An Assessment of the Acute Kidney Injury Network Creatinine-Based Criteria in Patients Submitted to Mechanical Ventilation

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Summary

Background and objectives The aim of our study was to assess the new diagnostic criteria of acute kidney injury (AKI) proposed by the Acute Kidney Injury Network (AKIN) in a large cohort of mechanically ventilated patients.

Design, setting, participants, & measurements This is a prospective observational cohort study enrolling 2783 adult intensive care unit patients under mechanical ventilation (MV) with data on serum creatinine concentration (SCr) in the first 48 hours. The absolute and the relative AKIN diagnostic criteria (changes in SCr $\geq$0.3 mg/dl or $\geq$50% over the first 48 hours of MV, respectively) were analyzed separately. In addition, patients were classified into three groups according to their change in SCr (ΔSCr) over the first day on MV (ΔSCr): group 1, $\Delta SCr \leq -0.3$ mg/dl; group 2, ΔSCr between -0.3 and $+0.29$ mg/dl; and group 3, $\Delta SCr \geq +0.3$ mg/dl). The primary end point was in-hospital mortality, and secondary end points were intensive care unit and hospital length of stay, and duration of MV.

Results Of 2783 patients, 803 (28.8%) had AKI according to both criteria: 431 only absolute (AKI_A), 362 both relative and absolute (AKI_{R+A}), and 10 only relative. The relative criterion identified more patients when baseline SCr (SCr_0) was <0.9 mg/dl and the absolute when SCr_0 was >1.5 mg/dl. The diagnosis of AKI was associated with mortality.

Conclusions Our study confirms the validity of the AKIN criteria in a population of mechanically patients and the criteria's relationship with the baseline SCr.

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Introduction

Acute kidney injury (AKI) is a frequent and serious clinical condition in critically ill patients that is associated with an increased need for renal replacement therapy (RRT), a longer hospital stay, a higher cost, a higher incidence of end-stage renal disease, and a higher early and late mortality (1–3). Thus, early recognition of AKI is important to optimize therapy to prevent or to minimize the associated adverse outcomes. Yet, unfortunately, there is still no agreement regarding an operative definition of AKI. More than 30 definitions can be found in the literature, which makes it difficult to compare studies on epidemiology, prevention, or treatment of AKI (4). Efforts to develop a consensus definition have been made by the Acute Dialysis Quality Initiative (ADQI) (5). This group proposed a definition and classification of AKI based on changes in serum creatinine concentration (SCr) and/or urine output, which is known as the Risk, Injury, Failure, and End-stage (RIFLE) classification. This classification has been validated by several studies in adults and children (6–13). More recently, the Acute Kidney Injury Network (AKIN) was established, which is a multidisciplinary and intersociety group aimed at improving the care of patients with AKI through the development of uniform standards and classification of the disorder (14,15). A definition based on small changes in SCr and/or urine output within a time frame of 48 hours was proposed. The rationale is to find sensitive and inclusive criteria that consider the relationship between small changes in SCr and mortality, as well as the fact that early detection of kidney injury could prevent or attenuate further damage.

The AKIN definition was proposed as an interim definition/staging system that needs to be validated and, consequently, modified according to emergent evidence (16–20). Some studies compared the AKIN *versus* the RIFLE definitions (17–19), and others assessed only AKIN definitions (16,20). To date, no

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study has assessed separately the accuracy of each component of the AKI criteria based on changes in relative or absolute rise in SCr.

On the other hand, it has been shown that not only increases but also reductions in SCr are associated with worse outcomes (21). Hence, the inclusion of a drop in SCr as a diagnostic criterion for AKI has been proposed by some authors (20).

The aim of the present study was to evaluate the two creatinine-based AKIN diagnostic criteria in a large cohort of critically ill patients under mechanical ventilation (MV). The primary end point was in-hospital mortality, and secondary end points were intensive care unit (ICU) and hospital length of stay and duration of MV. As a secondary aim, we assessed the relationship of a negative variation in SCr with hospital mortality.

Patients and Methods

Study Population

The VENTILA Group database was used for this study (22). This is a prospective, observational cohort including 4968 consecutive adult patients who received MV (invasive or noninvasive) for at least 12 hours in 349 ICUs from 23 countries, from March 1, 2004, to March 31, 2004. The Institutional Review Board of each participating institution approved the study protocol. Only patients who were ventilated for 48 hours or more and had at least two determinations of SCr within the first 48 hours of MV were included in the study. Patients with missing SCr values or unknown status at hospital discharge were excluded. The database did not register information on preadmission renal function, urine output, or need of renal replacement therapy. Demographic data (age, simplified acute physiology score [SAPS II], gender, weight, and height) and indication for MV were collected for each patient. Information on ventilator settings, arterial blood gases, SCr, serum bilirubin, platelet count, complications, and organ dysfunction were recorded daily until death, ICU discharge, or day 28, whichever came first. Laboratory tests, including SCr, were performed in each institution. A complete description of the cohort can be found elsewhere (22).

Data Analysis

AKI was diagnosed according to the AKIN criteria by an absolute increase in SCr of ≥0.3 mg/dl (>26.4 μmol/L) and/or a percentage increase of ≥50% (1.5-fold) within the first 48 hours of MV (10). The first SCr determination after starting MV was considered as baseline (SCr_0), over which the AKIN criteria were applied. Day 0 was the day of initiation of MV, with day 1 starting at 8:00 a.m. the next calendar day. The difference of SCr was calculated as the maximum variation of any value of SCr on day 0, day 1, or day 2. The relationship between AKI and several outcomes, including in-hospital mortality, ICU, and hospital length of stay and duration of mechanical ventilation was studied.

For the second aim of the study patients were classified into three groups according to the variation of SCr (ΔSCr) between day 0 and day 1 of MV as follows: group 1 (ΔSCr ≤ −0.3 mg/dl); group 2 (ΔSCr from −0.30 to +0.29 mg/dl); and group 3 (ΔSCr ≥ +0.3 mg/dl). One hundred seventy-five patients with an SCr of 4 mg/dl at day 0 were excluded for the analysis. We selected this time frame because the peak change in SCr occurred in the first 24 hours of MV in the majority of cases and also to avoid confusion resulting from the inclusion of patients with both positive and negative changes in SCr during periods of time longer than 24 hours. Clinical characteristics and mortality rate were analyzed between groups.

Statistical Analyses

Continuous variables are expressed as mean and SD, or median and interquartile range (IQR), and compared using the *t* test and ANOVA or the Mann–Whitney test where appropriate. Categorical variables are expressed as proportions and 95% confidence intervals and were compared by the χ^2 test. Statistical significance was accepted as a two-sided $P < 0.05$. In-hospital mortality was adjusted for prognostic factors by multivariate analysis using a conditional logistic regression model and a forward stepwise selection method correcting for collinearity. Variables that reached a $P < 0.10$ in the univariate model were included in the multivariate model. The statistical package SPSS version 15.0 (Chicago, IL) was used for the analysis.

Results

We studied 2783 patients with at least two determinations of SCr available within the first 48 hours of MV. Baseline characteristics and outcomes of the general population are summarized in Table 1. All-cause ICU mortality rate was 37% and in-hospital mortality was 43% (Table 2). Eighty-three percent of patients were started on MV within the first 24 hours of ICU admission (2222 out of 2669 patients with data on time of initiation of MV).

Eight-hundred three patients (28.8%) fulfilled the AKIN diagnostic criteria according to their change in SCr (absolute and/or relative) over the first 48 hours under MV. Patients with and without AKI showed differences in age, gender, severity of illness, SCr_0, indication for mechanical ventilation, hospital length of stay, and mortality rate (Table 1 and Table 2). Of the 803 patients, 431 (53.7%) had AKI according to only the absolute criterion (AKI_A), 362 (45.1%) according to both the absolute and the relative criteria (AKI_{R+A}), and the remaining 10 patients according to only the relative criterion. The latter group was not considered for the analysis because of the low number of cases. AKI_A and AKI_{R+A} groups showed no significant differences in clinical characteristics (demographics, reason for MV, and physiologic variables) and mortality (53.6% *versus* 57.7%, respectively), but they did differ in age (62.9 ± 16.1 *versus* 57.9 ± 17.4 years, respectively; $P < 0.000$) and SCr_0 (median [IQR]: 2 [1.3 to 3.4] *versus* 1.1 [0.8 to 1.6], respectively; $P < 0.001$).

We analyzed whether the prevalence of AKI defined by the absolute or by the relative and absolute criteria was related to SCr_0. The prevalence of AKI was highly dependent on SCr_0 and the diagnostic criteria adopted (Figure 1). As SCr_0 rises, the prevalence of AKI was higher if patients met only the absolute criterion. On the other hand, the prevalence of AKI remained stable over the entire range of SCr_0 if the relative and absolute criteria were met. Of note, no patient met the absolute

Table 1. Clinical characteristics of patients with and without AKI

	All Cases (2783)	AKI (803)	Non-AKI (1980)	*P*
Age, years, mean (SD)	59 (17)	61 (17)	58 (17)	0.01
Men, *n* (%)	1691 (61)	513 (64)	1178 (59)	0.03
SAPS II, points, median (IQR)	44 (33 to 56)	49 (37 to 61)	42 (32 to 53)	0.01
SCr_0, mg/dl, median (IQR)	1.1 (0.8 to 1.8)	1.5 (1.0 to 2.4)	1.0 (1.0 to 1.6)	0.01
Main reason for mechanical ventilation, *n* (%)				
chronic obstructive pulmonary disease	148 (5)	28 (3)	120 (6)	0.01
asthma	21 (1)	2 (0.2)	19 (1)	0.05
other chronic pulmonary disease	48 (2)	8 (1)	40 (2)	0.07
coma	492 (18)	98 (12)	394 (20)	0.01
neuromuscular disease	34 (1)	4 (0.5)	30 (1.5)	0.03
acute respiratory failure				
postoperative	405 (15)	146 (18)	259 (13)	0.01
pneumonia	363 (13)	117 (15)	246 (12)	0.13
sepsis	328 (12)	116 (14)	212 (11)	0.01
trauma	187 (7)	33 (4)	154 (8)	0.01
congestive heart failure	160 (6)	63 (8)	97 (5)	0.01
cardiac arrest	149 (5)	51 (6)	98 (5)	0.13
ARDS	106 (4)	32 (4)	74 (4)	0.74
aspiration	89 (3)	22 (3)	67 (3)	0.40
other ARF	253 (9)	83 (10)	170 (9)	0.14

Quantitative data are displayed as median, interquartile range, except for age (mean, SD). Qualitative data, as percentage across rows. Statistical significance was assessed between patients with and without AKI (*t* test for age, Mann–Whitney for SAPS II and SCr_0. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; IQR, interquartile range; SAPS, simplified acute physiology score; SCr_0, serum creatinine at day 0.

Table 2. Outcomes of patients with and without AKI

	All cases (2783)	AKI (803)	Non-AKI (1980)	*P*
Invasive mechanical ventilation,[a] *n* (%)	2669 (96)	781 (97)	1888 (95)	0.02
Days between hospital and ICU admission, mean (SD)	4.7 (15.0)	5.6 (17.5)	4.3 (13.9)	0.04
Days between ICU admission and mechanical ventilation, mean (SD)	0.5 (1.9)	0.6 (2.1)	0.4 (1.9)	0.10
Days on mechanical ventilation, median (IQR)	6 (4 to 10)	6 (4 to 10)	5 (4 to 9)	0.74
ICU length of stay, days, median (IQR)	10 (6 to 18)	12 (6 to 20)	11 (7 to 19)	0.31
Hospital length of stay, days, (IQR)	20 (11 to 35)	19 (10 to 33)	20 (11 to 35)	0.03
ICU mortality, *n* (%)	1023 (37)	397 (50)	626 (32)	0.01
In-hospital mortality, *n* (%)	1207 (43)	445 (55)	762 (38)	0.01

Summary data on outcomes, according to the objectives of the study. Time-dependent variables (days on mechanical ventilation, ICU, and hospital length of stay) were considered only in survivors. AKI, acute kidney injury; ICU, intensive care unit; IQR, interquartile range.
[a]There were a few patients receiving only noninvasive mechanical ventilation at study entry, explaining why the percentage of patients in this row is not 100%.

criterion when SCr_0 was lower than 0.60 mg/dl. Thus, meeting simultaneously the relative and absolute criteria improves the accuracy of the definition, regardless of the baseline SCr. AKI was identified as an independent predictor of all-cause in-hospital mortality (odds ratio 1.65, 95% confidence interval 1.23 to 2.14) (Table 3).

Finally, the three groups of ΔSCr showed differences in clinical characteristics and mortality. Considering group 2 as the reference group, patients with a negative ΔSCr (group 1) were older, had higher SCr_0, had worse values of SAPS II, pH, PA/FiO_2, and serum bilirubin, and had a higher mortality rate (Table 4 and Table 5).

Discussion

It has been shown that small increments in SCr are associated with a higher mortality rate, need for RRT, and end-stage renal disease (2,21,23,24). Thus, the Acute Kidney Injury Network recently proposed new definition criteria based on small changes in SCr and/or reduction in urine output. One of the advantages of the AKIN definition is that it requires only two SCr values within 48 hours, eliminating the need for a baseline SCr.

Risk factors for AKI included age, disease severity, and several comorbidities (Table 1). Unlike other studies (2), we did not find that the female gender was associated with

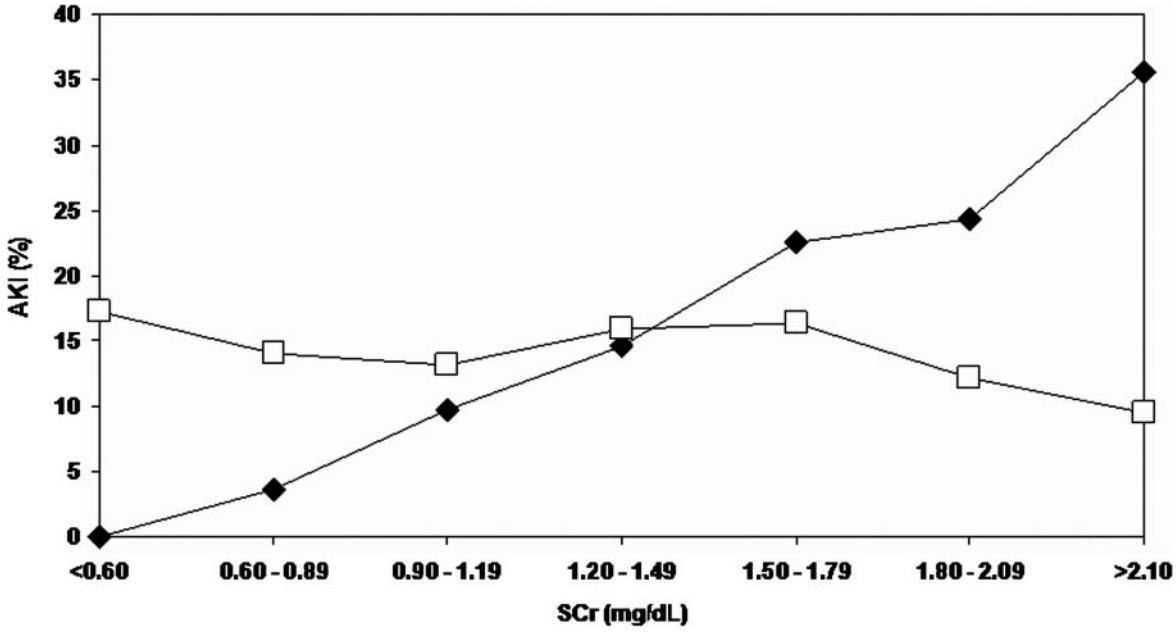

Figure 1. | Prevalence of AKI diagnosed by the absolute criterion (431 patients) or both the relative and the absolute criteria (362 patients). Solid diamonds: absolute criterion. Open squares: relative and absolute criterion. Very few patients met only the relative criterion and thus are not included in the analysis. AKI, acute kidney injury, SCr, serum creatinine concentration.

Table 3. Risk factors for in-hospital mortality according to multivariate analysis

	Odds ratio	95% confidence interval	*P*
Age	0.98[a]	0.97 to 0.99	<0.01
SAPS II	0.98[a]	0.97 to 0.99	<0.01
Serum creatinine at day 0	0.93[a]	0.86 to 1.01	0.07
Serum bilirubin at day 0	0.94[a]	0.90 to 0.98	0.02
Respiratory rate at day 0	0.97[a]	0.95 to 0.99	0.06
PEEP at day 0	1.05[a]	1.01 to 1.09	0.08
Hospital length of stay	1.03[a]	1.02 to 1.03	<0.01
Days on mechanical ventilation	0.96[a]	0.95 to 0.98	<0.01
Hemorrhagic stroke	1.94	1.19 to 3.14	0.07
Cardiac arrest	2.53	1.42 to 4.53	0.02
ARDS	2.34	1.23 to 4.28	0.06
Hospital pneumonia	2.58	1.41 to 4.78	0.02
Trauma	0.51	0.29 to 0.91	0.02
Sepsis	1.44	1.08 to 1.93	0.01
AKI	1.65	1.23 to 2.14	<0.01

Only variables that remained in the equation after forward stepwise selection method are displayed. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; PEEP, positive end expiratory pressure; SAPS, simplified acute physiology score.
[a]Per unit of variation: age (years); SAPS II (point); serum creatinine and serum bilirubin (mg/dl); duration of mechanical ventilation and hospital length of stay (days).

mortality, but rather male patients were more likely to develop AKI (Table 1). We cannot explain this discrepancy on the basis of our results.

Our findings support the validity of the new AKIN creatinine-based criteria, either by the absolute or by the relative rise of SCr, because patients with AKI had worse clinical outcomes such as adjusted mortality rate, hospital length of stay, and days on MV (Table 2 and Table 3). In addition to AKI, reasons for MV (hospital pneumonia, acute respiratory distress syndrome, cardiac arrest, hemorrhagic stroke, and sepsis) were strongly associated with outcome as is usually reported (22).

We found different prevalence of AKI according to the definition criteria (Figure 1). Eight hundred three of 2783 patients (28.8%) had AKI based on any AKIN criterion (AKI_A or AKI_{R+A} or AKI_R), but the prevalence dropped to 372 (13.4%) if both criteria had to be met (AKI_{R+A}). Moreover, when AKI_A and AKI_{R+A} were analyzed as separate populations, it was found that having to meet both criteria (absolute and relative) was more accurate in patients with

Table 4. Characteristics of the three groups of ΔSCr; quantitative variables at day 0

	Group 1	Group 2	Group 3	*P*
Age, years, mean (SD)	60.9 (16.0)	57.8 (17.7)	59.7 (16.9)	0.01
Weight, kg, mean (SD)	76.4 (21.0)	76.4 (20.8)	78.2 (21.6)	<0.01
SAPS II, median (IQR)	47 (37 to 60)	42 (32 to 53)	49 (37 to 64)	<0.01
pH, mean (SD)	7.34 (0.11)	7.37 (0.10)	7.32 (0.13)	0.01
Pa/FiO_2, mean (SD)	217 (116)	239 (121)	201 (114)	0.01
Serum bilirubin, mg/dl, mean (SD)	2.41 (4.7)	1.67 (2.58)	2.42 (4.33)	0.01
Serum creatinine, mg/dl, mean (SD)	1.89 (0.82)	1.07 (0.59)	1.58 (0.82)	0.01
Platelet count, 10^3/ml, mean (SD)	207 (115)	218 (124)	177 (115)	<0.01

Relevant quantitative parameters were analyzed between the three ΔSCr groups. Laboratory values are from day 0. Patients with SCr ≥ 4 mg/dl were excluded from this analysis. IQR, interquartile range; SAPS, simplified acute physiology score.

Table 5. Characteristics of the three groups according to the value of ΔSCr; qualitative variables

	Group 1 (*n* = 351)	Group 2 (*n* = 1553)	Group 3 (*n* = 704)	*P*
Men (*n*, %)	218 (62.1)	904 (57.3)	457 (64.9)	0.06
Sepsis (*n*, %)	43 (15.0)	140 (9.0)	103 (14.6)	0.01
Trauma (*n*, %)	19 (5.4)	131 (8.4)	31 (4.4)	0.01
Cardiac arrest (*n*, %)	29 (8.3)	64 (4.1)	44 (6.3)	0.01
DA>15 μg/kg per min and/or NE >0.1 μg/kg per min (*n*, %)	69 (19.7)	206 (13.3)	192 (27.3)	0.01
In-hospital mortality (*n*, %)	147 (41.9)	569 (36.6)	393 (55.8)	0.01

Variables are expressed as percentage of patients having the condition: men, sepsis, trauma, cardiac arrest, use of vasoactive drugs during first 24 hours in the ICU, in-hospital mortality. Data were compared by χ^2 between groups 1 and 2. Patients with SCr ≥ 4 mg/dl were excluded from this analysis. DA, dopamine; NE, norepinephrine.

low values of SCr_0, whereas meeting only the absolute criterion detected more patients if SCr_0 was higher. The level of SCr at the start of MV in each subset of patients was in accordance with this finding because SCr_0 was higher in AKI_A and lower in AKI_{R+A} patients. These findings bring up the question of whether the AKIN creatinine-based definition and classification system is accurate and independent of the use of a relative or an absolute increase in SCr, and of the baseline renal function.

In a recent publication, Waikar and Bonventre (25) hypothesized that "the percentage change of SCr will significantly delay the diagnosis of AKI in patients with chronic kidney disease because the level of baseline kidney function may influence the kinetics of creatinine rise after an acute injurious event to the kidney." In fact, on the basis of a simulation model that relies on the basic mass balance principle, the authors demonstrated that percentage changes in SCr are highly dependent on steady state and baseline renal function. Thus, they suggest that AKIN and RIFLE definitions based on a percentage increase of SCr do not perform adequately for the diagnosis of AKI in the presence of chronic kidney disease. An absolute rise of SCr seems to be more appropriate for an early identification of patients with AKI. In line with the proposal of Waikar and Bonventre (25), our findings suggest that the diagnosis criterion based on the percentage increase of SCr could underestimate and/or delay the identification of patients with AKI, particularly when the initial SCr is above normal values. On the other hand, in patients with low values of SCr, such as the elderly or pregnant women, the relative criterion diagnosis seems to be more accurate.

Another interesting finding of our study was that the subset of patients characterized by a reduction of SCr over the first 24 hours in the ICU showed a higher mortality rate than those showing no change in SCr (Table 4 and Table 5). These patients were similar to patients with AKI (group 3) in terms of age, gender, SAPS II, and percentage of patients with sepsis, trauma, cardiac arrest, hemodynamic failure, and some physiologic variables at the beginning of MV (pH, plateau pressure, and serum bilirubin). Interestingly, SCr_0 in group 1 was the highest, when compared with those of groups 2 and 3.

We have no satisfactory explanation for the finding of a high mortality rate in patients showing a decrease in SCr. It could be hypothesized that these patients were captured in the recovery phase of a previously existing AKI at the start of MV. This is actually likely according to the study design, as patients were included in the database not at the time of ICU admission but at the time of the initiation of MV. To minimize this effect, we excluded from this analysis (Table 4 and Table 5) patients with SCr ≥4 mg/dl. Also, it is reasonable to think that SCr could drop because of hemodilution secondary to fluid administration, which is likely, considering the severity of illness of these patients. Little attention has been paid to this point in the literature. Lassnigg *et al.* were the first to describe the association of a negative variation in SCr with mortality in cardiac surgery patients (21) and this finding was con-

firmed in a later study by the same group (26). This relationship was mentioned also by other investigators such as Ostermann *et al.* (20) who included the reduction in SCr value in the definition of AKI. Future prospective studies should confirm this finding.

Our study has some limitations. First, as the original database was designed to look at mechanically ventilated patients, we had to set the initial time point of the current study in the moment of initiation of MV. This could have led in our study to an underestimation of the true incidence of AKI. We think, however, that the effect of choosing the time of initiation of MV, rather than the time of ICU admission, as the initial reference point in time is probably not very important for estimating the incidence of AKI, as most patients (83%) started to receive MV within 24 hours of ICU admission. Second, some important information, such as urine output, baseline SCr, the characteristics of fluid resuscitation, or need of RRT was lacking in the database. Third, the database contains information from self-appointed ICUs that may not be representative of the practice in the different geographical regions. Fourth, in this multicenter multinational study, local laboratories made different determinations, and information on the specific laboratory method used was not captured in the database. Therefore, the results reported could be biased because of intragroup or intergroup variability. The large sample size studied could minimize this bias. Fifth, missing data on previous renal function, RRT, and other variables (*e.g.,* fluid challenge, hemodilution, and drug interaction) hinder the proposal of a plausible explanation for the relationship between a negative ΔSCr and outcome.

Among the strengths of the study, we can mention the large sample size, with patients from many different geographical regions, making it reasonable to assume that indeed they may be representative of critically ill patients from different areas of the world. Second, the design of the study allowed us to test separately both components of the creatinine-based definition, confirming the accuracy of the definition provided that each component was applied in relation to the initial SCr. Third, we provide evidence to support the emerging concept of the relationship between a negative variation of SCr and mortality in mechanically ventilated patients.

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Disclosures

None.

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