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RESEARCH

Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study

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2013级硕士：张江茜

导师：康　焰

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Abstract

Introduction: Early and aggressive volume resuscitation is fundamental in the treatment of hemodynamic instability in critically ill patients and improves patient survival. However, one important consequence of fluid administration is the risk of developing fluid overload (FO), which is associated with increased mortality in patients with acute kidney injury (AKI). We evaluated the impact of fluid balance on mortality in intensive care unit (ICU) patients with AKI.

Methods: The data were extracted from the Beijing Acute Kidney Injury Trial. This trial was a prospective, observational, multicenter study conducted in 30 ICUs among 28 tertiary hospitals in Beijing, China, from 1 March to 31 August 2012. In total, 3107 patients were admitted consecutively, and 2526 patients were included in this study. The data from the first 3 sequential days were analyzed. The AKI severity was classified according to the Kidney Disease: Improving Global Outcomes guidelines. The daily fluid balance was recorded, and the cumulative fluid balance was registered at 24, 48, and 72 h. A multivariate analysis was performed with Cox regression to determine the impact of fluid balance on mortality in patients with AKI.

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Abstract

Results: Among the 2526 patients included, 1172 developed AKI during the first 3 days. The mortality was 25.7 % in the AKI group and 10.1 % in the non-AKI group ($P < 0.001$). The daily fluid balance was higher, and the cumulative fluid balance was significantly greater, in the AKI group than in the non-AKI group. FO was an independent risk factor for the incidence of AKI (odds ratio 4.508, 95 % confidence interval 2.900 to 7.008, $P < 0.001$) and increased the severity of AKI. Non-surviving patients with AKI had higher cumulative fluid balance during the first 3 days (2.77 [0.86–5.01] L versus 0.93 [−0.80 to 2.93] L, $P < 0.001$) than survivors did. Multivariate analysis revealed that the cumulative fluid balance during the first 3 days was an independent risk factor for 28-day mortality.

Conclusions: In this multicenter ICU study, the fluid balance was greater in patients with AKI than in patients without AKI. FO was an independent risk factor for the incidence of AKI and increased the severity of AKI. A higher cumulative fluid balance was an important factor associated with 28-day mortality following AKI.

Introduction

Early fluid resuscitation → expand intravascular volume
maintain organ perfusion

Fluid administration → increases the risk of **fluid overload (FO).**

↓

an expansion of interstitial space
increased venous pressure

↓

tissue edema
renal blood flow ↓ GFR ↓
ACS, AKI
organ dysfunction
adverse outcomes

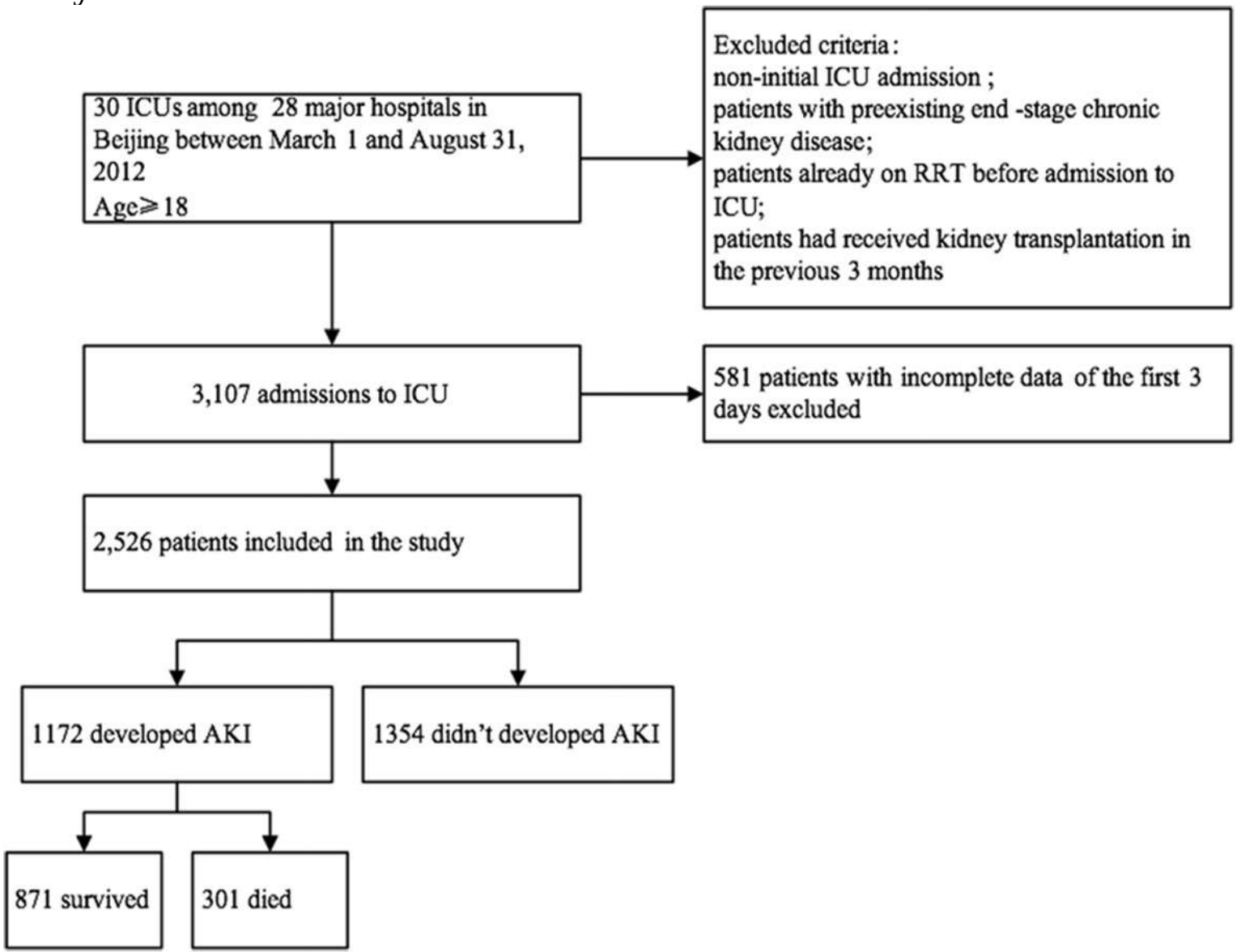
Introduction

- Patients with FO: adjusted odds ratio (OR) for mortality was 2.07
- Survivors: less FO
- A negative mean daily fluid balance decreased risk of death and with more ICU-free and hospital-free days

To date, there has been no multicenter study conducted on patients with AKI of Chinese descent.
Thus…

Material and methods

Study flowchart



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Material and methods

Study design: prospective, multicenter, observational study

Data collection: demographics, anthropometrics, admission diagnosis, comorbidities, daily vital signs, and laboratory values, APACHE II, SAPS II, SOFA, RRT, mortality, hourly urine output, fluid balance(the difference between fluid intake and fluid output), use of diuretics.
Fluid output included all body fluids, including urine, excrement, and, if applicable, dialysis ultrafiltrate.
The patients were followed until death, hospital discharge, or for 28 days.

Material and methods

Definitions

AKI cohort: patients who developed AKI within the first 72 h

AKI severity: KDIGO

AKI stage: the worst stage during the first 3 days

Baseline creatinine: the lowest known SCr value during the previous 3 months

For patients without these values or without renal failure,baseline SCr was estimated by using the Modification of Diet in Renal Disease equation, assuming a GFR of 75 ml/min/1.73 m2.

For patients with chronic renal failure but not receiving dialysis, the initial SCr value upon admission was used as the baseline value

Oliguria: urine output <500 ml/day

Daily fluid balance: daily AKI numbers

Cumulative fluid balance at 24, 48, and 72 h: all patients with AKI in the first 3 days

Adjusted for body weight: percentage of fluid accumulation

sum of daily (fluid intake [liters] − total output [liters])/body weight (kilograms)

FO: fluid accumulation greater than 10 % of the baseline weight

Material and methods

Statistical analysis

Mann–Whitney U test
Mantel–Haenszel $\chi 2$ test
Logistic regression model
Multivariate Cox regression analysis
Kaplan–Meier product limit survival plot
P value less than 0.05

Results

Study population

Table 1 Patient characteristics of all patients and compared between patients with and patients without acute kidney injury

Characteristics	All (n = 2526)	AKI (n = 1172)	Non-AKI (n = 1354)	*P* value
Age (yr)	64 (52–77)	67 (54–78)	63 (50–75)	<0.001
Male sex	1578 (62.5)	742 (63.3)	836 (61.7)	0.434
APACHE II score	14 (10–20)	17 (12–23)	13 (9–17)	<0.001
SAPS II score	34 (26–46)	40 (31–52)	31 (24–39)	<0.001
SOFA score	6 (4–9)	7 (5–10)	5 (3–7)	<0.001
Vasoactive therapy	1009 (40.0)	576 (49.1)	433 (32.0)	<0.001
Mechanical ventilation	1702 (67.4)	818 (69.8)	884 (65.3)	0.017
Baseline creatinine (μmol/L)	81.9 (69.0–96.0)	84.9 (73.0–97.0)	79.8 (66.8–95.0)	<0.001
Sepsis	808 (32.0)	512 (43.7)	296 (21.9)	<0.001
Fluid balance within 24 h (L)	0.57 (−0.19 to 1.43)	0.64 (−0.20 to 1.70)	0.53 (−0.18 to 1.30)	<0.001
Fluid balance within 48 h (L)	0.88 (−0.37 to 2.30)	1.06 (−0.38 to 2.82)	0.73 (−0.37 to 1.91)	<0.001
Fluid balance within 72 h (L)	1.12 (−0.48 to 2.86)	1.40 (−0.49 to 3.54)	0.91 (−0.48 to 2.44)	0.001
Use of diuretics (%)	1500 (59.4)	872 (74.4)	628 (46.4)	<0.001
28-day mortality	438 (17.3)	301 (25.7)	137 (10.1)	<0.001
Length of ICU stay (days)	6 (4–11)	7 (5–14)	5 (4–9)	<0.001

Data are expressed as median (interquartile range) or number (percent)

Results

Characteristics of patients with AKI

Table 2 Characteristics of patients with acute kidney injury, by outcome

Characteristics	AKI (n = 1172)	Survivors (n = 871)	Non-survivors (n = 301)	*P* value
Male sex	742 (63.3)	548 (62.9)	194 (64.5)	0.677
Age (yr)	67 (54–78)	64 (52–77)	74 (60–82)	<0.001
ICU admission				
APACHE II score	17 (12–23)	15 (11–21)	23 (17–29)	<0.001
SAPS II score	40 (31–52)	37 (28–47)	52 (41–64)	<0.001
SOFA score	7 (5–10)	7 (4–10)	9 (7–12)	<0.001
Vasoactive therapy	576 (49.1)	419 (48.1)	157 (52.2)	0.229
Mechanical ventilation	818 (69.8)	614 (70.5)	204 (67.8)	0.383
Baseline creatinine (μmol/L)	84.9 (73.0–97.0)	84.0 (72.1–97.0)	86.9 (75.0–97.8)	0.78
Sepsis	512 (43.7)	309 (35.5)	203 (67.4)	<0.001
Comorbid diseases				
Cancer	164 (14.0)	112 (12.9)	52 (17.2)	0.067
Hypertension	523 (44.6)	379 (43.5)	144 (47.8)	0.202
Cardiovascular	274 (23.4)	177 (20.3)	97 (32.2)	<0.001
Chronic kidney disease	111 (9.5)	79 (9.1)	32 (10.6)	0.493
Diabetes	240 (20.5)	173 (19.9)	67 (22.2)	0.407

Data are expressed as median (interquartile range) or number (percent)

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Results

Characteristics of patients with AKI

Table 2 Characteristics of patients with acute kidney injury, by outcome

Characteristics	AKI (n = 1172)	Survivors (n = 871)	Non-survivors (n = 301)	*P* value
Category of ICU admission diagnosis				
Respiratory	208 (17.7)	125 (14.4)	83 (27.6)	<0.001
Neurologic	178 (15.2)	134 (15.4)	44 (14.6)	0.781
Postsurgery	556 (47.4)	443 (50.8)	113 (37.5)	<0.001
Cardiovascular	233 (19.9)	170 (19.5)	63 (20.9)	0.615
ICU course				
Cumulative fluid balance in 3 days (L)	1.40 (−0.49 to 3.54)	0.93 (−0.80 to 2.93)	2.77 (0.86–5.01)	<0.001
Oliguria	96 (8.2)	46 (5.3)	50 (16.6)	<0.001
Use of diuretics (%)	872 (74.4)	635 (72.9)	237 (78.7)	0.047
Outcomes				
AKI stage				
1	496 (42.3)	424 (48.7)	72 (23.9)	
2	289 (24.7)	215 (24.7)	74 (24.6)	<0.001
3	387 (33.0)	232 (26.6)	155 (51.5)	
RRT	222 (18.9)	125 (14.4)	97 (32.2)	<0.001
Length of ICU stay (days)	7 (5–14)	7 (4–13)	8 (6–14)	0.001

Data are expressed as median (interquartile range) or number (percent)

Results

Fluid balance and the incidence of AKI

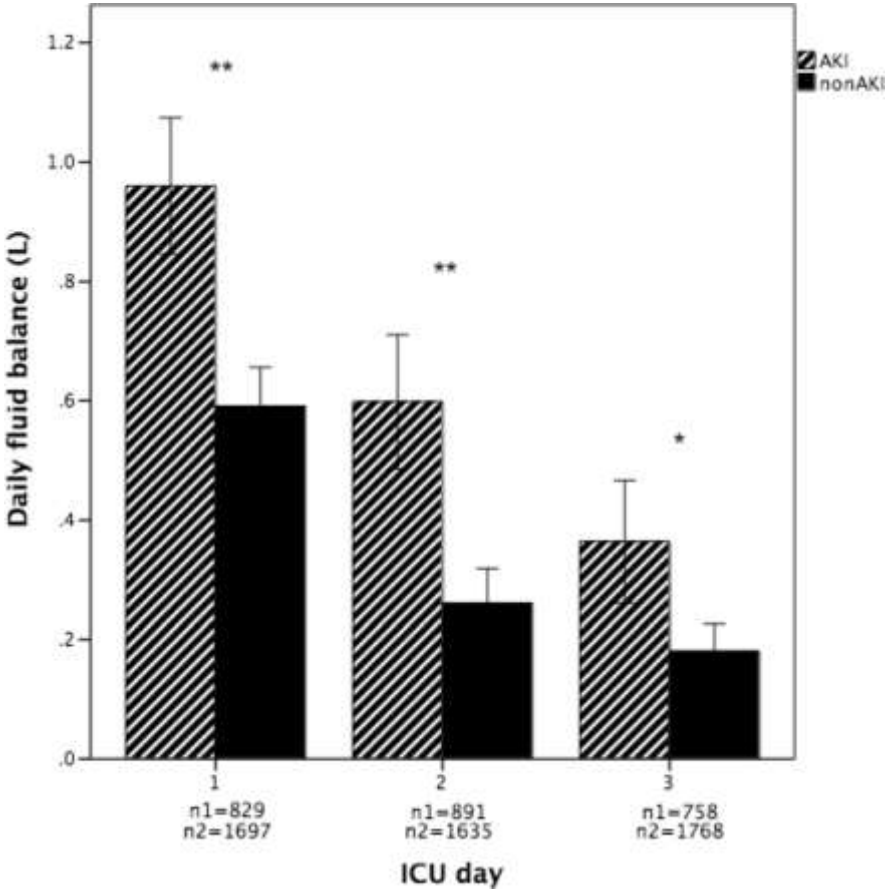

Fig. 2 Daily fluid balance in AKI and non-AKI in the first 3 days of ICU stay (mean ± SE of the mean). *P = 0.007; **P < 0.001. n1 represents patients with AKI; n2 represents patients without AKI

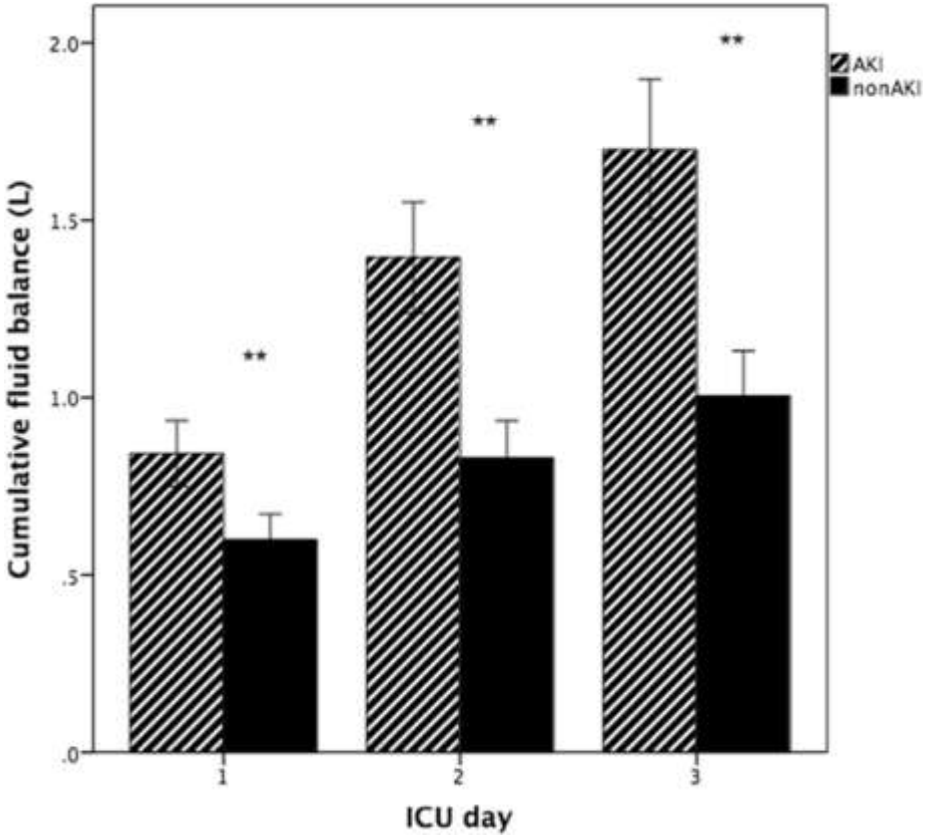

Fig. 3 Cumulative fluid balance in AKI and non-AKI at 24, 48, and 72 h of ICU stay (mean ± SE of the mean). **P < 0.001

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Results

Fluid balance and the incidence of AKI

TableS1 Logistic regression analysis of AKI incidence in critically ill patients

Characteristic	OR	95%CI	P
APACHEII	1.019	1.001--1.039	0.043
SAPS II	1.010	1.001--1.019	0.035
SOFA	1.168	1.133--1.204	0.000
Sepsis	1.324	1.082-1.620	0.006
FO	4.508	2.900-7.008	0.000

Results

Fluid balance and the incidence of AKI

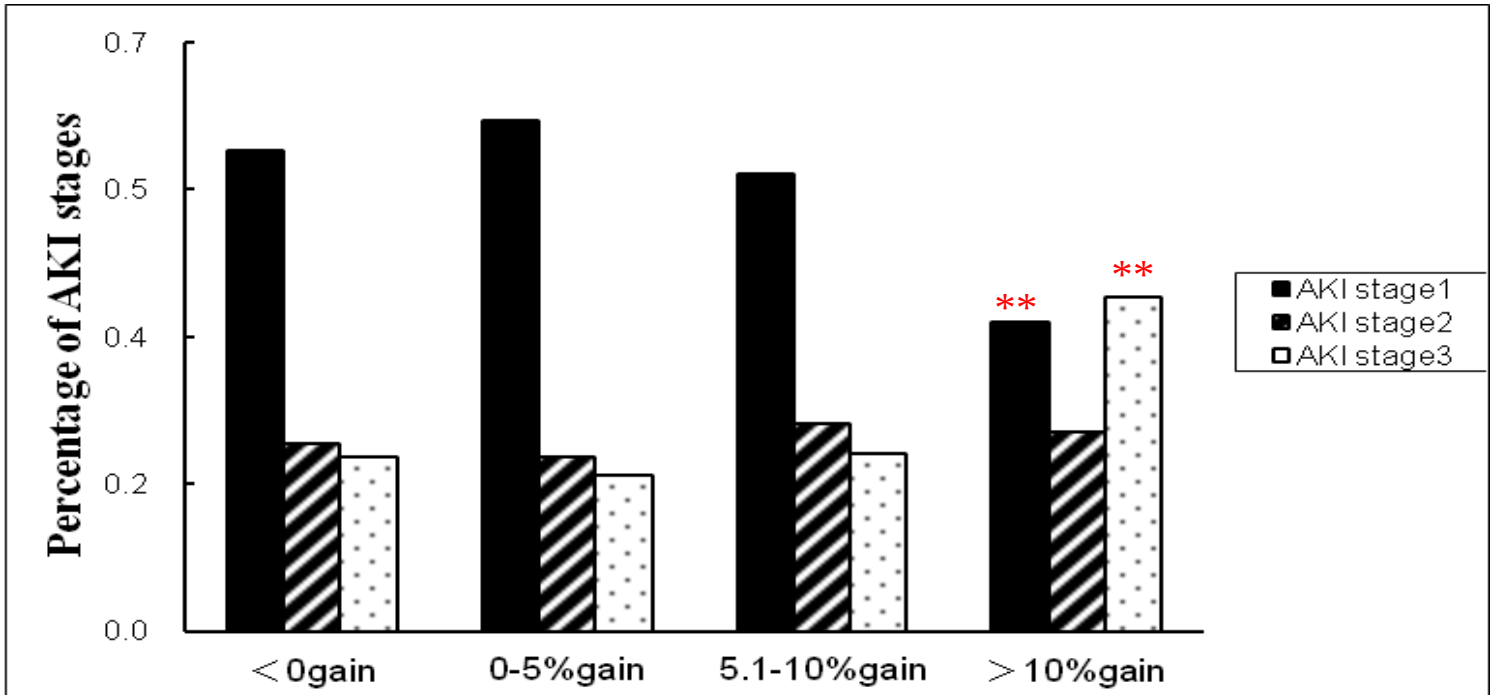

Figure S1 Percentage of AKI stages by fluid accumulation in 3 days relative to baseline weight in AKI patients.

P value is the comparing result of the neighboring groups.*P >0.05; **P <0.001.

Results

Fluid balance and the mortality of patients with AKI

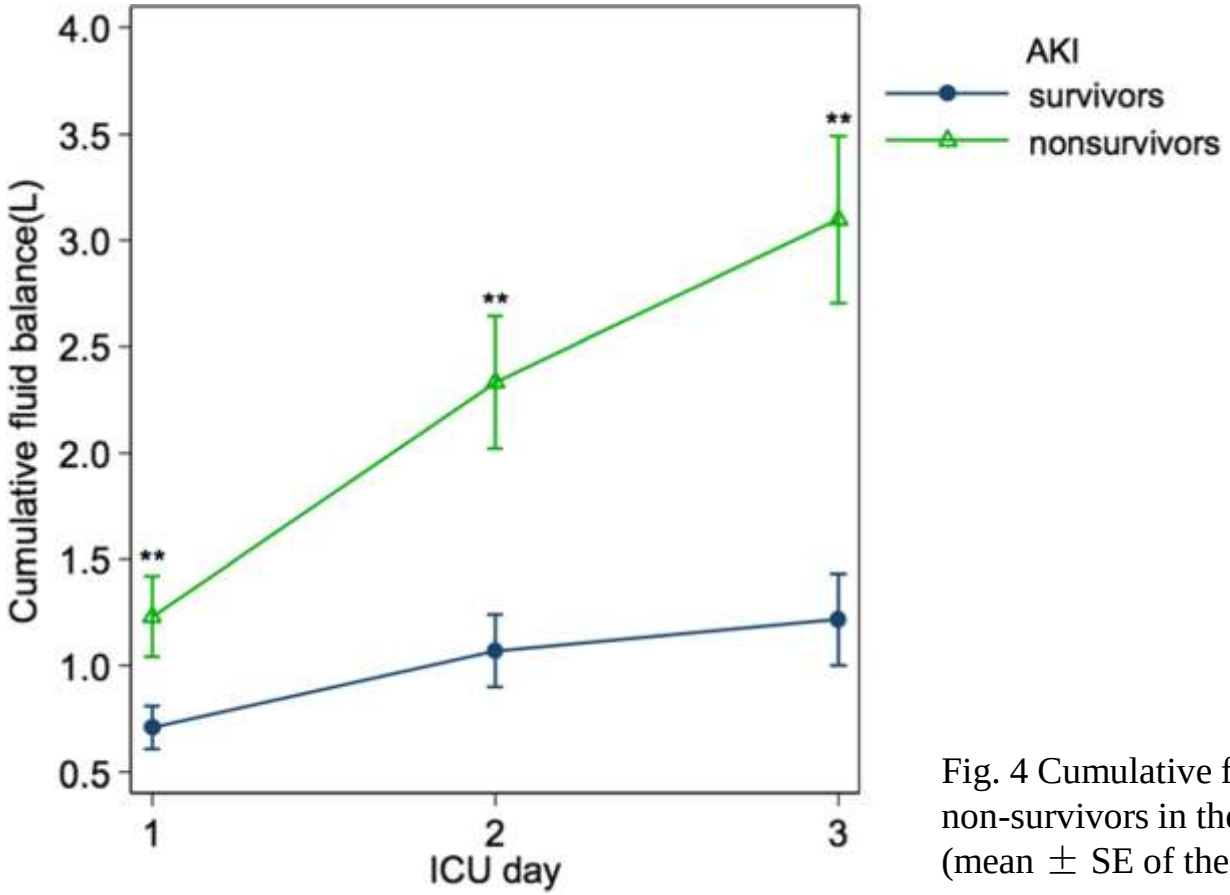

Fig. 4 Cumulative fluid balance in AKI survivors and non-survivors in the first 3 days of their ICU stay (mean ± SE of the mean). **P < 0.001

Results

Fluid balance and the mortality of patients with AKI

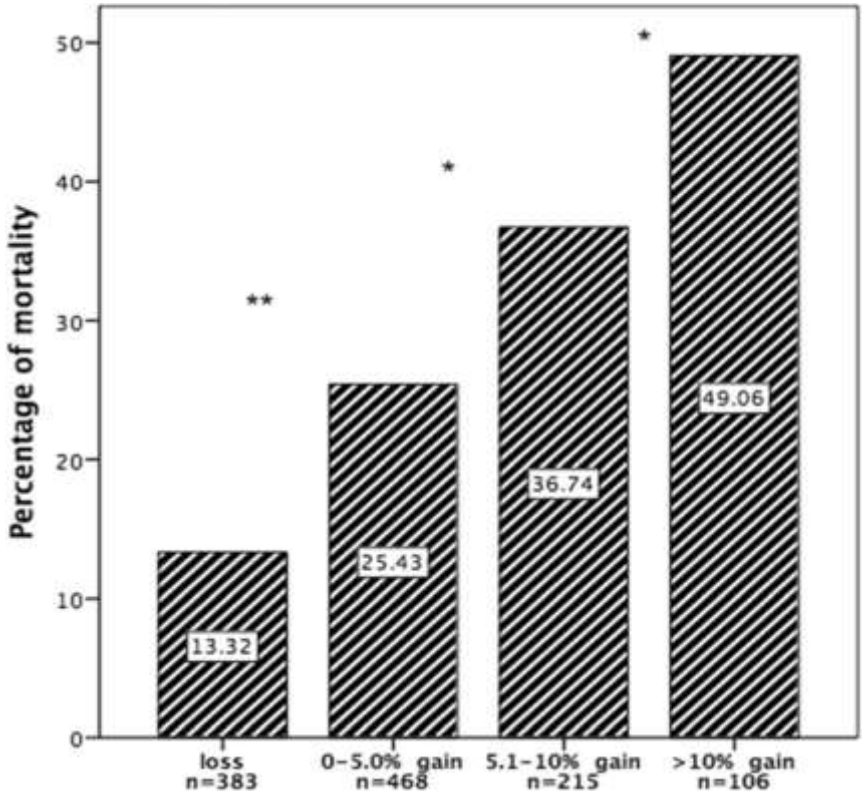

Fig. 5 Mortality rate by fluid accumulation in 3 days relative to baseline weight in patients with AKI. P value is the result of comparing the neighboring groups. *P < 0.05; **P < 0.001

Results

Fluid balance and the mortality of patients with AKI

Table 3 Multivariate Cox regression analysis of 28-day mortality in critically ill patients with acute kidney injury

Characteristic	Hazard ratio	95 % CI	*P* value
Age	1.013	1.005–1.020	0.002
SAPS II	1.021	1.014–1.029	<0.001
Cumulative fluid balance in 3 days	1.041	1.012–1.072	0.006
Sepsis	1.278	0.961–1.701	0.092
Postsurgery	0.760	0.595–0.971	0.028
CRRT	3.166	2.463–4.069	<0.001

Results

Fluid balance and the mortality of patients with AKI

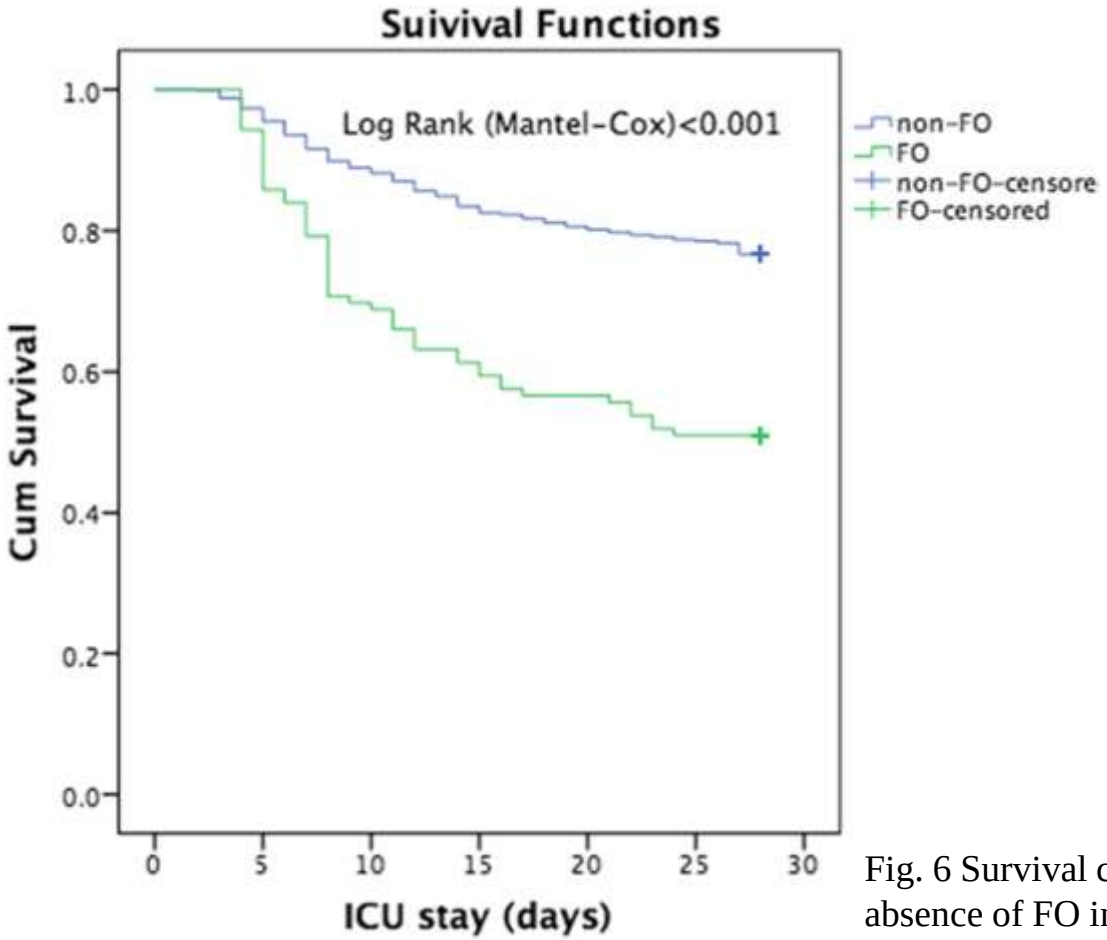

Fig. 6 Survival curve of 28-day mortality by the presence or absence of FO in the patients with AKI in the ICU

Results

Fluid balance and the mortality of patients with AKI

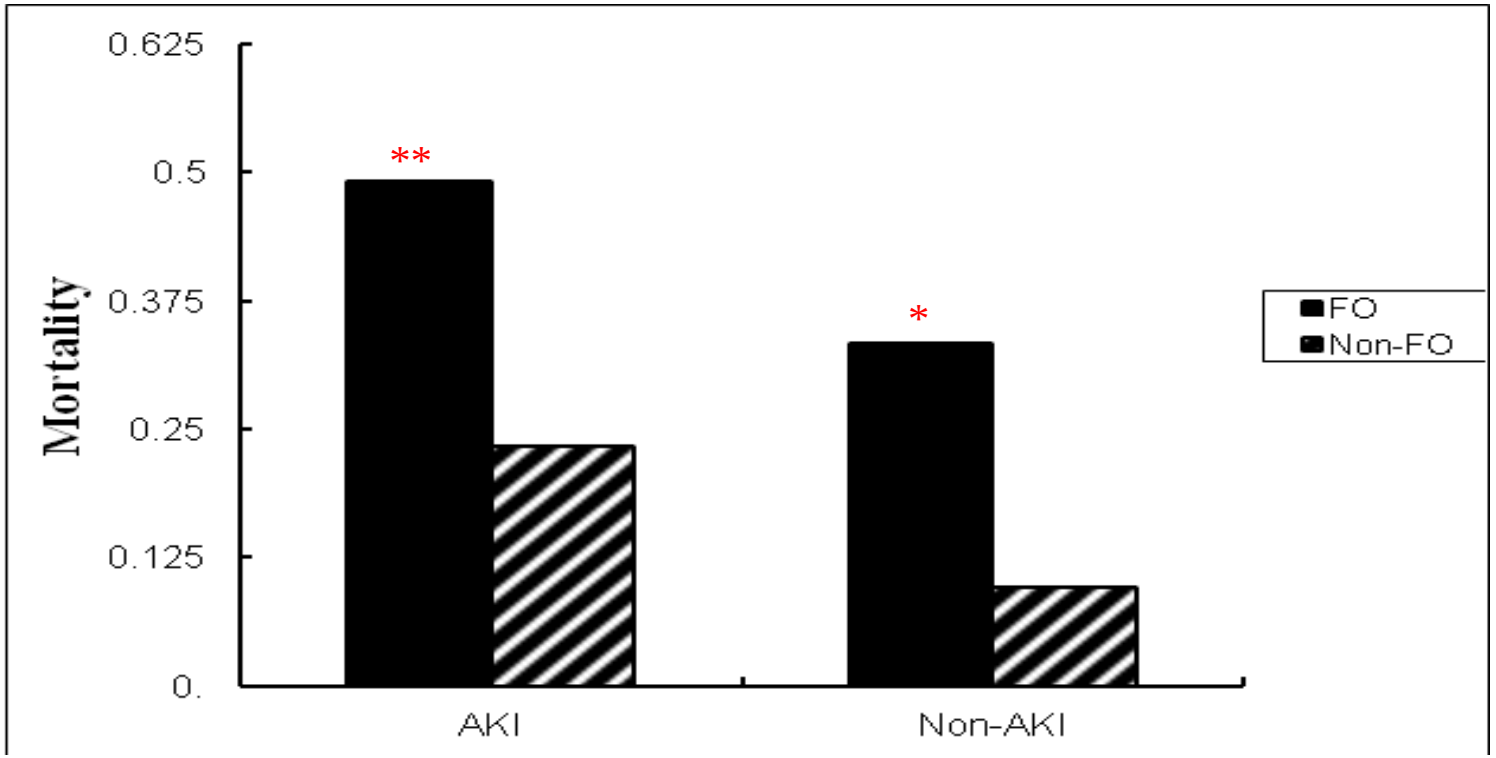

Figure S2 Mortality of FO/Non-FO by the presence or absence of AKI in the overall patients in the ICU.
*P =0.001; **P <0.001.

Discussion

…
However, we could not determine the relationship between a positive fluid balance and the incidence of AKI, because we failed to determine the fluid balance before ICU admission, which might have influenced the incidence of AKI and outcomes.

Fluid therapy, rather than preserving renal function, actually precipitates or worsens AKI by causing FO. Positive fluid balance triggers AKI after cardiac surgery.
On the contrary, the use of goal-directed therapy (GDT) strategies for perioperative hemodynamic optimization have been associated with decreased surgical complications and reduced risk of postoperative AKI.

Discussion

In our study, FO affected the incidence of AKI and the severity of AKI. AKI severity increased significantly when the fluid volume was more than 10 %. Fluid accumulation was associated with adverse outcomes in patients with AKI, and this finding is consistent with those of prior studies.

- Teixeira et al. 10 Italian ICUs, mean fluid balance (MFB) was higher (P = 0.008) in patients with AKI. 28-day mortality, non-survivor patients with AKI had significantly higher MFB than survivors.
- Vaara et al. 17 ICUs, FO in renal support therapy (RST) was associated with a higher risk of death at 90 days (OR 2.6) after adjustment for severity of illness, RST onset time, RST modality, and sepsis.
- FO in septic patients with AKI was associated with higher mortality at 60 days.
- Several other studies: positive fluid balance increased mortality among ICU patients.

Discussion

The relationship of fluid accumulation and mortality associated with AKI is complex.
The cause or the result?
There are many factors that affect the prognosis of patients with AKI, and we needed to further explore this issue.
Greater fluid accumulation increased mortality among patients with AKI. In contrast, the mortality of patients with a negative fluid balance was the lowest.

Discussion

RRT might be effective in reducing FO and increasing survival. However, in our study, RRT was an independent risk factor for 28-day mortality(HR 3.166). The mortality of patients treated with RRT was higher. This finding may be explained partly by increased illness severity upon ICU admission.

Table S2 Characteristics of patients with AKI, stratified by treatment with or without RRT

	RRT (n=222) Median(IQR) Number (%)	**Non－RRT (n=950) Median(IQR) Number (%)**	**P value**
Age(years)	66（52-79）	67（54-78）	0.64
Male gender	148(66.7)	594(62.5)	0.28
APACHEII	23(17 to 29)	16(11to 22)	<0.001
SAPSII	48(38 to 62)	38(29 to 50)	<0.001
SOFA	10(7-13)	7(5-9)	<0.001
Vasoactive therapy	121(54.5)	455(47.9)	0.086
Sepsis	512（43.7）	296（21.9）	<0.001
28-day mortality	97（43.7）	204（21.5）	<0.001
Length of ICU stay (days)	11(7-19)	7(4-12)	<0.001

Discussion

Merits

Detailed insights into fluid balance and mortality in critically ill patients with AKI in Beijing, China.

KDIGO criteria, reducing underestimation or late recognition of AKI.

3-day sequential data included, decrease selection bias, more credible results.

Insight into the significance of fluid accumulation in terms of degree and duration.

Discussion

Limitations

Fluid balance before ICU admission was not measured.

Fluid gain could be the result of either overzealous fluid therapy or poor urine output; we could not differentiate between the two components.

There are many factors that affect the prognosis of patients with AKI. Fluid balance is one of these factors, and we need to further explore this issue.

We failed to determine the type of fluid given (i.e., colloid versus crystalloid, parenteral versus enteral), which may have influenced outcomes.

We also excluded patients who had been in the ICU for fewer than 3 days but had more severe illness, and our results could have been a little more meaningful if we had included such patients.