, some trials have adjusted Cr for fluid balance for AKI staging.[10] However, these studies have not used UO criteria in conjunction with the Cr criteria. Plausibly, patients who have markedly positive fluid balance, and consequently, the largest increase in Cr when adjusted for fluid retention, have also decreased UO and would fulfill the AKI diagnosis with UO criteria if assessed. Moreover, the physiological rationale for the applied adjustment equations and the use of a cumulative fluid balance over several days to correct a single Cr measurement has been questioned.[11] Additionally, this approach has not been validated against any gold standard measure of renal function, which further questions its validity.

In this post hoc analysis of the Finnish Acute Kidney Injury (FINNAKI) cohort, we aimed to assess if adjusting plasma Cr for cumulative fluid balance using the previously proposed method would result in a significantly different incidence of AKI when used with or without UO criteria. Second, we investigated whether patients having AKI using adjusted instead of unadjusted Cr values and vice versa had different outcomes in terms of 90-day mortality.

Editor Comments

It has been suggested that when diagnosing acute kidney injury (AKI) using plasma creatinine (Cr) values, there is better predictive value for later outcomes if Cr values are adjusted for fluid balance, which is itself an estimate with some uncertainty. This secondary analysis from a large intensive care unit (ICU) database study found that adjusting Cr values for estimated fluid balance probably has limited value for improving AKI prognostic value for important ICU outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design, setting, and participants

This is a post hoc analysis of the FINNAKI study, which was a prospective, observational, multicenter study conducted in 17 Finnish intensive care units (ICUs) between September 2011 and February 2012, studying the incidence, risk factors, and outcomes of AKI.[2] We included all emergency ICU admissions, regardless of the expected length of ICU stay, and all elective patients expected to stay in the ICU for more than 24 hours. We excluded (1) patients under 18 years of age; (2) elective patients whose expected length of stay was less than 24 hours; (3) readmitted patients who had received renal replacement therapy (RRT) during the previous ICU stay; (4) patients on chronic dialysis; (5) patients with insufficient language skills or not permanently living in Finland; (6) intermediate care patients; (7) transferred patients who had already participated in the study for 5 days; and (8) organ donors. In the current analysis, we further excluded patients with an ICU length of stay less than 24 hours, patients transferred to other ICU during the first 5 days, those with missing data on fluid input or output or weight, and those who commenced RRT already prior to ICU admission (Figure 1). The Ethics Committee of the Department of Surgery in Helsinki University Hospital approved the FINNAKI study protocol with a written informed consent from each patient or their next of kin and the use of a deferred consent (reference number 18/13/03/02/2010). Statistics Finland provided data about 90-day survival status.

2.2 | Data source, variables, and data collection

The clinical data including chronic and present health status, daily fluid input and output, and information on administered RRT were prospectively collected using a standardized case report form filled in daily by the intensivist. Day 1 was defined as the calendar day of admission, which in most cases was less than 24 hours. Subsequent days were 24-hour periods thereafter. Observation period was the first 5 days unless discharged earlier. We measured UO hourly and plasma Cr daily. Admission diagnoses and physiologic data of the first 5 days of ICU stay were collected from the database of the Finnish Intensive Care Consortium maintained by Tieto Ltd as described in the original report.[2]

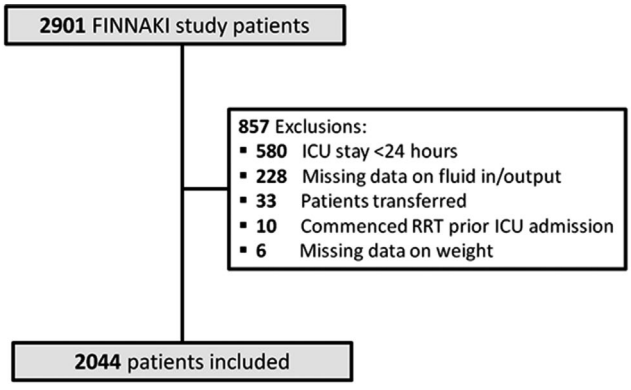

FIGURE 1 Flowchart of study inclusion. ICU, intensive care unit; RRT, renal replacement therapy

Fluid balance was calculated as follows: daily total fluid output (UO, ultrafiltration, losses to drains and from gastrointestinal tract, and a surrogate for evaporation) was subtracted from the daily total input (including intravenous crystalloids, colloids, blood products, drug infusions, nutrition, and per oral intake). The fluid balance at the time of each Cr measurement was calculated as the cumulative fluid balance from ICU admission until the Cr measurement. The fluids were prescribed by the intensivists guided by the recommendations valid at the time of the patient enrollment.[12,13]

Baseline Cr was defined as the most recent value from the previous year excluding the week preceding admission. If baseline Cr was not available, we estimated it using the Modification of Diet in Renal Disease (MDRD) equation as recommended assuming a glomerular filtration rate of 75 mL/min/1.73 m^2.[14] Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to assess AKI stage per observation day based on Cr, UO, and the need for RRT.[15]

The highest observed Cr of the five observation days was selected and used to determine the highest unadjusted Cr stage according to the KDIGO criteria. To calculate the adjusted stage based on Cr, all measured Cr values were adjusted for the fluid balance at the Cr sampling time. The adjustment was performed using the same algorithm as previously, using patient weight recorded on ICU admission[9,16]:

$$\text{Adjusted Cr} = \text{Cr} \times \frac{(0.6 \times \text{patient weight}) + \text{cumulative balance in liters}}{(0.6 \times \text{patient weight})}.$$

Next, the highest adjusted Cr was used to determine the highest adjusted KDIGO Cr stage. The KDIGO stages based on both unadjusted and adjusted Cr were then combined with the KDIGO stages based on UO and RRT.

Finally, we studied the incidence of AKI in subgroups based on admission type, patient sex, presence of septic shock as well as quartiles according to the Simplified Acute Physiology Score II (SAPS II), and fluid balance used for adjustment of the highest adjusted Cr value.

2.3 | Statistical analysis

We present the data as means (with standard deviations [SDs]) or medians (with interquartile ranges [IQRs]) depending on distributions. Categorical data are presented in proportions and point estimates of incidences with 95% confidence intervals (CIs), using Wilson's interval for binomial probabilities when the number of successes was below 5. We calculated CIs for the absolute difference in point estimates with Newcombe's paired method.[17] When comparing mortality rates between non-paired groups, we used Wilson's method for non-paired samples. Student's *T* test, Mann–Whitney *U* test, and χ^2 or Fisher's exact test were used as appropriate to assess whether patients who fulfilled different criteria had varying characteristics and outcomes. $P < 0.05$ were considered statistically significant. Analyses were conducted in Stata 16, R Studio 3.6.1, and SPSS 24 for Mac (IBM Corp).

TABLE 1 Baseline characteristics of included population

Variable	N/data available (%) or median [IQR]
Age (y)	64 [53-74]
Gender (male)	1331/2044 (65)
Baseline plasma creatinine (from patient records, μmol/L)	76 [62-92]
Comorbidity	
Chronic obstructive pulmonary disease	192/2030 (9.5)
Hypertension	999/2031 (49)
Atherosclerosis	276/2012 (14)
Diabetes	444/2044 (22)
Heart failure	250/2028 (12)
Chronic kidney disease	137/2034 (6.7)
Chronic liver failure	75/2026 (3.7)
Admission type	
Emergency	1722/2018 (85)
Operative	799/2043 (39)
Diagnostic group (APACHE II)	
Cardiovascular, operative	390/2043 (19)
Cardiovascular, non-operative	277/2043 (14)
Respiratory tract, non-operative	253/2043 (12)
Gastrointestinal tract, operative	187/2043 (9)
Neurological, non-operative	182/2043 (9)
Gastrointestinal tract, non-operative	128/2043 (6)
Metabolic	128/2043 (6)
Sepsis	120/2043 (6)
Neurological, operative	100/2043 (5)
Other (<4% each)	278/2043 (14)
Other	
Septic shock	490/2044 (24)
Received norepinephrine (first 24 h in ICU)	1368/2044 (67)
SOFA score (day 1, points)	7 [5-10]
SAPS II score (points)	37 [29-50]
Mechanical ventilation in ICU	1526/2044 (75)
Length of stay ICU (d)	3.1 [1.9-5.9]

Note: Age, Sequential Organ Failure Assessment score and Simplified Acute Physiology Score II data were available of all 2044 patients. Baseline creatinine and length of stay data were available of 1330 and 2043 patients, respectively.

Abbreviations: ICU, intensive care unit; SAPS, Simplified Acute Physiology Score.

3 | RESULTS

3.1 | Patients

Of 2901 FINNAKI study patients, 857 patients were excluded leaving 2044 patients in the current analysis (Figure 1). Baseline Cr was

available in 1330 patients (65%), and among 714 patients (35%) without, the MDRD back calculation was used. Table 1 presents the baseline patient characteristics and ICU admission diagnoses of the cohort. Altogether 1722 patients (85%) were acutely admitted, 490 patients (24%) had septic shock, and 1368 patients (67%) received norepinephrine within the first 24 hours of ICU admission. The median length of ICU stay was 3 days (IQR 2-6 days); 657 patients (32%) were discharged, and 125 patients (6%) deceased before 5 days. In total, 201 patients (9.8%) received RRT during the first 5 days of ICU admission. At 90-day follow-up, 456 patients (22%) had died.

3.2 | Adjusted Cr values and fluid balance

Altogether 7279 Cr values were studied. The median [IQR] number of Cr measurements per patient was 4 [2-5], and the median [IQR] day on which the highest Cr was measured was Day 2 [2-3]. For the highest adjusted Cr value for a patient, the median fluid balance placed in the adjustment algorithm was 17 (−167 to 616) mL. The mean difference between the adjusted and unadjusted Cr of all observations was 5 (±15) μmol/L (Figure 2).

3.3 | Adjusted versus unadjusted plasma Cr and AKI based on Cr criterion only

Of 2044 patients, altogether 616 (30%; 95% CI: 28%-32%) had AKI based on the unadjusted plasma Cr, whereas 654 (31%; 95% CI: 29%-34%) had AKI using the adjusted Cr. The absolute difference in incidence was 2% (95% CI: 1%-3%), and 38 additional patients were diagnosed as having AKI using the adjusted Cr. Figure S1 presents the highest stage of AKI based on Cr. In total, 53 patients were classified as having AKI on adjusted Cr but not on unadjusted Cr, and 15 patients were classified as having AKI on unadjusted but not on adjusted Cr (Table 2). There was no significant difference in incidence changes among patients having no baseline Cr available and MDRD used ($P = .31$). The characteristics of the patients who had AKI based on Cr after adjustment only are shown in Supporting Information, Table S1.

In the subgroup of patients (n = 511) who were in the highest quartile regarding the fluid balance used for adjustment (667-12 198 mL), the incidence of AKI was 4% lower when using unadjusted Cr values (95% CI: 2%-6%).

In patients with AKI based on both unadjusted and adjusted Cr, the 90-day mortality rate was 31% (95% CI: 28%-35%). Of the patients without AKI, 244 (18%) had died at 90-day follow-up. Among the 53 patients who had AKI after adjustment of Cr but not based on unadjusted Cr, mortality rate was 40% (95% CI: 26%-53%), but this was not significantly different compared to patients who had AKI based on both adjusted and unadjusted Cr criteria (difference in mortality rate 8% (95% CI: −7% to 22%). Compared to those 15 patients with AKI before but not after adjustment, of whom two deceased (13.3%), the difference was 26% (95% CI: 8%-57%), and to those without AKI before or after adjustment 21% (95% CI: 7%-35%).

3.4 | Adjusted versus unadjusted plasma Cr and AKI based on Cr, UO, and RRT (full criteria)

All results were similar when the Cr criteria were combined with UO and RRT criteria (Table 3, Figure 3, and additional results in Supporting Information). Moreover, we did not detect any significant differences in AKI incidence in various subgroups when using the full set of KDIGO criteria (Figure 4).

4 | DISCUSSION

In this large observational cohort of ICU patients, adjusting plasma Cr for cumulative fluid balance did not result in clinically meaningful differences in AKI incidence compared to using unadjusted Cr value when only the KDIGO Cr criteria were applied. Also, AKI incidence based on the full set of KDIGO diagnostic criteria (Cr, UO, and RRT) remained essentially unchanged. Moreover, we did not detect

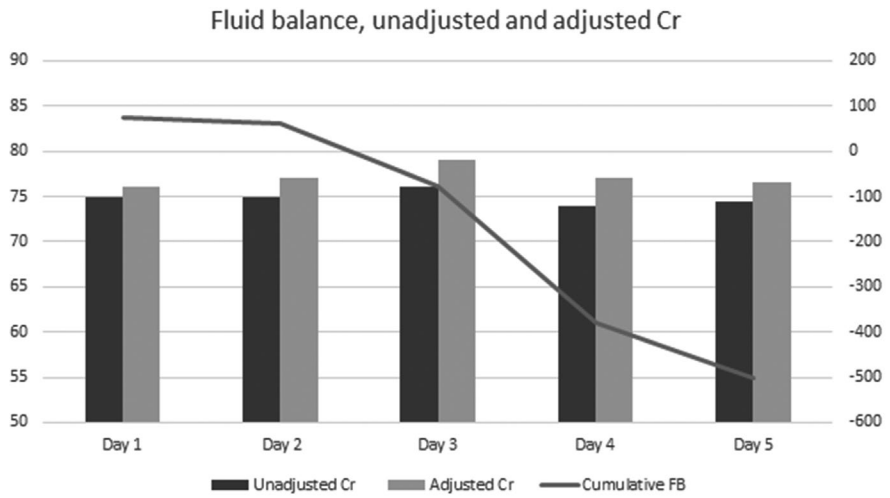

FIGURE 2 Observed unadjusted creatinine versus adjusted creatinine values. Description: Figure shows the mean Cr (umol/L), and the median fluid balance (mL) per day. Number of observations per day: Day 1:1536; Day 2:1905; Day 3:1402; Day 4:1018; Day 5:760. Cr, creatinine; FB, fluid balance

TABLE 2 Cross tabulation of AKI based on Cr criterion only

	No AKI-adjusted Cr, n (%; 95% CI)	AKI-adjusted Cr, n (%; 95% CI)
No AKI based on unadjusted Cr	1375 (67.3; 65.2-69.3)	53 (2.6; 1.9-3.3)
Mortality rate at 90 d	244 (17.7; 15.7-19.8)	21 (39.6; 26.5-53.9)
AKI based on unadjusted Cr	15 (0.7; 0.4-0.12)	601 (29.4; 27.4-31.4)
Mortality rate at 90 d	2 (13.3; 3.7-37.8)	189 (31.4; 27.7-35.3)

Note: Abbreviation: AKI, acute kidney injury.

TABLE 3 Cross tabulation of AKI based on all KDIGO criteria

	No AKI-adjusted Cr, n (%; 95% CI)	AKI-adjusted Cr, n (%; 95% CI)
No AKI-unadjusted Cr	1122 (54.9; 52.7-57.1)	31 (1.5; 1.0-2.2)
Mortality rate at 90 d	180 (16.0; 13.9-18.3)	8 (25.8; 11.8-44.6)
AKI-unadjusted Cr	12 (0.6; 0.3-1.0)	879 (43.0; 40.8-45.2)
Mortality rate at 90 d	1 (8.3; 4.3-35.4)	267 (30.4; 27.3-33.5)

Note: Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

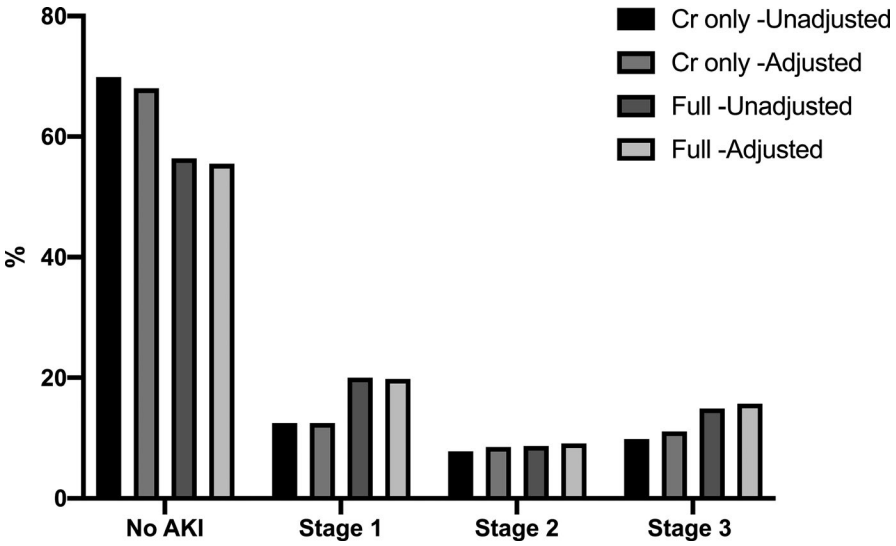

FIGURE 3 The highest KDIGO stages using either only unadjusted or adjusted Cr values or these in combination with urine output and renal replacement therapy criteria. AKI, acute kidney injury; Cr, creatinine; Full, creatinine, urine output and renal replacement therapy; KDIGO; Kidney Disease: Improving Global Outcomes

differences in 90-day mortality among reclassified AKI patients using the full set of KDIGO criteria.

4.1 | AKI incidence

The incidence of AKI among the critically ill has varied markedly in epidemiological studies.[18] The use of Cr criteria alone, as in most data collected from administrative databases, results in poor sensitivity[19] and possibly underestimation of mild injury and acute-on-chronic cases. Patients who accumulate fluids may be more susceptible to having "unrecognized" AKI. Macedo et al investigated patients from the Program to Improve Care in Renal Disease (PICARD) study conducted in 1999-2001 and reported that as much as 25% of critically ill patients with AKI would have been recognized ≥1 day earlier had Cr been adjusted for fluid balance, and these patients had higher cumulative fluid balance than the rest of the cohort.[7] The individuals with the highest cumulative fluid balance often have low UO as a contributing factor. Using the UO criteria could therefore compensate for not adjusting Cr for fluid balance. In the present study, the number of patients that changed category in either direction after Cr adjustment was 68 (3%) when only Cr criteria were applied and 43 (2%) using Cr, UO, and RRT criteria. Adjusting plasma Cr did not markedly change the incidence of AKI even when assessed using the Cr criteria only. One explanation for this might be that the overall fluid balance was markedly lower compared to the studies conducted in early 2000s reporting positive balances between +5 and +10 L.[7,20] However, in our analysis, even in the subgroup of patients in the highest fluid balance quartile (with balance from 0.7 up to 12 L), adjustment for fluid balance led to the reclassification of less than 5% of patients when using Cr criteria only. Since previous studies have used less sensitive AKI definitions than we did, the incidences are

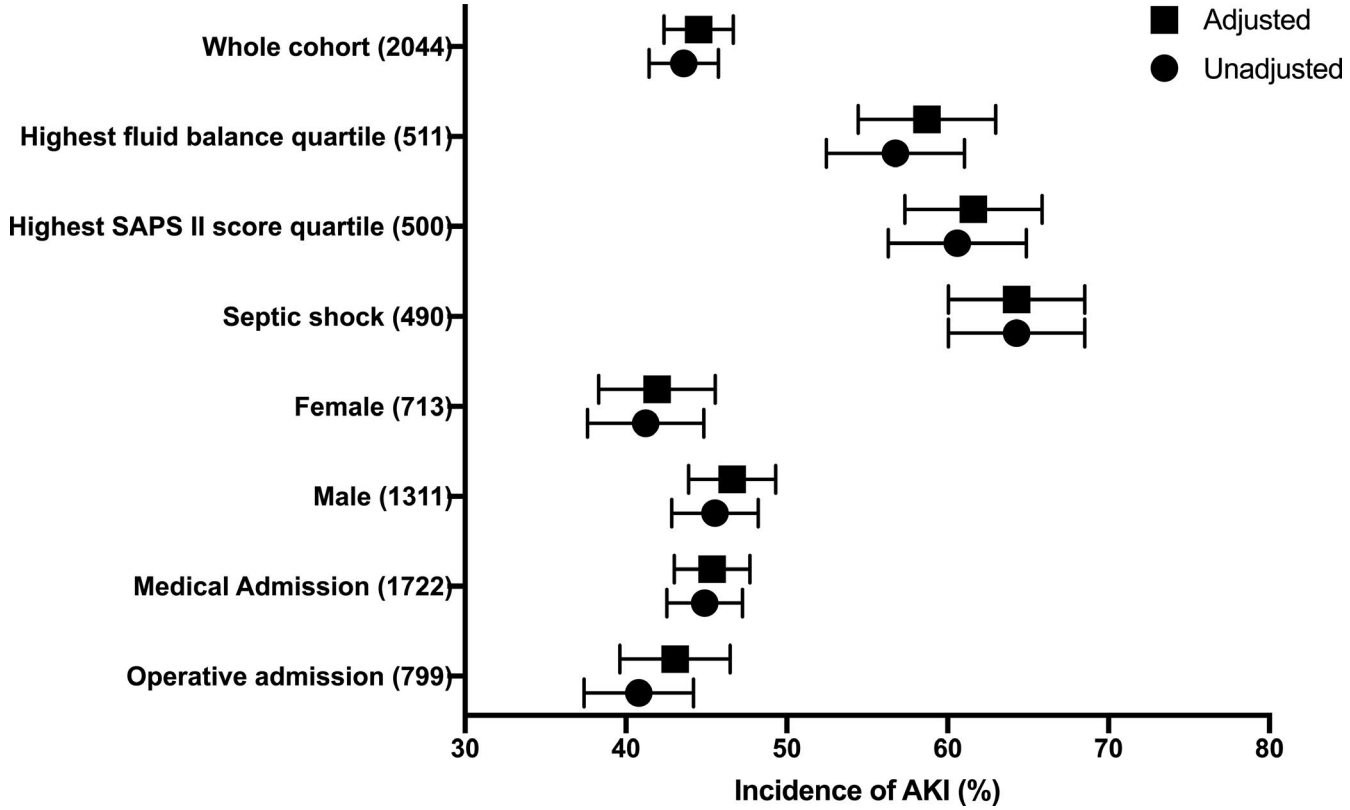

FIGURE 4 Incidence of acute kidney injury using the urine output, renal replacement therapy, and unadjusted or adjusted creatinine criteria. Description: Error bars denote 95% confidence intervals. Numbers in parenthesis indicate the number of patients in the group. Highest fluid balance quartile > 667 mL (up to 12 198 mL). Highest SAPS II score quartile > 50 points (up to 102). AKI, acute kidney injury; SAPS, Simplified Acute Physiology Score

not directly comparable, and the effect of Cr adjustment may vary. The FACT trial used the Acute Kidney Injury Network criteria and Macedo and colleagues defined AKI as a 0.5 mg/dL increase in sCr. Additionally, the Macedo study population differed from ours with a greater proportion of patients having prior CKD compared to our cohort (31% vs 6.7%).

4.2 | Mortality

The analysis from the FACT trial reported higher mortality rate among patients whose AKI was "unrecognized" before adjusting their observed Cr for fluid balance compared to those who were initially diagnosed with AKI but did not have AKI after Cr adjustment.[9] These patients also had positive fluid balance, which is associated with increased mortality, and might therefore explain their findings.[9] Our findings in 90-day mortality when using the Cr criteria only are in line with these previous results, albeit we discovered a very low number of reclassified patients altogether, and therefore, our findings must be interpreted with caution. However, we did not detect any differences in the mortality rates between the reclassified patient groups when the full set of KDIGO criteria was used. These findings support our hypothesis that using the UO criterion in addition to Cr helps recognizing patients with high risk. Macedo and colleagues did not detect differences in in-hospital mortality either, despite the observed delay of AKI diagnosis in their analysis.[7]

4.3 | Clinical implications and generalizability

Fluid accumulation is associated with adverse outcomes per se.[21,22] Our data were collected in 2011-2012, roughly 10 years later than the PICARD and FACTT data.[20,23] Meanwhile, the clinical practice in fluid prescription may have changed due to more cautious treatment recommendations and earlier de-resuscitation protocols.[24] As fluid overload is becoming less frequent in ICUs, need for adjusting Cr for fluid balance to reveal "missed" AKI may abate. The other extreme, hypovolemia, could erroneously elevate plasma/serum Cr, but after the initial phase of ICU admission, it is probably far less common than fluid overload. Corroborating this, we detected 53 (3%) patients who did not have AKI by the non-adjusted Cr criterion but changed category after adjustment, and only 15 (1%) patients who changed category in the opposite direction. The numbers were even smaller when the full set of KDIGO criteria was used.

Besides the inherently non-exact estimation of cumulative fluid balance, including insensible losses, the correction formula used to calculate adjusted Cr has received criticism. Cr adjustment is based on the assumption that volume expansion is as instant

as a single Cr measurement.[11] The equation could predict Cr before volume expansion accurately if Cr was measured immediately after a substantial intravenous fluid bolus, but as time goes by, Cr dilution leads to reduced Cr excretion and accumulation of Cr in the body water. Thus, the dilution effect will be short-lived.[11] Therefore, instead of adjusting Cr for cumulative fluid balance, avoiding Cr measurements immediately after a fluid bolus or during the first hours of resuscitation in the ICU might be considered to not get falsely low values. We think our non-selected study cohort of consecutive patients well represents mixed ICU patient population in countries with similar circumstances. Based on our results, adjusting Cr for cumulative fluid balance in future studies conducted in corresponding cohorts of ICU patients seems unnecessary.

4.4 | Limitations and strengths

Some limitations in the present study must be mentioned. First, this was a post hoc analysis of a multicenter observational study. Despite considerable sample size, some of the groups were too small to rule out statistically significant differences in mortality. However, relevance of this limitation is likely to be minor, given the small size of these groups. Second, only the admission weight of the patients was recorded, so we could not compare the calculated cumulative fluid balance with the actual weight. Obtaining accurate weight data has been a problem in previous studies as well.[9,25,26] Third, we did not have data on fluid balance before admission to ICU. Fourth, we used the MDRD to back-estimate a baseline if this was missing and the incidence of AKI was lower in patients with whom the MDRD was used, possibly resulting from missed AKI diagnoses. However, the number of patients that changed category after Cr adjustment was similar between patients having prior Cr measurement available and those who did not. So, using MDRD did not change the main results. Unfortunately, the absence of data before ICU stay remains a problem in ICU AKI research.

Last, fluid administration practice may have changed towards even more restrictive since the collection of our data. However, more restrictive fluid therapy regimens would further support the unnecessity of Cr adjustment. As a strength, we tested the consequences of adjusting Cr for cumulative fluid balance, as suggested in previous studies,[7,9,10] in a large non-selected cohort of ICU patients using full KDIGO criteria instead of only Cr or older AKI criteria.

5 | CONCLUSION

Adjusting Cr for cumulative fluid balance produced little change in AKI staging, no clinically meaningful alteration in AKI incidence, and no difference in 90-day mortality between patients who changed category from non-AKI to AKI after adjustment and those who did not when using Cr, UO, and RRT criteria. Using adjusted Cr values to diagnose AKI does not seem worthwhile in critically ill patients.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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