Cumulative Fluid Balance: The Dark Side of the Fluid*

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In critical care patients, fluids are one of the most frequently prescribed medications. Since the first infusion in cholera patients by Latta (1), the lifesaving potential of fluids in hypovolemia-induced shock states have been repeatedly confirmed in everyday praxis. However, over the past decades, evidence has accumulated pointing out the dark side of the fluid administration (FA). In 1990, Lowell et al (2) described the association between perioperative weight gain induced by deliberate FA and patients' mortality. Postoperative fluid overload (FO; weight gain higher than 10%) has been associated with three-time higher mortality and FO over 20% with fatal outcome (2). The FA's adverse effect has been ascribed mainly to increase in post–capillary pressure and/or extravasation leading to edema formation, polycompartment syndrome, and prolongation of oxygen diffusion distance (3). Diverse patients' populations are affected by fluid accumulation in various extents; naturally those with acute lung (4) and/or kidney injury (5) create the most important groups.

In this issue of *Critical Care Medicine*, Neyra et al (6) convey results of their retrospective single-center cohort study of 2,632 patients with severe sepsis or septic shock. Unlike others (7–9), Neyra et al (6) divide the patients into four subgroups according to the presence of chronic kidney disease (CKD) and/or acute kidney injury (AKI) based on premorbid serum creatinine levels. This enables the authors to study the 72-hour cumulative fluid balance (CFB) among these groups in separate. Both CFB and AKI (but not CKD) were independently associated with increased mortality in the entire cohort. CFB (per 1 L) and FO (per 1%) increased mortality in general and in each subgroup (adjusted odds ratio ranging from 1.04 to 1.09). However, different cut-offs were found for CFB associated with mortality among subgroups (CKD with AKI 5.9 L, AKI only 4.3 L, CKD only 3.8 L, and those without 1.5 L). The primary analysis was further strengthened by inducing a validation cohort of 3,056 septic patients with imputed values of premorbid creatinine showing similar results. Strength of the study is the use of contemporary sepsis, CKD and AKI definitions and adjustment for usual critical ill–dependent confounders. Contrary, two major limitations have to be mentioned: the study excluded patients with the most severe CKD (glomerular filtration below 15 mL/min/1.73 m^2 or chronic dialysis) and fluids administered prior to ICU admission (presumably 1–2 L of initial fluid resuscitation) were missed by the analysis.

Reading this (6) and also other articles (7, 9), it seems that third-day CFB should be included into our routine predictive Sequential Organ Failure Assessment–like scores, and that fluid accumulation has to be avoided at any cost. But is the association between CFB and mortality really so straightforward? At least three reasons call for caution.

1) Association does not mean causality, especially when not consistently reported in the literature (8). Fluids as any drugs may be harmful, but association between CFB and mortality may be by large an epiphenomenon. The striking difference between cutoff values predicting mortality between AKI/CKD subgroups is interpreted in a causative manner by the authors. As if "training to intermittent overload" in patients with renal disease made them less prone to experience fluids adverse effects. But the major difference was between AKI and non-AKI patients (similar to the study by Wang et al [9]), so another explanation is possible: we may view this as different fluids needs (and ability to excrete) in patients of similar severity. When considering other substances used to overcome acute hemodynamic instability (i.e., catecholamines), their dose is also associated with mortality (10). But it is not only the dose of norepinephrine itself but also mainly the intensity of disease (and hence vasoplegia) what is indicative of the outcome.
2) Is CFB really what matters? Fluids are never administered as free water even though often perceived so. Use of 1 L of normal saline means administration of 9 g of NaCl what equals 3.6 g of sodium. This is almost double the recommended daily dose. Sodium surplus equal to median CFB in Neyra et al (6) (provided saline was used) could range from 5 to 10 g. Unlike free water that passively goes "to and fro" over most of the body, sodium is, in order to maintain the cells' integrity, actively expelled from cells (at cost of one ATP per three sodium molecules). Increasing sodium loads naturally boost either the cells' energy demands or intracellular sodium (and water) content. Besides, increased chloride levels were already found to be associated with mortality in similar population (11). Because urinary excretion of osmotic load is limited (contrary to water), accumulation of solutes may be of major importance than CFB itself.
3) Can we avoid CFB, how and when? As pointed previously, adequate fluid resuscitation and initial positive CFB is still the mainstay during first phases of critical illness (12). FA's

*See also p. 1891.

Key Words: fluid resuscitation/management; kidney; sepsis

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adverse effects seem to be the price we have to pay for the life of an unstable patient; therefore, we should administer only the amount necessary. However, we still lack clear-cut goals to define "amount necessary"; therefore, FA is extremely variable and often "unguided" (13). In addition, fluids are not indicated as volume replacement only. We use them to administer drugs or nutrients. The identification of the transition from ebb (salvage and optimization) to flow phases (stabilization and deescalation) is often very difficult. This turning point is even more critical when spontaneous mobilization of fluids does not occur and patient's CFB is rising. Should we try to manipulate the CFB by the use of medication or dialysis? And when to start? Neyra et al (6–8) use the third-day CFB, but the separation between survivors and nonsurvivors started already after 24 hours in another study (9). Therefore, in some patients, one has to act even before day 3. In the Fluid and Catheter Treatment Trial lite protocol, active fluid removal was started once the patient was stable without vasopressors (14). Other authors aimed for negative balance even in the presence of vasoactive medication (15). Hence, day 3 CFB may serve as some sort of final countdown.

At any case, knowing that the dark side exists should not hinder us from using the force of fluids. Rather it should lead us to vigilance in administration of each drop given or fluid challenge performed. Studies, like this one by Neyra et al (6), could help us to delineate important milestones or warning signs on the trajectory of CFB (6). The information added by this article is that significant differences may be expected in patients with AKI and/or CKDs.

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Cumulative Fluid Balance and Mortality in Septic Patients With or Without Acute Kidney Injury and Chronic Kidney Disease*

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*See also p. 1945.

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Objective: Incident acute kidney injury and prevalent chronic kidney disease are commonly encountered in septic patients. We examined the differential effect of acute kidney injury and chronic kidney disease on the association between cumulative fluid balance and hospital mortality in critically ill septic patients.

Design: Retrospective cohort study.

Setting: Urban academic medical center ICU.

Patients: ICU adult patients with severe sepsis or septic shock and serum creatinine measured within 3 months prior to and 72 hours of ICU admission. Patients with estimated glomerular filtration rate less than 15 mL/min/1.73 m^2 or receiving chronic dialysis were excluded.

Interventions: None.

Measurements and Main Results: A total of 2,632 patients, 1,211 with chronic kidney disease, were followed up until hospital death or discharge. Acute kidney injury occurred in 1,525 patients (57.9%), of whom 679 (44.5%) had chronic kidney disease. Hospital mortality occurred in 603 patients (22.9%). Every 1-L increase in cumulative fluid balance at 72 hours of ICU admission was independently associated with hospital mortality in all patients (adjusted odds ratio, 1.06 [95% CI] 1.04–1.08; $p < 0.001$), and in each acute kidney injury/chronic kidney disease subgroup (adjusted odds ratio, 1.06 [1.03–1.09] for acute kidney injury+/chronic kidney disease+; 1.09 [1.05–1.13] for acute kidney injury–/chronic kidney disease+; 1.05 [1.03–1.08] for acute kidney injury+/chronic kidney disease–; and 1.07 [1.02–1.11] for acute kidney injury–/chronic kidney disease–). There was a significant interaction between acute kidney injury and chronic kidney disease on cumulative fluid balance ($p = 0.005$) such that different cumulative fluid balance cut-offs with the best prognostic accuracy for hospital mortality were identified: 5.9 L for acute kidney injury+/chronic kidney disease+; 3.8 L for acute kidney injury–/chronic kidney disease+; 4.3 L for acute kidney injury+/chronic kidney disease–; and 1.5 L for acute kidney injury–/chronic kidney disease–. The addition of cumulative fluid balance to the admission Sequential Organ Failure Assessment score had increased prognostic utility for hospital mortality when compared with Sequential Organ Failure Assessment alone, particularly in patients with acute kidney injury.

Conclusions: Higher cumulative fluid balance at 72 hours of ICU admission was independently associated with hospital mortality regardless of acute kidney injury or chronic kidney disease presence. We characterized cumulative fluid balance cut-offs associated with hospital mortality based on acute kidney injury/chronic kidney disease status, underpinning the heterogeneity of fluid regulation in sepsis and kidney disease. (*Crit Care Med* 2016; 44:1891–1900)

Key Words: acute kidney injury; chronic kidney disease; cumulative fluid balance; mortality; sepsis

Sepsis is the most common cause of ICU admissions and is associated with significant morbidity and mortality (1, 2). Acute kidney injury (AKI) is a frequent complication in critically ill patients and occurs in nearly 45% of septic patients and 60% of those with septic shock (3–5). The combination of sepsis and AKI may synergistically increase mortality rates to up to 50% (5–7). Most patients with sepsis have preexisting comorbidities, including chronic kidney disease (CKD) (1). When compared with those without CKD, those with CKD have a higher incidence and severity of sepsis, as well as increased mortality from sepsis (8–10). CKD is now recognized as a relevant poor prognostic factor in patients with sepsis (11, 12).

Despite the known benefits of fluid therapy in sepsis (13–15), the recognition of potential deleterious effects of excessive fluid administration is alarming. Humphrey et al (16) demonstrated a significant decrease in mortality with a fluid-conservative resuscitation strategy in a small sample with acute respiratory distress syndrome. More recently, Wiedemann et al (17) showed that a fluid-conservative approach shortened the duration of mechanical ventilation in patients with acute lung injury. Subsequent studies have proposed "fluid accumulation" or "positive fluid balance" as a marker of adverse outcomes in patients with septic shock (2, 18, 19). Importantly, fluid overload (defined as fluid accumulation > 10% above baseline weight) and mean daily fluid balance were independently associated with mortality in critically ill patients with AKI (20, 21).

Previous studies have not investigated the impact of cumulative fluid balance (CFB) on adverse outcomes based on incident AKI and/or prevalent CKD stratification. The purpose of the present study was to determine whether CFB was independently associated with hospital mortality in critically ill septic patients with or without incident AKI and prevalent CKD, and whether a differential effect of AKI or CKD on this association could be identified. We also investigated whether the addition of CFB to the admission Sequential Organ Failure Assessment (SOFA) score would improve the prognostic accuracy for hospital mortality.

MATERIALS AND METHODS

Study Design and Participants

We conducted a single-center, retrospective cohort study utilizing a database of patients with severe sepsis or septic shock admitted to the ICU in an urban, tertiary care hospital. Study participants were identified using administrative-linked electronic databases for ICU admissions from May 2007 to April 2012. Severe sepsis or septic shock was defined by Angus et al (1) criteria, using *International Classification of Diseases*, 9th Revision, Clinical Modification (*ICD*-9-CM) codes (22) for both a bacterial or fungal infection and a diagnosis of acute organ dysfunction excluding gastrointestinal failure. We included adult patients admitted from the emergency department (ED) to the ICU with a diagnosis of severe sepsis or septic shock who had at least one serum creatinine (SCr) measured and documented in the electronic medical records (EMRs) at two different time points: within 3 months prior to and within the first 72 hours of admission. Patients with absent or incomplete recorded daily fluid balance within the first 72 hours of ICU stay and those with estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m^2 or receiving chronic dialysis were excluded. The protocol was approved by the institutional review board (7044).

Study Variables

Baseline SCr was defined as the most recent SCr within the 3-month period before ICU admission, which was used to calculate the baseline eGFR using the four-variable Modification of Diet in Renal Disease (MDRD) study equation (23). Patients were categorized as having AKI if the baseline SCr increased by 0.3 mg/dL or more or by 150% or more or required acute dialysis as defined by Kidney Disease: Improving Global Outcomes SCr-based criteria (24). The highest SCr within 72 hours of admission was used to determine the occurrence of AKI. Preexisting CKD was defined as baseline eGFR of 15–59 mL/min/1.73 m^2 in the absence of chronic dialysis or end-stage renal disease.

CFB was calculated as follows: total fluid input minus total fluid output within the first 72 hours of ICU stay. Subject-specific variables were obtained from EMR. Acute Physiology and Chronic Health Evaluation II (APACHE II) (25) and SOFA (26) scores were calculated integrating clinical and laboratory data from the first day of ICU admission. Oliguria was defined as urine output less than 500 mL within 24 hours. Prevalent comorbidity was identified using ICD-9-CM codes, except for anemia that was defined as admission hematocrit less than 39% for men and less than 36% for women. Data pertaining to drug exposure, RBC transfusion, mechanical ventilation, and acute dialysis were based on hospital billing codes for the indexed admission. All collected data were validated through comprehensive individual review of 10% of EMR by data management personnel blinded to the study.

Study Outcome

The observation period was from admission to the ICU until the time of hospital death or discharge. The primary outcome measure was all-cause hospital mortality, adjudicated based on EMR review by data management personnel blinded to the study.

Statistical Analysis

The study sample was analyzed as a whole group and stratified into four subgroups by the occurrence of AKI (incident

AKI) and preexisting CKD (prevalent CKD) as follows: AKI+/CKD+, AKI–/CKD+, AKI+/CKD–, and AKI-/CKD–. Categorical data were reported as percentages and continuous data as means ± SD or median [25th–75th percentile]. Comparisons between groups for categorical variables were made using the Fisher exact test. For continuous variables, analysis of variance was used for Gaussian and Wilcoxon rank-sum test for non-Gaussian distributed data.

Multivariable logistic regression models were constructed for hospital mortality as the dependent variable and to evaluate CFB as an independent variable. The two-way interaction between incident AKI and prevalent CKD (AKI × CKD) on CFB and on hospital mortality was first evaluated in the entire cohort to validate subgroup stratification if significant ($p < 0.1$). CFB was modeled as a continuous variable (per 1-L increase) and categorical variable (≥ vs < cut-off value). Optimal predicted probability cut-offs were determined by Youden's index from receiver-operating characteristic (ROC) analysis. Candidate variables for the multivariable models included demographic data (age, gender, and race); comorbidities (diabetes, hypertension, heart failure, and anemia); indicators of critical illness (SOFA and APACHE II scores, oliguria, mechanical ventilation, RBC transfusion, and length of hospital stay [LOS]); and drug exposure (vasoactive drug and diuretic). LOS was dichotomized as greater than or equal to vs less than median value of 12 days. Inclusion into the final model was based upon significance of univariable results and clinical relevance. Only one of two variables was included in the event of collinearity between variables.

To test the model performance of CFB plus admission SOFA score versus SOFA alone for the prediction of hospital mortality, ROC-areas under the curve were compared and continuous net reclassification index (NRI) and absolute integrated discrimination improvement (IDI) were calculated (27). NRI quantifies the hospital mortality events correctly reclassified with the addition of CFB to the model that included SOFA alone. IDI measures the increment in the predicted probabilities for the hospital mortality subset and the decrement for the subset without hospital mortality. The 95% CI reported for the logistic regression odds ratios (ORs) were based on Wald estimation. Two-sided p values of less than 0.05 indicated statistical significance. Spreadsheet software and SAS 9.4 (SAS Institute, Cary, NC) were used in data acquisition and analysis.

Sensitivity Analyses

CFB Adjustment by Body Weight. We adjusted CFB by ICU admission body weight (W) in order to quantify fluid overload percentage (FO) using the following formula: FO = [(W + CFB/W) – 1] × 100%. FO was similarly evaluated as an independent variable in multivariable logistic regression models for hospital mortality.

Multiple Imputation Method for Missing Baseline SCr Values. A total of 3,070 patients had to be excluded from the primary analysis because of absence of baseline SCr within 3 months prior to ICU admission. As a part of a sensitivity analysis, these missing SCr values were imputed using a linear regression model derived from subject-specific characteristics of the primary study cohort (2,632 patients). Log-transformed SCr was the dependent variable and independent predictors included age, gender, race, diabetes, hypertension, APACHE II score, and their interactions. The association between CFB and hospital mortality was further evaluated in this secondary cohort of 5,688 patients (2,632 with known baseline SCr + 3,056 with imputed baseline SCr, after exclusion of 14 patients with imputed baseline eGFR < 15 mL/min/1.73 m^2) (28).

Propensity-Regression Analysis. The primary cohort logistic regression model of CFB (independent variable) and hospital mortality (dependent variable) included a continuous propensity score as a covariate for statistical adjustment. This propensity score was generated from all available study covariates that influenced the occurrence of AKI and/or CKD.

Standardized Mortality Ratio Determination to Examine the Relationship Between CFB and Hospital Mortality. Standardized mortality ratio (SMR) for each AKI/CKD subgroup by CFB quintiles was calculated as follows: SMR = observed/predicted mortality; where predicted mortality was determined by the multivariable logistic regression estimate for each AKI/CKD subgroup.

RESULTS

Clinical Characteristics

Of 6,490 patients admitted from the ED to the ICU with the diagnosis of severe sepsis or septic shock, 3,858 were excluded due to the following reasons: no recorded measures of baseline SCr within 3 months before admission; incomplete CFB data at 72 hours; or receiving chronic dialysis (**Fig. 1**). The primary study cohort included 2,632 patients: 1,211 (46%) with preexisting CKD defined as an eGFR of 15–59 mL/min/1.73 m^2 and 1,421 (54%) without CKD (eGFR ≥ 60 mL/min/1.73 m^2). AKI occurred in 1,525 patients (57.9%), 679 with pre-existing CKD (44.5%) and 846 without CKD (55.5%) (Fig. 1). A total of 238 patients (9.0%) required acute dialysis for AKI.

Clinical characteristics of the cohort are reported in **Table 1**. Patients who suffered from AKI, independently of CKD status, had a higher frequency of pressor or inotrope requirement, higher APACHE II and SOFA scores, and more frequent use of mechanical ventilation (Table 1). The median LOS (25th–75th percentile) was 12 days (7–21 d) in the entire cohort. In the CKD group, LOS was not different based on the presence of AKI, whereas in the non-CKD group, those with AKI had a LOS of 12 days (7–20 d) when compared with those without AKI, 13 (8–22; p =0.01) (Table 1). Importantly, this difference was influenced by the observation that AKI patients who died had shorter LOS than their non-AKI counterparts: 9 days (4–19 d) versus 14 days (7–25 d), p = 0.007 (data not shown).

Study Outcomes

A total of 603 patients (22.9%) died during the observation period, median LOS of 10 days (4–20 d). A higher proportion of patients with AKI (28.1%) versus without AKI (15.8%) died ($p < 0.001$). There was significant interaction between AKI and CKD (AKI × CKD) on hospital mortality (p =0.04): 173 patients

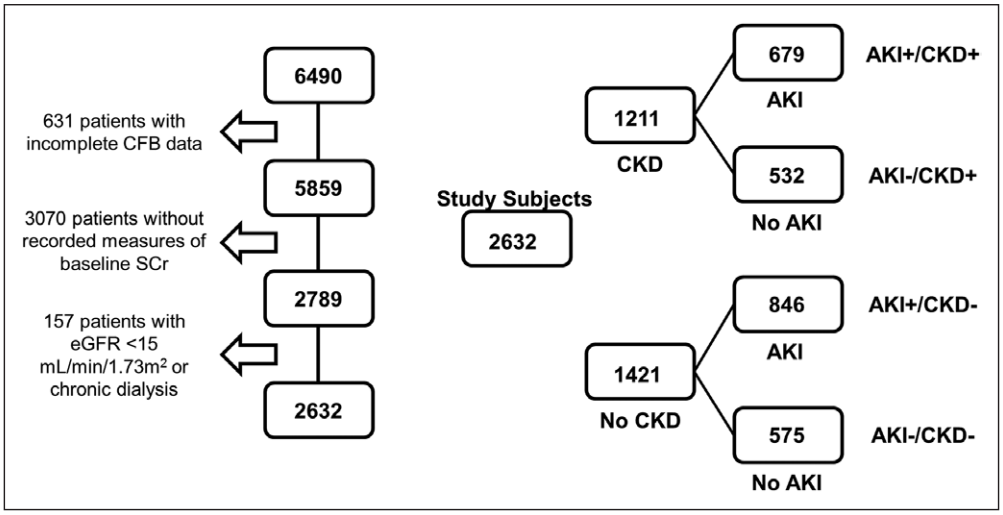

Figure 1. Cohort derivation and study scheme. AKI = occurrence of acute kidney injury, CFB = cumulative fluid balance, CKD = preexisting chronic kidney disease, eGFR = estimated glomerular filtration rate, SCr = serum creatinine.

with AKI (25.5%) versus 91 without AKI (17.1%) died in the CKD group ($p < 0.001$) and 255 with AKI (30.1%) versus 84 without AKI (14.6%) died in the non-CKD group ($p < 0.001$).

CFB (mean ± SD) at 72 hours was higher in those who died: 7.67 ± 7.94 versus 2.95 ± 6.05 L in survivors ($p < 0.001$). CFB was also higher in those with AKI requiring dialysis (9.16 ± 8.91 L) than in those with AKI not requiring dialysis (4.61 ± 7.24 L) or in those who did not suffer from AKI (2.80 ± 5.60 L; p for trend < 0.001). CFB was independently associated with hospital mortality in the entire cohort (adjusted OR per 1-L increase [95% CI], 1.06 [1.04–1.08]; $p < 0.001$). The occurrence of AKI was an independent predictor of hospital mortality (adjusted OR, 1.28 [1.01–1.62]; $p = 0.04$) but preexisting CKD was not ($p = 0.22$).

There was a significant interaction between AKI and CKD (AKI × CKD) on CFB ($p = 0.005$) (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B857; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/B861). After subgroup stratification by incident AKI and prevalent CKD, univariable analyses revealed a significant association between CFB and hospital mortality in all subgroups (**Fig. 2*A***). After multivariable adjustment, every 1-L increase of CFB at 72 hours was independently associated with hospital mortality, with adjusted ORs (95% CI) of 1.06 (1.03–1.09; $p < 0.001$) for AKI+/CKD+; 1.09 (1.05–1.13; $p < 0.001$) for AKI–/CKD+; 1.05 (1.03–1.08; $p < 0.001$) for AKI+/CKD–; and 1.07 (1.02–1.11; $p = 0.002$) for AKI–/CKD– (Fig. 2*A* and **Table 2**). A similar association with hospital mortality was found when CFB was adjusted by ICU admission body weight (FO per 1% increase). The adjusted ORs (95% CI) were as follows: 1.04 (1.01–1.06; $p = 0.005$) for AKI+/CKD+; 1.06 (1.03–1.10; $p < 0.001$) for AKI–/CKD+; 1.04 (1.02–1.06; $p < 0.001$) for AKI+/CKD–; 1.05 (1.02–1.09; $p = 0.003$) for AKI–/CKD– (**Fig. 2*B***).

CFB Cut-Offs

For each of the four AKI/CKD subgroups, different CFB cut-offs with the best prognostic accuracy for hospital mortality were identified: 5.9 L for AKI+/CKD+; 3.8 L for AKI–/CKD+; 4.3 L for AKI+/CKD–; and 1.5 L for AKI–/CKD–. The CFB cut-off was lowest if both AKI and CKD were absent (**Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/B858). A stronger association with hospital mortality was found when CFB was tested as a dichotomized variable (≥ vs < cut-off value). The adjusted ORs (95% CI) were as follows: 2.65 (1.70–4.12; $p < 0.001$) for AKI+/CKD+; 2.34 (1.41–3.89; $p = 0.001$) for AKI–/CKD+; 2.37 (1.60–3.50; $p < 0.001$) for AKI+/CKD–; 2.61 (1.53–4.45; $p < 0.001$) for AKI–/CKD– (**Supplemental Fig. 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/B859; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/B861).

Utility of CFB and SOFA Score for the Prediction of Hospital Mortality

CFB at 72 hours was combined with the admission SOFA score in ROC plots for the prediction of hospital mortality in each of the four AKI/CKD subgroups (**Fig. 3**). In all subgroups, the model (SOFA + CFB) significantly improved the predictive value for hospital mortality when compared with SOFA alone. This observation was more pronounced in those patients who suffered from AKI regardless of whether CKD was present or absent. The model (SOFA + CFB) significantly improved the risk reclassification of hospital mortality over admission SOFA score alone, as evident by NRI and IDI metrics (**Table 3**).

Sensitivity Analyses

After multiple imputation of missing baseline SCr values, a secondary cohort of 5,688 patients was generated (2,632 with known baseline SCr + 3,056 with imputed baseline SCr). In this secondary cohort, results were essentially the same: CFB was also independently associated with hospital mortality in all patients, adjusted OR per 1-L increase (95% CI) 1.07 (1.06–1.08; $p < 0.001$). After subgroup stratification by incident AKI and prevalent CKD, CFB at 72 hours was also independently associated with hospital mortality, adjusted ORs (95% CI) of 1.07 (1.05–1.09; $p < 0.001$) for AKI+/CKD+; 1.07 (1.04–1.09; $p < 0.001$) for AKI–/CKD+; 1.05 (1.04–1.07; $p < 0.001$) for AKI+/CKD–; and 1.07 (1.03–1.10; $p < 0.001$) for AKI–/CKD– (**Supplemental Fig. 3*A***, Supplemental Digital Content 4, http://links.lww.com/CCM/B860; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/B861). Furthermore, this independent association persisted after adjustment by ICU admission body weight or FO (**Supplemental Fig. 3*B***,

TABLE 1. Patient Characteristics Stratified by Acute Kidney Injury/Chronic Kidney Disease Subgroups

Variable	AKI+/CKD+ (*n* = 679)	AKI−/CKD+ (*n* = 532)	AKI+/CKD− (*n* = 846)	AKI−/CKD− (*n* = 575)	AKI × CKD Interaction
Demographics					
Age (yr), mean ± SD	69.4 ± 14.2[a]	70.0 ± 14.8[a]	62.8 ± 15.8	61.5 ± 16.4	0.13
Women (%)	336 (49.5)[b]	284 (53.4)[b]	355 (42)	254 (44.2)	0.001
African-American (%)	261 (38.4)[b]	178 (33.5)[b]	401 (47.4)[e]	238 (41.4)	< 0.001
Chronic conditions					
Baseline serum creatinine[f] (mg/dL), mean ± SD	1.80 ± 0.66[a]	1.86 ± 0.73[a]	0.93 ± 0.24	0.92 ± 0.23	0.12
Baseline estimated glomerular filtration rate based on Modification of Diet in Renal Disease Study equation[f] (mL/min/1.73 m^2), mean ± SD	41.7 ± 11.7[a,e]	40.0 ± 12.5[a]	93.4 ± 36.2	92.3 ± 29.7	0.04
Diabetes (%)	176 (25.9)[b]	136 (25.6)[b]	170 (20.1)	99 (17.2)	0.001
Hypertension (%)	181 (26.7)[a,d]	213 (40.0)[b]	432 (51.1)	297 (51.7)	< 0.001
Systolic heart failure (%)	30 (4.4)	15 (2.8)	25 (3)	18 (3.1)	0.36
Anemia (%)	600 (89)	455 (86.7)	722 (86.4)	488 (85.6)	0.26
Drug exposure (%)					
Diuretic	47 (6.9)	45 (8.5)	66 (7.8)	55 (9.6)	0.12
Statin	257 (37.9)[a]	185 (34.8)[b]	211 (25)	151 (26.3)	< 0.001
Iodine contrast	103 (15.2)[a,e]	115 (21.6)[a]	222 (26.2)[e]	199 (34.6)	< 0.001
Aminoglycoside	44 (6.5)[b]	33 (6.2)[b]	101 (11.9)	66 (11.5)	< 0.001
Critical indicators					
Oliguria (%)	112 (20.2)[c,d]	24 (5.6)	105 (14.7)[d]	16 (3.3)	0.002
Cumulative fluid balance (total fluid input minus output within the first 72 hr of ICU admission) (L), mean ± SD	4.16 ± 7.34[a,e]	2.85 ± 5.91	5.55 ± 7.50[d]	2.74 ± 5.31	0.005
Fluid overload percentage 72 hr, %, mean ± SD	5.7 ± 9.7[b]	4.7 ± 9.1	8.0 ± 11.1[d]	4.0 ± 7.7	0.001
Length of hospital stay[d] (d), median [25th-75th percentile]	12.0 [6.0–21.0]	12.0 [7.0–20.0][b]	12.0 [7.0–20.0][e]	13.0 [8.0 –22.0]	0.07
Pressor or inotrope (%)	290 (42.7)[d]	144 (27.1)	366 (43.3)[d]	167 (29.0)	< 0.001
Mechanical ventilation (%)	297 (43.7)[e]	190 (35.7)	407 (48.1)[e]	219 (38.1)	< 0.001
Blood transfusion (%)	19 (2.8)	19 (3.6)	29 (3.4)	18 (3.1)	0.77
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	14.5 ± 7.3[d]	12.2 ± 5.8[b]	13.4 ± 6.9[e]	11.1 ± 6.1	0.91
Sequential Organ Failure Assessment score score,[d] median [25th–75th percentile]	5.0 [3.0–9.0][d]	4.0 [2.0–6.0][b]	5.0 [3.0–8.0][d]	3.0 [1.0–6.0]	0.002

AKI = occurrence of acute kidney injury, CKD = preexisting chronic kidney disease.

CKD vs no CKD for the same AKI status, [a]$p < 0.0001$.

CKD vs no CKD for the same AKI status, [b]$p < 0.01$.

CKD vs no CKD for the same AKI status, [c]$p < 0.05$.

AKI vs no AKI for the same CKD status, [d]$p < 0.0001$.

AKI vs no AKI for the same CKD status, [e]$p < 0.01$.

[f]Data were log-transformed before analysis. Comparisons for categorical variables were made using the Fisher Exact test. For continuous variables, analysis of variance was used for Gaussian and Wilcoxon rank-sum test for non-Gaussian distributed data.

Anemia is defined as the hematocrit < 39% for men and < 36% for women; fluid overload percentage is defined as [(W + CFB/W)−1] × 100%, W is ICU admission body weight; iodine contrast is defined as only if IV or intra-arterial; oliguria is defined as urine output < 500 mL in 24 hr.

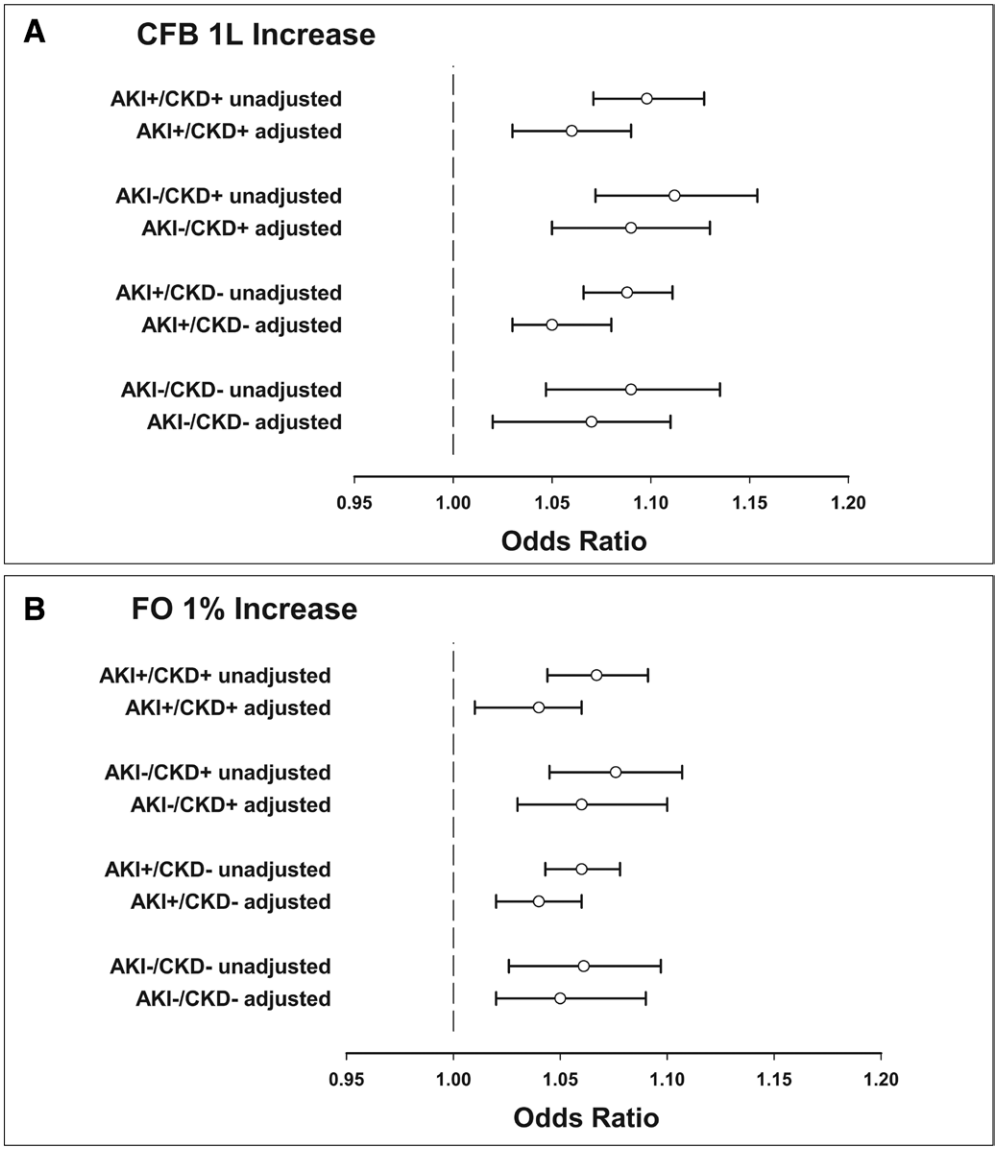

Figure 2. Forest plots of unadjusted and adjusted odds ratios for hospital mortality in the primary cohort ($n = 2{,}632$). **A**, Cumulative fluid balance (CFB) per 1-L increase at 72 hr of ICU admission. Adjusted odds ratio (95% CI) for hospital mortality in the entire cohort 1.06 (1.04–1.08); (**B**) fluid overload percentage (FO) per 1% increase at 72 hr of ICU admission. Adjusted odds ratio (95% CI) for hospital mortality in the entire cohort 1.04 (1.03–1.06). AKI = occurrence of acute kidney injury; CKD = preexisting chronic kidney disease.

Supplemental Digital Content 4, http://links.lww.com/CCM/B860; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/B861).

The propensity-regression adjusted OR for hospital mortality in the primary cohort was 1.09 (95% CI, 1.07–1.11; $p < 0.001$) for every 1-L increase in CFB at 72 hours. In addition, there was a stepwise increase in SMR across CFB quintiles, evident in the entire cohort and in each AKI/CKD subgroup (**Fig. 4**).

DISCUSSION

The principle new finding in our study is that the association of higher CFB with hospital mortality is evident in all critically ill septic patients, regardless of the occurrence of AKI and/or preexisting CKD. However, we found a significant interaction between AKI/CKD categories and CFB such that for the first time, to our knowledge, we characterized different CFB cut-offs associated with hospital mortality based on whether AKI and/or CKD were present. Finally, we showed that combining CFB at 72 hours and admission SOFA score improves the predictive value of the universally accepted SOFA score for hospital mortality.

Fluid therapy in septic shock consists of initial fluid resuscitation followed by conservative fluid management and regulation (29–32). The inflammatory cascade of sepsis is thought to disrupt the endothelial surface, alter the microvascular system, and cause capillary leakage (33–35). Fluid therapy may enhance filling pressures and improve microcirculation in early sepsis but not in late sepsis (15, 36). In this context, detrimental consequences of fluid accumulation in critically ill patients, including mortality, have been previously reported in acute lung injury (17, 37), in sepsis (2, 38), and in patients with AKI with or without requirement for dialysis (20, 21, 39–41).

An observational study of 198 ICUs in 24 European countries revealed that CFB within the first 72 hours of sepsis onset was directly associated with higher mortality, with an OR per 1-L increase of 1.1 (1.0–1.1; $p = 0.001$) (2). A secondary analysis of this study later reported that CFB was associated with increased mortality specifically in the subgroup of patients with AKI (29). One limitation of this study was that AKI was defined as a SCr of greater than 3.5 mg/dL (310 μmol/L) or urine output of less than 500 mL/d, and baseline SCr was not taken into consideration for AKI definition. Our investigation extends these findings by using a more contemporary and accepted AKI definition taking the baseline SCr into account. Later, Bouchard et al (20) reported that fluid overload defined as greater than 10% increase in body weight was associated with 60-day mortality in critically ill patients with AKI, with or without requirement for dialysis. Although this analysis did consider the

TABLE 2. Multivariable Analysis of Hospital Mortality as the Dependent Variable and Cumulative Fluid Balance as the Study Independent Variable in All Acute Kidney Injury/Chronic Kidney Disease Subgroups

Clinical Variables	AKI+/CKD+ aOR (95% CI)	*p*	AKI−/CKD+ aOR (95% CI)	*p*	AKI+/CKD− aOR (95% CI)	*p*	AKI−/CKD− aOR (95% CI)	*p*
Cumulative fluid balance, per 1-L increase	1.06 (1.03–1.09)	< 0.001	1.09 (1.05–1.13)	< 0.001	1.05 (1.03–1.08)	< 0.001	1.07 (1.02–1.11)	0.002
Age, per 10-yrincrease	1.05 (0.91–1.22)	0.52	1.40 (1.16–1.68)	< 0.001	1.08 (0.96–1.21)	0.21	1.12 (0.96–1.30)	0.15
Sequential Organ Failure Assessment, per 1-unit score	1.07 (1.01–1.13)	0.02	1.08 (1.00–1.17)	0.04	1.05 (1.00–1.11)	0.05	1.08 (1.00–1.17)	0.07
Length of hospital stay, < 12 vs ≥12 d	0.70 (0.45–1.07)	0.10	0.74 (0.44–1.24)	0.26	0.57 (0.39–0.83)	0.003	1.02 (0.63–1.66)	0.94
Mechanical ventilation, yes vs no	1.65 (1.02–2.65)	0.04	2.81 (1.58–4.99)	< 0.001	2.78 (1.82–4.24)	< 0.001	1.57 (0.90–2.73)	0.11
Oliguria, yes vs no	1.85 (1.11–3.08)	0.02	–	–	2.31 (1.42–3.75)	< 0.001	–	–

AKI = occurrence of acute kidney injury, CKD = preexisting chronic kidney disease, aOR = adjusted odds ratio.

Candidate variables for the multivariable models included demographic data (age, gender, and race); comorbidities (diabetes, hypertension, heart failure, and anemia); indicators of critical illness (Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation II [APACHE II] scores, oliguria, mechanical ventilation, RBC transfusion, and length of hospital stay); and drug exposure (vasoactive drug and diuretic). Inclusion into the final model (depicted in the Table 2) was based upon significance of univariable results ($p < 0.10$) and clinical relevance. APACHE II was not included in the multivariable model because of collinearity with the SOFA score. No collinearity between cumulative fluid balance (CFB) and oliguria was detected in all subgroups (variance inflation factor =1.0). Model C statistic (95% CI): 0.71 (0.65–0.76) for AKI+/CKD+, 0.75 (0.69–0.81) for AKI−/CKD+, 0.74 (0.69–0.78) for AKI+/CKD−, and 0.67 (0.61–0.74) for AKI−/CKD−. Oliguria is defined as urine output < 500 mL in 24 hr.

baseline SCr in the definition of AKI, only patients for whom a nephrology consultation for AKI was obtained were included, which could have led to selection bias. In addition, a non-AKI control group was not included for comparison, and the influence of preexisting CKD was not examined. Furthermore, fluid overload was defined arbitrarily as the accumulation of fluid from 3 days prior to nephrology consultation until hospital discharge, which may not represent a uniform CFB estimate in patients who develop AKI later in the course of ICU stay. In contrast, we used a widely accepted definition for CFB as net fluid accumulated over the first 72 hours of ICU stay. This strategy has been previously tested (2) and provides clinically useful information to more uniformly risk-stratify critically ill septic patients using CFB as an additional clinical parameter.

More recently, Teixeira et al (41) confirmed the association of higher fluid balance with mortality in ICU patients with AKI and demonstrated higher CFB in nonsurvivors than in survivors in the first 7 days of ICU stay. However, this study included only 132 participants with AKI, and the adjudication of AKI occurrence for the primary analysis was based on SCr of greater than or equal to 3.5 mg/dL (310 µmol/L) or urine output less than 500 mL/d, without the use of baseline SCr to assess absolute or relative changes in SCr. Furthermore, recent studies have shown that higher fluid overload at the time of acute dialysis initiation for AKI was associated with 90-day mortality (39) and worse renal recovery at 1 year (40).

Another important finding in our study was that patients without preexisting CKD that did not develop AKI had the lowest CFB and FO cut-offs associated with hospital mortality. A possible explanation for this observation may be that although in patients without kidney disease excess fluid is usually self-regulated and excreted by preserved renal function, this subgroup may be more susceptible to the negative consequences of acute fluid accumulation than those with preexisting CKD. Patients with CKD, particularly those with edema, may have greater interstitial system adaptation to fluid overload than patients with preserved kidney function (42). The adaptive response and compliance of the interstitial system (43) can tolerate up to 4.5 L of excess total body fluid before edema becomes evident on physical examination (44). Ebah et al (45) demonstrated in patients with CKD stages 3 to 5 and obvious edema that both interstitial volume and pressure were significantly increased in comparison with healthy volunteers. This observation may illustrate chronic fluid overload adaptation (42). An additional observation was that FO cut-offs were all lower than the more than 10% FO cut-off associated with mortality previously reported in literature (20, 46, 47) (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/B858). The heterogeneity of these different cut-offs for adverse hospital outcomes in the context of critical illness, sepsis, and kidney disease may be prognostically important but needs further investigation for validation. The purpose of our study was to characterize this heterogeneity rather than to determine specific cut-offs that are readily available for implementation in clinical practice.

Our study has important strengths that need to be delineated. First, we utilized universally accepted AKI and CKD definitions, taking into consideration the baseline SCr. Second,

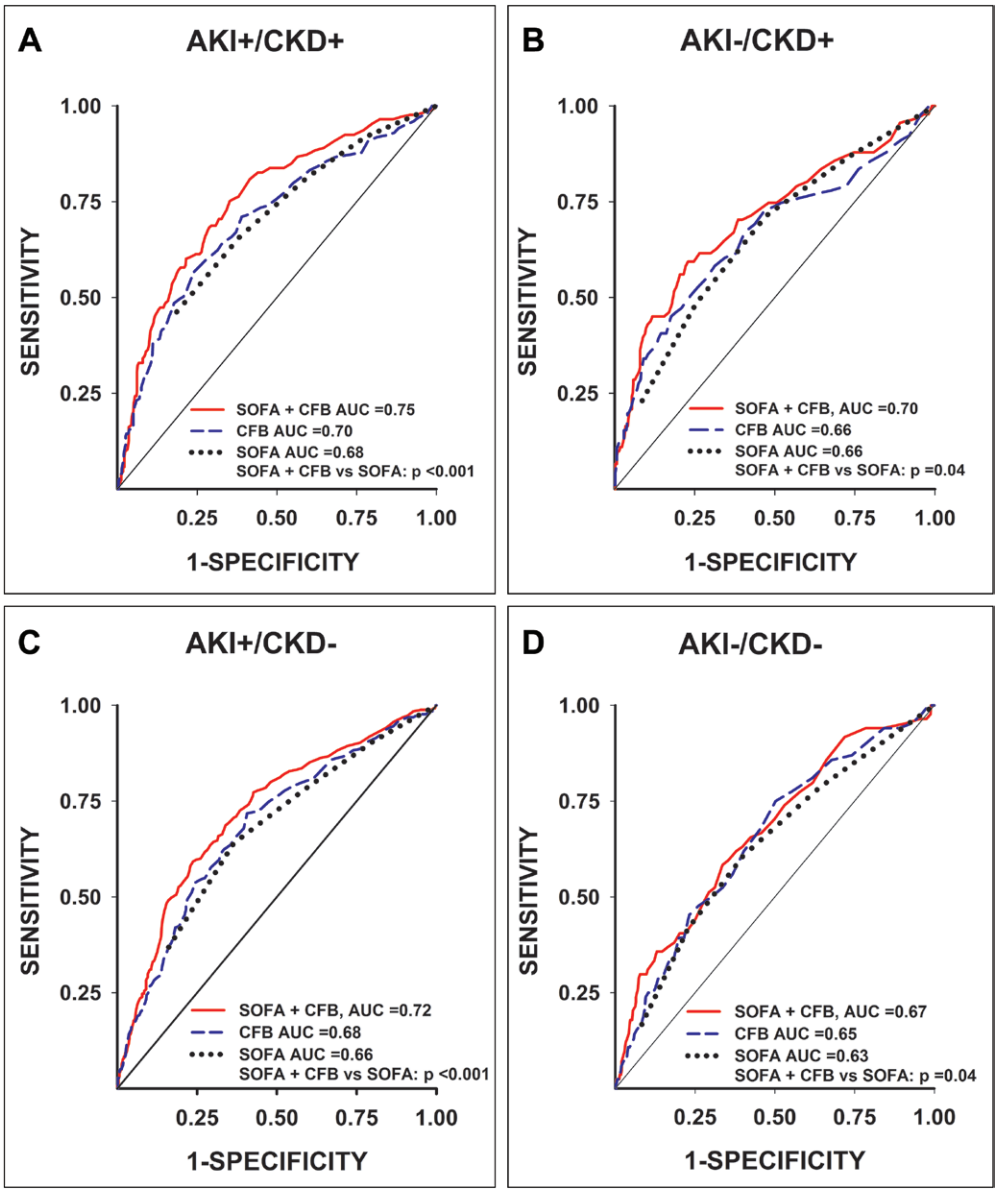

Figure 3. Receiver-operating characteristic plots representing the area under the curve (AUC) for the prediction of hospital mortality by the model of admission Sequential Organ Failure Assessment (SOFA) score + cumulative fluid balance (CFB) at 72 hr (red), CFB at 72 hr (blue), and SOFA score (black). Comparison *p* values of SOFA + CFB vs SOFA alone for each acute kidney injury (AKI)/chronic kidney disease (CKD) subgroup were calculated.

we adjusted the analyses for appropriate confounders, including objective and comprehensive critical illness indicators. Third, we demonstrated a significant interaction between AKI/CKD categories and CFB and therefore justified our subgroup stratification. Fourth, we characterize CFB cut-offs associated with hospital mortality in each AKI/CKD subgroup. Fifth, we performed rigorous sensitivity analyses: 1) CFB adjustment by ICU admission body weight (FO); 2) imputation method of missing values of baseline SCr to overcome the selection bias inherent to the lack of these data in all participants; 3) propensity-regression analysis; and 4) SMR determination to further examine the association between CFB relative to baseline and risk-adjusted hospital mortality. Sixth, the accuracy of CFB data collection was validated by individual EMR review of 10% of data. Finally, unique to our study is the stratification of participants based on kidney disease status (e.g., the occurrence of AKI and preexisting CKD), and the use of CFB both as continuous and categorical independent predictors.

Our study also has important limitations. First, we did not have hourly urine output data for all participants and therefore did not use urine output criteria for AKI adjudication. Nonetheless, we included oliguria (urine output < 500 mL/d) as a potential confounder in the multivariable models. Second, data pertaining to fluid administration prior to ICU admission were not available for inclusion in the study. However, given that the study subjects are from an institution where standardized goal-directed fluid resuscitation is generally practiced, we can assume similar patterns of pre-ICU fluid therapy for most if not all participants. Third, the determination of eGFR by using the MDRD equation may have led to overclassification of CKD status in a small number of patients although this would have affected only less than 10% of the cohort. Fourth, although we adjusted for confounding by rigorous multivariable regression analyses, residual confounding by unmeasured covariates may not have been completely eliminated. Howbeit, different sensitivity analyses, including propensity-regression analysis, confirmed our results.

CONCLUSIONS

Higher CFB at 72 hours of ICU admission was independently associated with hospital mortality in adult patients with severe sepsis or septic shock, regardless of AKI or CKD presence. The combination of CFB at 72 hours and admission SOFA score improved the predictive value of SOFA score for hospital mortality. Stratification of patients by the occurrence of AKI and preexisting CKD identified different CFB cut-offs associated with hospital mortality, with the lowest CFB cut-off in those without incident AKI

TABLE 3. Improvement in the Discrimination of Admission Sequential Organ Failure Assessment Score for the Prediction of Hospital Mortality by Combining Sequential Organ Failure Assessment Score + Cumulative Fluid Balance at 72 Hours in All Acute Kidney Injury/Chronic Kidney Disease Subgroups

Model Performance Metric	AKI+/CKD+ ($n = 679$)	AKI−/CKD+ ($n = 532$)	AKI+/CKD− ($n = 846$)	AKI−/CKD− ($n = 575$)
Receiver-operating characteristic area under the curve (95% CI)				
CFB	0.70 (0.65, 0.75)	0.66 (0.60, 0.73)	0.68 (0.64, 0.72)	0.65 (0.58, 0.71)
SOFA	0.69 (0.64, 0.73)	0.66 (0.59, 0.72)	0.66 (0.62, 0.70)	0.63 (0.56, 0.70)
SOFA + CFB	0.74 (0.70, 0.79)	0.71 (0.64, 0.77)	0.72 (0.68, 0.75)	0.67 (0.60, 0.73)
p[a] SOFA vs SOFA + CFB	< 0.001	0.04	< 0.001	0.08
Continuous NRI[b] (95% CI)	0.53 (0.37, 0.70)	0.38 (0.16, 0.60)	0.46 (0.32, 0.61)	0.35 (0.13, 0.58)
NRI events correctly reclassified	0.21 (0.15, 0.27)	0.01 (0.002, 0.06)	0.14 (0.10, 0.19)	0.07 (0.03, 0.15)
NRI nonevents correctly reclassified	0.32 (0.28, 0.36)	0.37 (0.33, 0.42)	0.33 (0.29, 0.37)	0.28 (0.24, 0.32)
Absolute IDI[c] (95% CI)	0.052 (0.032, 0.072)	0.058 (0.028, 0.087)	0.053 (0.036, 0.070)	0.023 (0.008, 0.037)
IDI events	0.039 (0.019, 0.079)	0.047 (0.019, 0.113)	0.037 (0.020, 0.068)	0.019 (0.005, 0.076)
IDI nonevents	−0.013 (−0.028, −0.006)	−0.010 (−0.024, −0.004)	−0.016 (−0.03, −0.009)	−0.003 (−0.014, −0.001)

AKI = occurrence of acute kidney injury, CFB = cumulative fluid balance (total fluid input minus output within the first 72 hr of ICU admission), CKD = preexisting chronic kidney disease, IDI = integrated discrimination improvement, NRI = net reclassification index, SOFA = Sequential Organ Failure Assessment.

[a]p value compares model receiver-operating characteristic area under the curve for Sequential Organ Failure Assessment (SOFA) + cumulative fluid balance (CFB) vs SOFA alone. Net reclassification index and integrated discrimination improvement are presented as proportions.

[b]Net reclassification index evaluates the incremental effect of adding CFB to SOFA score for the prediction of hospital mortality and quantifies the net number of individuals reclassified correctly using the model of SOFA + CFB compared with SOFA alone with upward reclassification considered beneficial.

[c]Absolute integrated discrimination improvement measures the increment in the predicted probabilities for the hospital mortality subset and the decrement for the subset without hospital mortality between the model of SOFA + CFB vs SOFA alone.

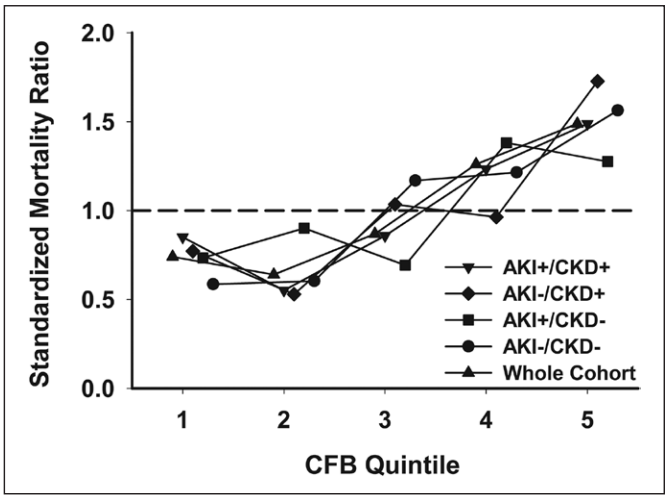

Figure 4. Association between cumulative fluid balance relative to baseline and risk-adjusted hospital mortality. Standardized mortality ratio (SMR) for each acute kidney injury (AKI)/chronic kidney disease (CKD) subgroup by cumulative fluid balance expressed as quintiles was calculated as follows: SMR = observed/predicted mortality; where predicted mortality was determined by the multivariable logistic regression estimate for each AKI/CKD subgroup.

or prevalent CKD. The characterization of different CFB cut-offs underpins the heterogeneity of fluid regulation in critical illness, sepsis, and kidney disease. These differences should be further investigated in future prospective studies in which measurements of interstitial volume and microcirculatory dynamics, in addition to intravascular volume, can be used for guiding fluid therapy in critically ill patients with or without kidney disease.

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