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Original Article

Early and minimal changes in serum creatinine can predict prognosis in elderly patients receiving invasive mechanical ventilation: A retrospective observational study

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ABSTRACT

Background: Emerging evidence suggests that minimal acute kidney injury (stage 1 AKI) is associated with increased hospital mortality rates. However, for those who do not meet the AKI diagnostic criteria, whether a small increase in serum creatinine (SCr) levels is associated with an increased mortality rate in elderly patients is not known. Therefore, we aimed to investigate small elevations in SCr of <26.5 μmol/L within 48 h after invasive mechanical ventilation (MV) on the short-term mortality of critically ill patients in the geriatric population.

Methods: We conducted a retrospective, observational, multicenter cohort study enrolling consecutive elderly patients (≥75 years) who received invasive MV from January 2008 to December 2020. Recursive partitioning was used to calculate the ratio of SCr rise from baseline within 48 h after MV and divided into six groups, (1) <10%, (2) 10%–<20%, (3) 20%–<30%, (4) 30%–<40%, (5) 40%–<50%, and (6) ≥50%, where the reference interval was defined as the ratio <10% based on an analysis, which confirmed that the lowest mortality risk was found in this range. Clinical data and laboratory data were noted. Their general conditions and clinical characteristics were compared between the six groups. Prognostic survival factors were identified using Cox regression analysis. Kaplan–Meier survival analysis was employed for the accumulative survival rate.

Results: A total of 1292 patients (1171 men) with a median age of 89 (interquartile range: 85–92) with MV were suitable for further analysis. In all, 376 patients had any stage of early AKI, and 916 patients had no AKI. Among 916 non-AKI patients, 349 patients were in the ratio <10%, 291 in the 10%–<20% group, 169 in the 20%–<30% group, 68 in the 30%–<40% group, 25 in the 40%–<50% group, and 14 in the ≥50% group. The 28-day mortality rates in the six groups from the lowest (<10%) to the highest (≥50%) were 8.0%, 16.8%, 28.4%, 54.4%, 80.0%, and 85.7%, respectively. In the multivariable-adjusted analysis, patients with a ratio of 10%–<20% (hazard ratio [HR]=2.244; 95% confidence interval [CI]: 1.410 to 3.572; P=0.001), 20%–<30% (HR=3.822; 95% CI: 2.433 to 6.194; P <0.001), 30%–<40% (HR=10.472; 95% CI: 6.379 to 17.190; P <0.001), 40%–<50% (HR=13.887; 95% CI: 7.624 to 25.292; P <0.001), and ≥50% (HR=13.618; 95% CI: 6.832 to 27.144; P <0.001) had relatively higher 28-day mortality rates. The 90-day mortality rates in the six strata were 30.1%, 35.1%, 45.0%, 60.3%, 80.0%, and 85.7%, respectively. Significant interactions were also observed between the ratio and 90-day mortality: patients with a ratio of 10%–<20% (HR=1.322; 95% CI: 1.006 to 1.738; P=0.045), 20%–<30% (HR=1.823; 95% CI: 1.356 to 2.452; P <0.001), 30%–<40% (HR=3.751; 95% CI: 2.601 to 5.410; P <0.001), 40%–<50% (HR=5.735; 95% CI: 3.447 to 9.541; P <0.001), and ≥50% (HR=6.305; 95% CI: 3.430 to 11.588; P <0.001) had relatively higher 90-day mortality rates.

Conclusions: Our study suggests that a ≥ 10% SCr rise from baseline within 48 h after MV was independently associated with short-term all-cause mortality in mechanically ventilated elderly patients.

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Introduction

Mechanical ventilation (MV) is a life-support therapy that often required in the care of critically ill patients.[1] Its use in clinical practice is not exempt of risk and may have a greater risk of developing subsequent complications, such as acute kidney injury (AKI), which develops in 17%–30% of patients over the first 48 h under invasive MV and is associated with an increased need for renal replacement therapy (RRT), a longer hospital length of stay, healthcare-associated costs, and an excessive mortality of up to 55%–61%.[2–4] Therefore, it is of great importance to protect the kidney in the diagnosis and treatment of patients with MV.[2,4,5]

AKI is characterized by a sudden impairment in renal function. Emerging evidence suggests that even minimal acute kidney injury (stage 1 AKI) is associated with increased long-term mortality rates in critically ill patients.[6–8] For example, Nin et al.,[7] in an international, prospective, observational cohort study with a median age of 59 years, showed an increase in the risk of death of 1.37 for patients with an early and small acute change in serum creatinine (SCr) greater than 26.5 μmol/L 48 h after MV. Similarly, Sparrow et al.,[8] in a retrospective cohort of patients with a mean age of 65 years, demonstrated that an absolute increase in SCr of 26.5 μmol/L within 48 h was associated with a 3.6-fold increase in the risk of in-hospital mortality.

However, for those patients who did not develop AKI, it remains unknown whether more subtle changes in SCr post-invasive MV are associated with an increased mortality rate in elderly patients. Therefore, the aim of this study was to investigate small elevations in SCr of <26.5 μmol/L within 48 h after invasive MV on short-term mortality in such patients.

Methods

Study population

This is a retrospective multicenter study that included all consecutive critically ill elderly patients (≥75 years) with life-threatening impairment of the cardiovascular, respiratory, or neurological system requiring in-hospital intubation between January 2008 and December 2020 in any of four medical centers of the Chinese PLA General Hospital. The study design was approved by the Clinical Ethics Committee of the Chinese PLA General Hospital (Number: S2017–054–01). The requirement to obtain written informed consent from each patient was waived because this was an observational retrospective study. The patients' information was anonymous and de-identified. This study was conducted in accordance with the Declaration of Helsinki. The exclusion criteria were patients with a history of chronic kidney disease (CKD) stage 4–5,[9] those who had undergone RRT before MV, nephrectomy, kidney transplantation, those who had less than two SCr examinations, those with missing or incomplete medical history, those with a hospital stay of <48 h and postoperative patients undergoing intubation in the operating room for the purposes of general anesthesia.

Early AKI was diagnosed exclusively based on SCr levels, that is an SCr increase of more than or equal to 26.5 μmol/L within 48 h after MV.[10] For those who did not fulfill the early AKI diagnostic criteria, we calculated the ratio of SCr rise from baseline within 48 h after MV ($\Delta SCr_{48\ h}/SCr_{baseline}$). ΔSCr was the difference between the peak SCr value and the baseline value for each patient on days 0, 1, or 2.[3,11] Day 0 was the day of initiation of MV, with day 1 beginning at 8:00 a.m. the next calendar day.[12] Peak SCr was the maximum available value within 48 h after MV. The baseline SCr level was defined as the most recent measurement in the previous 3 months.[13] When there were no prior SCr records, we used the lowest SCr level during hospitalization as the baseline SCr level.[14] The ratio was divided into six groups, (1) <10%, (2) 10%–<20%, (3) 20%–<30%, (4) 30%–<40%, (5) 40%–<50%, and (6) ≥50%, where the reference interval was defined as the ratio <10% based on an analysis, which confirmed that the lowest mortality risk was found in this range. Sepsis was defined according to the Sepsis-3 criteria.[15]

Data collection

Clinical data were noted, including the demographic profile (age, sex, and body mass index [BMI]) and comorbidities (history of coronary disease, hypertension, cerebrovascular diseases, chronic obstructive pulmonary disease [COPD], CKD, and diabetes mellitus), the reason for MV, the need for RRT, and mean arterial pressure (MAP). Baseline SCr, SCr on day 0, peak SCr within 48 h under MV, and other laboratory data evaluated on day 0 included blood urea nitrogen (BUN), uric acid, serum albumin, C-reactive protein, neutrophil-lymphocyte ratio, and hemoglobin. The partial pressure of oxygen in arterial blood (PaO_2), arterial carbon dioxide tension ($PaCO_2$), fraction of inspired oxygen (FIO_2), and PaO_2/FIO_2 were also analyzed.

Statistical analysis

Continuous variables are presented as the mean±standard deviation or median (interquartile range), depending on the variable distribution. Discrete variables are presented as counts or percentages. Group comparisons were conducted using Analysis of variance (ANOVA) or the Kruskal–Wallis H test for continuous variables and Pearson's chi-squared or Fisher's exact test for categorical variables. Prognostic survival factors were identified using the Cox proportional hazards regression model. Survival probability was estimated using the Kaplan–Meier method for the eight potassium intervals, and curves were compared among groups using the log-rank test. A P <0.05 was considered significant. Statistical analyses were performed using SPSS version 21.0 for Windows software (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of patients included in the study

Between July 2008 and December 2020, 3271 patients were retrospectively enrolled in the study cohort. A total of 1979 patients were excluded (Figure 1); 1292 patients (1171, men) with a median age of 89 (85–92) years with MV were suitable for further analysis. In all, 376 patients had any stage of early AKI, and 916 patients had no AKI. Among 916 non-AKI patients, 349 patients were in the ratio <10%, 291 were in the 10%–<20% group, 169 were in the 20%–<30% group, 68 were in the

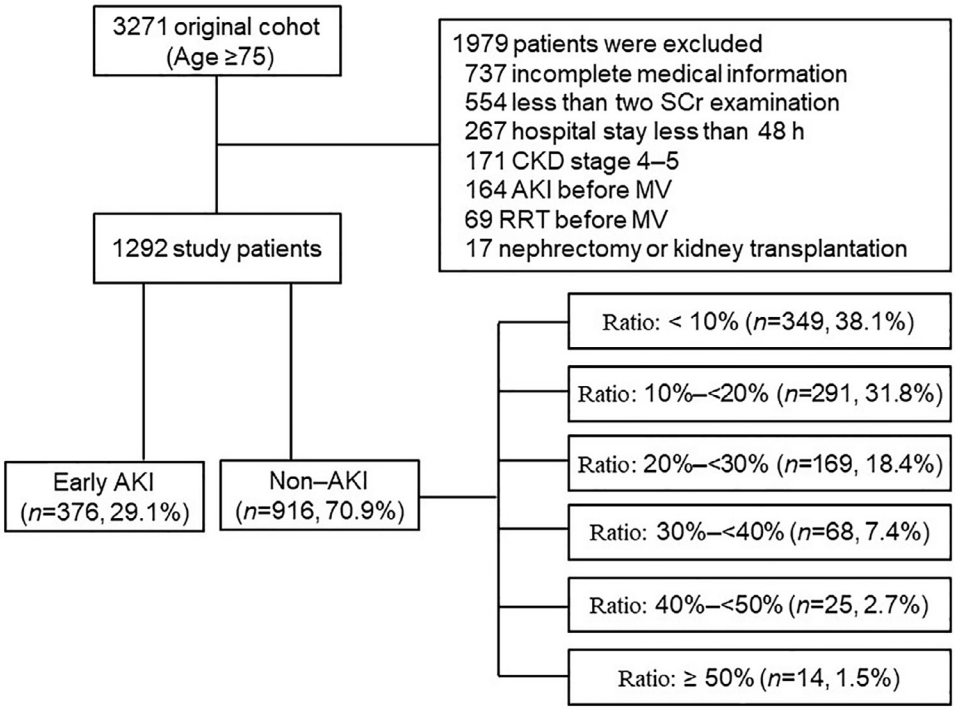

Figure 1. Flowchart of the inclusion and exclusion process of patients in this study. AKI: Acute kidney injury; CKD: Chronic kidney disease; MV: Mechanical ventilation; Ratio: $\Delta SCr_{48\ h}/SCr_{baseline.}$; RRT: Renal replacement therapy; SCr: Serum creatinine.

30%–<40% group, 25 were in the 40%–<50% group, and 14 were in the ≥50% group.

General conditions and clinical characteristics

The baseline characteristics and outcomes of the study population are summarized in Table 1. MAP (P=0.014), BUN (P=0.014), uric acid (P=0.002), $PaCO_2$ (P=0.023), PaO_2/FIO_2 (P=0.013), SCr on day 0 (P <0.001), and peak SCr (P <0.001) differed significantly among the six groups. Significant interactions were also observed between the ratio and both 28-day mortality (P <0.001) and 90-day mortality (P <0.001). The 28-day mortality rates in the six groups from the lowest (<10%) to the highest (≥50%) were 8.0%, 16.8%, 28.4%, 54.4%, 80.0%, and 85.7%, respectively. The 90-day mortality rates in the eight strata were 30.1%, 35.1%, 45.0%, 60.3%, 80.0%, and 85.7%, respectively. This suggests that as the ratio increases, the mortality rate also increases.

Survival analysis

Of the patients, 28-day mortality was 21.2% (194 of 916 patients). During the 90-day follow-up, 356 (38.9%) died. As shown in Table 2, Figures 2 and 3, among all the survivors from non-AKI, progression to a higher $\Delta SCr_{48\ h}/SCr_{baseline}$ ratio was associated with a decrease in survival. Survival curves for 28-day and 90-day all-cause mortality across categories of the ratio are presented in Figures 4 and 5.

In the multivariable-adjusted analysis, patients with a ratio of 10%–20% (hazard ratio [HR]=2.244; 95% confidence interval [CI]: 1.410 to 3.572; P=0.001), 20%–<30% (HR=3.822; 95% CI: 2.433 to 6.194; P <0.001), 30%–<40% (HR=10.472; 95% CI: 6.379 to 17.190; P <0.001), 40%–<50% (HR=13.887; 95% CI: 7.624 to 25.292; P <0.001), and ≥50% (HR=13.618; 95% CI: 6.832 to 27.144; P <0.001) had relatively higher 28-day mortality rates (Table 3).

Significant interactions were also observed between the ratio and 90-day mortality: patients with 10%–<20% (HR=1.322; 95% CI: 1.006 to 1.738; P=0.045), 20%–<30% (HR=1.823; 95% CI: 1.356 to 2.452; P <0.001), 30%–<40% (HR=3.751; 95% CI: 2.601 to 5.410; P <0.001), 40%–<50% (HR=5.735; 95% CI: 3.447 to 9.541; P <0.001), and ≥50% (HR=6.305; 95% CI: 3.430 to 11.588; P <0.001) had relatively higher 90-day mortality rates (Table 3).

Discussion

In this retrospective, multicenter cohort study, we found that elderly patients with a <10% SCr rise from baseline within 48 h after invasive MV had the lowest mortality rate. Any deviation compared with this group was accompanied by a substantial increase in the hazard of death. A small increase in the ratio of 10%–20% was already associated with a more than 2-fold increase in 28-day mortality, whereas a larger increase of ≥50% (which is known or presumed to have occurred within the prior 7 days, defined as late AKI or 7-day diagnostic window AKI) was associated with a 13-fold increase in 28-day mortality. In contrast to 28-day mortality, early and small changes in SCr are associated with a higher 90-day mortality in mechanically ventilated patients.

The relationship between small elevations in SCr and mortality has been shown in different subsets of patients.[6–8] For example, a prospective observational study by Nin et al.[7] enrolled 2807 adult patients with a median age of 59 years treated in the ICU and showed that an early and small change in SCr >26.5 μmol/L 48 h after MV in patients with normal baseline

Table 1
Characteristics of patients with the ratio of SCr rise from baseline within 48 h after MV.

Characteristics	$\Delta SCr_{48\ h}/SCr_{baseline}$						*P*-value
	<10% (*n*=349, 38.1%)	10%–<20% (*n*=291, 31.8%)	20%–<30% (*n*=169, 18.4%)	30%–<40% (*n*=68, 7.4%)	40%–<50% (*n*=25, 2.7%)	≥50% (*n*=14, 1.5%)	
Age (years)	89 (86–92)	89 (86–93)	88 (85–91)	88 (84–92)	90 (88–92)	87 (84–90)	0.263
Male sex	316 (90.5)	264 (90.7)	155 (91.7)	61 (89.7)	20 (80.0)	14 (100.0)	0.341
BMI (kg/m^2)	22.8 ± 2.9	23.0 ± 3.0	22.8 ± 2.8	22.3 ± 3.1	22.4 ± 1.7	23.0 ± 3.0	0.599
Comorbidity							
Coronary disease	248 (71.1)	208 (71.5)	113 (66.9)	47 (69.1)	20 (80.0)	9 (64.3)	0.743
Hypertension	244 (69.9)	212 (72.9)	119 (70.4)	55 (80.9)	20 (80.0)	11 (78.6)	0.406
Cerebrovascular diseases	181 (51.9)	157 (54.0)	89 (52.7)	30 (44.1)	13 (52.0)	6 (42.9)	0.756
COPD	136 (39.0)	128 (44.0)	78 (46.2)	35 (51.5)	9 (36.0)	5 (35.7)	0.318
Diabetes	148 (42.4)	111 (38.1)	60 (35.5)	21 (30.9)	11 (44.0)	3 (21.4)	0.252
CKD	74 (21.2)	68 (23.4)	35 (20.7)	9 (13.2)	6 (24.0)	2 (14.3)	0.513
Reason for MV							
Sepsis	134 (38.4)	113 (38.8)	62 (36.7)	31 (45.6)	11 (44.0)	8 (57.1)	0.570
Pneumonia	84 (24.1)	74 (25.4)	40 (23.7)	12 (17.6)	4 (16.0)	2 (14.3)	0.604
AECOPD	36 (10.3)	27 (9.3)	15 (8.9)	7 (10.3)	4 (16.0)	0	0.522
Acute heart failure	22 (6.3)	18 (6.2)	14 (8.3)	4 (5.9)	2 (8.0)	1 (7.1)	0.963
Acute coronary syndrome	10 (2.9)	9 (3.1)	10 (5.9)	1 (1.5)	1 (4.0)	2 (14.3)	0.232
Cardiac arrest	6 (1.7)	9 (3.1)	4 (2.4)	0	2 (8.0)	0	0.196
Emergency or urgent procedure	28 (8.0)	17 (5.8)	8 (4.7)	10 (14.7)	0	1 (7.1)	0.049
Airway obstruction	21 (6.0)	15 (5.2)	8 (4.7)	1 (1.5)	1 (4.0)	0	0.455
Neuromuscular disease	8 (2.3)	9 (3.1)	8 (4.7)	2 (2.9)	0	0	0.477
Parameters on day 0							
MAP (mmHg)	82 ± 21	83 ± 21	78 ± 21	79 ± 23	86 ± 21	94 ± 18	0.014
BUN (mmol/L)	9.8 (6.7–13.7)	9.6 (6.8–14.5)	10.1 (7.1–15.5)	9.7 (6.7–13.5)	12.9 (8.4–18.6)	14.6 (12.4–17.8)	0.014
Uric acid (μmol/L)	256.6 (167.8–356.0)	262.9 (185.0–347.2)	254.9 (175.5–354.6)	231.5 (171.1–386.6)	331.3 (251.8–453.7)	362.0 (274.1–490.9)	0.002
CRP (mmol/L)	4.3 (2.4–8.4)	4.4 (2.2–9.1)	4.3 (2.7–8.3)	4.3 (2.6–8.0)	4.6 (2.6–12.7)	7.4 (3.9–12.8)	0.522
NLR	6.4 (3.4–12.8)	6.2 (3.7–12.0)	7.3 (4.7–12.0)	6.3 (3.8–15.9)	9.5 (4.2–23.2)	11.7 (4.5–17.6)	0.260
Albumin (g/L)	33.5 ± 3.9	33.6 ± 4.0	33.0 ± 3.6	33.5 ± 3.7	34.2 ± 4.5	32.0 ± 3.5	0.343
Hemoglobin (g/L)	107 ± 20	107 ± 19	106 ± 17	107 ± 19	102 ± 23	101 ± 20	0.507
PO_2 (mmHg)	64.3 (54.3–78.9)	65.0 (55.8–76.5)	65.2 (54.2–73.6)	64.3 (52.5–87.2)	66.8 (58.7–71.0)	56.1 (48.6–68.1)	0.424
$PaCO_2$ (mmHg)	51.4 (40.3–67.7)	52.5 (36.8–65.4)	52.3 (36.4–66.9)	47.2 (34.3–61.0)	38.1 (32.5–56.1)	42.8 (35.6–74.3)	0.023
PaO_2/FIO_2 (mmHg)	141.8 (110.5–200.0)	146.6 (110.2–188.3)	133.0 (96.3–181.3)	136.6 (88.9–180.8)	168.0 (77.4–191.0)	99.5 (71.5–117.0)	0.013
Kidney function							
Baseline SCr (μmol/L)	75.0 (56.0–97.0)	74.0 (54.0–100.0)	73.0 (55.5–96.0)	65.0 (52.0–85.0)	85.0 (56.0–90.5)	74.5 (62.5–87.8)	0.080
SCr on day 0 (μmol/L)	73.2 (55.5–97.0)	74.4 (55.2–103.0)	75.5 (58.3–102.4)	66.3 (53.5–101.4)	111.0 (65.6–123.1)	114.7 (94.1–124.3)	<0.001
Peak SCr (μmol/L)	78.4 (58.5–102.6)	83.6 (61.0–114.8)	91.0 (68.2–120.0)	85.3 (69.8–115.7)	122.4 (80.7–131.3)	130.0 (106.1–136.2)	<0.001
28-day mortality	28 (8.0)	49 (16.8)	48 (28.4)	37 (54.4)	20 (80.0)	12 (85.7)	<0.001
90-day mortality	105 (30.1)	102 (35.1)	76 (45.0)	41 (60.3)	20 (80.0)	12 (85.7)	<0.001

Values are expressed as *n* (%), mean ± SD, or median (interquartile range).
AECOPD: Chronic obstructive pulmonary disease with acute exacerbation; BMI: Body mass index; BUN: Blood urea nitrogen; CKD: Chronic kidney disease; CRP: C-reactive protein; FIO_2: Fraction of inspired oxygen; MAP: Mean arterial pressure; MV: Mechanical ventilation; NLR: Neutrophil–lymphocyte ratio; PaO_2: Partial pressure of oxygen; PCO_2: Partial pressure of carbon dioxide, SCr: Serum creatinine.

Table 2
Association of categories of the ratio with 28-day and 90-day mortality.

Characteristic	28-day outcomes			90-day outcomes		
	Non-survivors (*n*=194, 21.2%)	Survivors (*n*=722, 78.8%)	*P*-value	Non-survivors (*n*=356, 38.9%)	Survivors (*n*=560, 61.1%)	*P*-value
$\Delta SCr_{48h}/SCr_{baseline}$			<0.001			<0.001
<10%	28 (14.4)	321 (44.5)		105 (29.5)	244 (43.6)	
10%–<20%	49 (25.3)	242 (33.5)		102 (28.7)	189 (33.8)	
20%–<30%	48 (24.7)	121 (16.8)		76 (21.3)	93 (16.6)	
30%–<40%	37 (19.1)	31 (4.3)		41 (11.5)	27 (4.8)	
40%–<50%	20 (10.3)	5 (0.7)		20 (5.6)	5 (0.9)	
≥50%	12 (6.2)	2 (0.3)		12 (3.4)	2 (0.4)	

Values are expressed as *n* (%).
SCr: Serum creatinine.

SCr was associated with a higher mortality rate. Similarly, in a study by Sparrow et al.,[8] which was a retrospective observational study including 81,651 patients with a median age of 66 years, the authors also reported that patients with an absolute increase in SCr of 26.5 μmol/L within 48 h were associated with a 1.6-fold increase in the risk of hospital length of stay and a 3.6-fold increase in the risk of in-hospital mortality. It should be noted that such hospital patients develop renal dysfunction that fulfills the time-frame criteria for AK, even if they have minimal AKI.

Liotta et al.[16] investigated 25,665 patients with a mean age of 67 who underwent primary isolated coronary artery bypass grafting and found that even small increases in the postoperative SCr values of <26 μmol/L were related to a small but significant increase in mortality over 6 years of follow-up. Similarly, Bernardi et al.,[17] in an observational cohort study of 7651 pa-

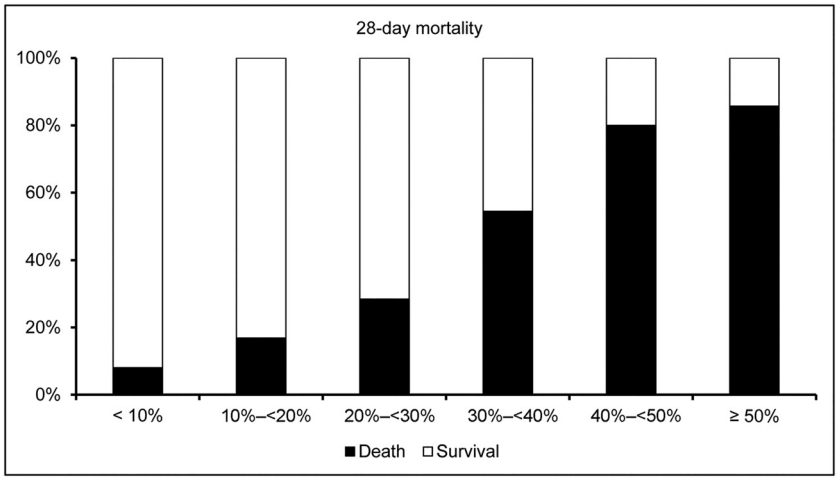

Figure 2. Bar chart showing that patients with ratio ≥10% had significantly poorer mean survival rates compared with control patients with ratio <10% at 28 days after enrollment.

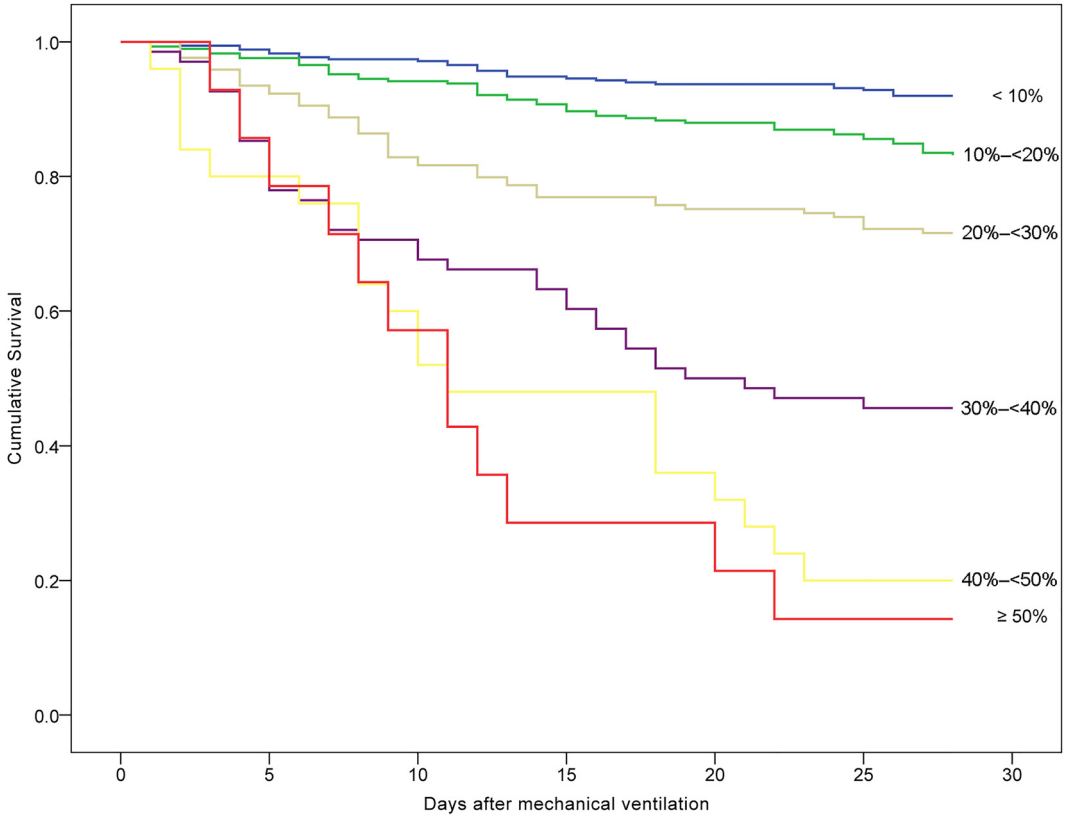

Figure 3. Kaplan–Meier survival curves for 28-day mortality according to $\Delta SCr_{48\ h}/SCr_{baseline}$ ratio during the time after MV (log-rank test: P <0.001). MV: Mechanical ventilation; SCr: Serum creatinine; $\Delta SCr_{48\ h}/SCr_{baseline}$: the ratio of SCr rise from baseline within 48 h after MV.

tients with a median age of 67 years, showed that even minimal increases in SCr levels of <26.5 μmol/L within 120 min after cardiac surgery were associated with 1.78-fold 30-day mortality rates. One meta-analysis by Coca et al.,[18] who determined the relationship between small changes in renal function and short-term mortality, found that a rise in SCr from 10% to 24% was associated with an approximately 1.8-fold increased risk of short-term death. Furthermore, patients with greater changes in SCr of 25%–49% had a relative risk of death of 3.0, and those with the largest change of ≥50% had the greatest relative risk of death of 6.9. Of note, the meta-analysis included studies performed in diverse populations, such as those who underwent cardiac surgery, acute congestive heart failure, or coronary arteriography, and those in the ICU and general ward. None were specifically conducted in an elderly population of critically ill patients under MV.

It is not clear how an increase in SCr of more than 1.1 times baseline decreases short-term survival. There are several other reasons for this result: (1) One possible explanation for this phenomenon is that the SCr level alone is a relatively late and unreliable marker of acute or sudden changes in renal dysfunction.[19] The most important limitation of SCr measurement in

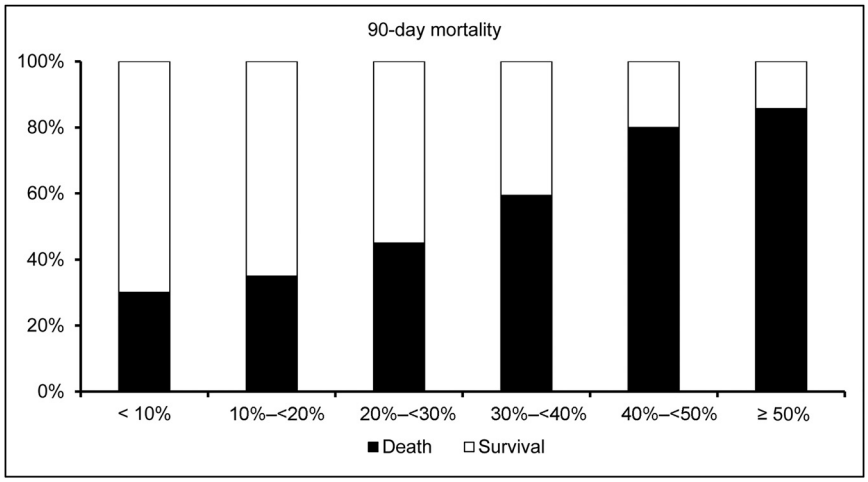

Figure 4. Bar chart showing that patients with ratio ≥10% had significantly poorer mean survival rates compared with control patients with ratio <10% at 90 days after enrollment.

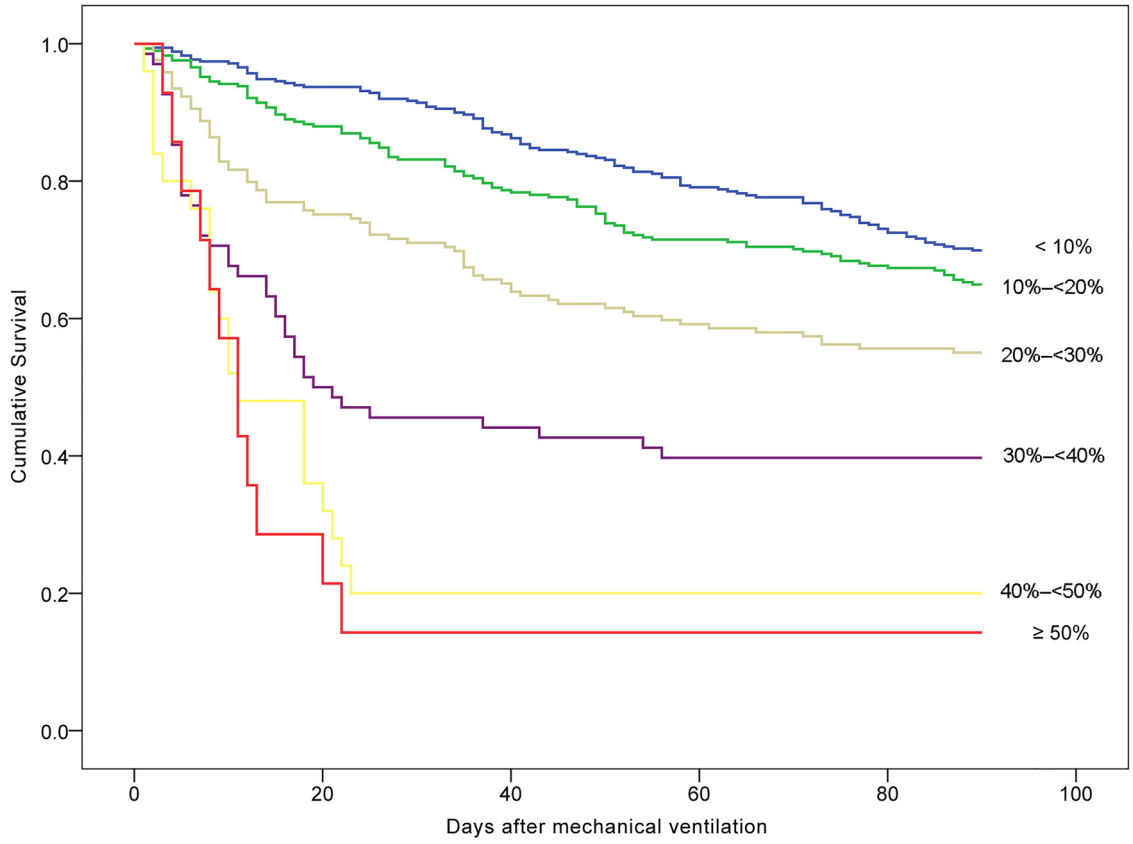

Figure 5. Kaplan–Meier survival curves for 90-day mortality according to $\Delta SCr_{48\ h}/SCr_{baseline}$ ratio during the time after MV (log-rank test: P <0.001). MV: Mechanical ventilation; SCr: Serum creatinine; $\Delta SCr_{48\ h}/SCr_{baseline}$: the ratio of SCr rise from baseline within 48 h after MV.

all patients is the delayed increase in this parameter after renal insult, particularly in elderly and critically ill patients. In addition, because of renal reserve, even in elderly individuals, up to 50% of renal function may be lost before SCr begins to rise, which will result in changes in SCr lagging behind changes in GFR by 48–72 h.[20,21] (2) Second, previous studies reported that the rate of missed AKI diagnosis was 53%–75%.[13,22,23] The data demonstrated that medical doctors in China still lack awareness of AKI in general, and the definition of AKI is neither uniformly known nor accepted in the non-nephrologic community.[24] Therefore, clinicians may pay little attention to small changes in SCr when treating patients with emergency endotracheal intubation. (3) Injurious MV strategies may affect the kidney by causing hemodynamic abnormalities and can cause hypotension and fluid reactive shock, affecting renal perfusion by decreasing GFR by reducing cardiac output and stimulating hormonal and sympathetic pathways.[14] MV through the manipulation of permissive hypercapnia or permissive hypoxemia can lead to renal hypoperfusion, decreased GFR, and functional renal insufficiency.[10]

Previous studies have shown persistent pulmonary, neuromuscular, cardiovascular, renal, cognitive, and immune dys-

Table 3
Multivariable Cox regression analyses for 28-day and 90-day mortality.

Risk factor	28-day mortality			90-day mortality		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Albumin (g/L)	0.937	0.899 to 0.977	0.002	0.947	0.918 to 0.975	<0.001
Hemoglobin (g/L)	0.986	0.978 to 0.993	<0.001	0.986	0.980 to 0.992	<0.001
PaO_2/FIO_2 (mmHg)	0.992	0.990 to 0.995	<0.001	0.995	0.993 to 0.997	<0.001
Uric acid (μmol/L)	1.002	1.001 to 1.003	<0.001	1.002	1.001 to 1.002	<0.001
NLR	–	–	–	1.011	1.000 to 1.021	0.042
$\Delta SCr_{48h}/SCr_{baseline}$			<0.001			<0.001
<10%	Reference	Reference		Reference	Reference	
10%–<20%	2.244	1.410 to 3.572	0.001	1.322	1.006 to 1.738	0.045
20%–<30%	3.822	2.433 to 6.194	<0.001	1.823	1.356 to 2.452	<0.001
30%–<40%	10.472	6.379 to 17.190	<0.001	3.751	2.601 to 5.410	<0.001
40%–<50%	13.887	7.624 to 25.292	<0.001	5.735	3.447 to 9.541	<0.001
≥50%	13.618	6.832 to 27.144	<0.001	6.305	3.430 to 11.588	<0.001

CI: Confidence interval; FIO_2: Fraction of inspired oxygen; HR: Hazard ratio; NLR: Neutrophil–lymphocyte ratio; PaO_2: Partial pressure of oxygen; SCr: Serum creatinine; $\Delta SCr_{48\ h}/SCr_{baseline}$: the ratio of SCr rise from baseline within 48 h after MV.

function after invasive MV.[4] It may be that the persistent proinflammatory milieu experienced by patients with an episode of sepsis is amplified by a decline in the ability of the kidneys to clear these toxic molecules. Alternatively, inflammatory injury to the kidneys may persist and feed a persistent systemic inflammatory phenotype. Our study strongly highlights the prognostic importance of small changes in SCr and thus may embolden efforts to identify even small elevations in SCr in acute medical conditions. Although a number of newer interventions are currently being tested, our findings certainly suggest that close follow-up after hospital discharge could be recommended in those with non-AKI, given the prolonged impact on survival in those with invasive and small elevations in SCr.

This study had the following limitations. First, the database was not designed primarily for the objective of the present study. Second, the analysis was performed retrospectively. Third, SCr as a marker of severity of the illness should be interpreted cautiously because SCr could be linked to changes in intravascular volume. Information concerning markers of volume status, such as the use of nephrotoxic drugs, was not available in our database. Fourth, the multicenter design of the study could bias the results because of laboratory variation. Fifth, we were not able to discern the specific causes of death.

Conclusions

Even minimal, acute changes in SCr are associated with increased short-term mortality. The change in SCr between baseline and peak within 48 h after MV ($\Delta SCr_{48\ h}/SCr_{baseline}$) may be a simple, widely available, and inexpensive marker for very early risk assessment after MV. Clinicians should pay attention to such early increases in SCr at least 1.1 times baseline to avoid the evolution of complications and further renal damage.

Author Contributions

Qinglin Li: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Guanggang Li:** Investigation, Methodology. **Dawei Li:** Data curation, Investigation. **Yan Chen:** Funding acquisition, Project administration. **Feihu Zhou:** Funding acquisition, Project administration, Writing – review & editing.

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Ethics Statement

This study was approved by the Ethics Committee of the Chinese PLA General Hospital (Number: S2017–054–01). The requirement for written informed consent was waived by the ethics committee of the designated hospital because this was an observational retrospective study.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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