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Association between fluid balance and survival in critically ill patients

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Abstract. Lee J, de Louw E, Niemi M, Nelson R, Mark RG, Celi LA, Mukamal KJ, Danziger J (Harvard-Massachusetts Institute of Technology, Cambridge, MA, USA; University of Waterloo, Waterloo, ON, Canada; and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA). Association between fluid balance and survival in critically ill patients. *J Intern Med* 2014; doi: 10.1111/joim.12274.

Objective. Although the consequences of chronic fluid retention are well known, those of iatrogenic fluid retention that occurs during critical illness have not been fully determined. Therefore, we investigated the association between fluid balance and survival in a cohort of almost 16 000 individuals who survived an intensive care unit (ICU) stay in a large, urban, tertiary medical centre.

Design. Longitudinal analysis of fluid balance at ICU discharge and 90-day post-ICU survival.

Measurements. Associations between fluid balance during the ICU stay, determined from the electronic bedside record, and survival were tested using Cox proportional hazard models adjusted for severity of critical illness.

Results. There were 1827 deaths in the first 90 days after ICU discharge. Compared with the lowest quartile of discharge fluid balance [median (interquartile range) −1.5 (−3.1, −0.7) L], the highest quartile [7.6 (5.7, 10.8) L] was associated with a 35% [95% confidence interval (CI) 1.13–1.61)] higher adjusted risk of death. Fluid balance was not associated with outcome amongst individuals without congestive heart failure or renal dysfunction. Amongst patients with either comorbidity, however, fluid balance was strongly associated with outcome, with the highest quartile having a 55% (95% CI 1.24–1.95) higher adjusted risk of death than the lowest quartile. Isotonic fluid balance, defined as the difference between intravenous isotonic fluid administration and urine output, was similarly associated with 90-day outcomes.

Conclusion. Positive fluid balance at the time of ICU discharge is associated with increased risk of death, after adjusting for markers of illness severity and chronic medical conditions, particularly in patients with underlying heart or kidney disease. Restoration of euvolaemia prior to discharge may improve survival after acute illness.

Keywords: diuresis, fluid balance, heart failure, oedema, survival, weight.

Introduction

Chronic fluid retention frequently occurs in individuals with underlying cardiac and renal disease and is associated with hypertension, pulmonary vascular congestion and death [1–5]. Due to abnormal sensation of body fluid volume, chronic activation of the renin–angiotensin–aldosterone axis maintains a fluid overloaded state, and requires treatment with dietary sodium restriction and diuretics to re-establish fluid balance [6]. The presence of pulmonary oedema is a widely accepted indication for diuretic therapy, although management of peripheral oedema is controversial [7–10].

The effect of fluid retention in hospitalized patients is not well known. As the landmark studies of Rivers *et al.* [11] outlining the benefit of early goal-directed therapy, aggressive intravenous fluid (IVF) administration has become the standard of care in the intensive care unit (ICU). Although spontaneous diuresis occurs following illness in many individuals, such diuresis may not happen in those with an underlying tendency towards fluid retention [12]. Fluid retention

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has been associated with worse outcomes in some [13–18] but not all [19] critically ill populations, yet has not been evaluated in a broader context.

The current study population was a large cohort of medical, surgical, cardiac and cardiothoracic intensive care patients, admitted to a single medical centre over a 7-year period, for whom fluid balance was carefully recorded. We aimed to further characterize the association between fluid balance during the ICU stay and 90-day mortality after discharge from the ICU, whilst accounting for demographic characteristics, reason for admission, severity of illness, length of stay, peak fluid balance and medical comorbidities. We also specifically investigated whether fluid balance has a greater effect on survival amongst patients with congestive heart failure (CHF) or acute kidney injury (AKI), or impaired renal function at the time of discharge, as we hypothesized that such patients would be at greatest risk of increased mortality.

Methods

Study population

We used the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-II) research database, a joint venture managed by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT), Cambridge, MA, USA, and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) Boston, MA, USA [20]. BIDMC is a 700-bed, urban, academic medical centre with 77 adult ICU (28 medical, 25 surgical, 16 cardiothoracic and eight cardiac) beds. The database contains high temporal resolution data from clinical systems, including laboratory results, electronic documentation and bedside monitor trends and waveforms, for all patients admitted to a BIDMC ICU between 2001 and 2008. Use of the MIMIC-II database has been approved by the institutional review boards of BIDMC and MIT. We restricted our analysis to those patients with an ICU stay of >24 h, because shorter stays are likely to reflect patients who either died or were transferred to a general ward very shortly after ICU admission.

Amongst the 21 694 ICU survivors, there were 17 644 with an ICU stay of 24 h or more. We excluded 342 individuals for whom documentation of fluid balance was not available, 759 who received dialysis (as dialytic fluid removal is not included in the electronic medical record), 1129 for whom renal function was not recorded and 19 with missing basic demographic information; the final sample comprised 15 395 unique first ICU hospitalizations.

Outcome

The primary outcome was death within 90 days of ICU discharge. Deaths were identified from the Social Security Death Index.

Exposures

The primary exposure was fluid balance in the ICU as determined on ICU discharge. This was automatically computed by the bedside electronic record and reflects the net cumulative balance of daily inputs and outputs. These variables include, but are not limited to, IVF, oral fluids, medications and blood products (inputs), as well as urine, stools and other body fluids (outputs). Total fluid balance was winsorized at the 0.5 and 99.5 percentiles to limit the effect of outliers. Isotonic fluid balance, as determined by the difference between total isotonic fluid administration (predominantly saline and lactated Ringer's solution) and total urine output, was evaluated as a secondary exposure.

Covariates

Demographic information included age, sex and race (categorized as White people, African–American, Asian, Hispanic, other or unknown). Medical comorbidities were determined using Elixhauser codes at discharge [21]. The ICU types were cardiac, surgical, cardiothoracic and medical units. Predictors of illness severity included the Simplified Acute Physiology Score (SAPS) at admission, as well as the peak SAPS and cumulative SAPS during the ICU stay, use of vasopressors, use of mechanical ventilation, length of ICU stay and the total amount of isotonic IVFs administered. The most positive fluid balance at any point during the ICU stay was considered the peak fluid balance. AKI during the ICU stay was defined as a 100% increase in peak serum creatinine compared with the levels at either ICU admission or discharge. The estimated glomerular filtration rate (eGFR) at the time of ICU discharge was calculated from the Modification of Diet in Renal

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Disease equation using the serum creatinine level at discharge [22].

Statistical analysis

Baseline characteristics were stratified by quartiles of fluid balance. Cox regression analyses were used to compare survival probabilities within 90 days of discharge from the ICU. Follow-up started on the first day after ICU discharge. Patients who survived for more than 90 days were censored. Binary indicator variables were created for all 30 Elixhauser comorbidities, rather than a summary score, and for use of mechanical ventilation, vasopressor use, the presence of AKI, eGFR <60 mL min^{-1} at discharge and quartiles of fluid balance. Race and ICU type were included as multicategory variables. Age, SAPS, laboratory values, administered IVFs, peak fluid balance and length of stay were all included as continuous variables.

Fluid balance at discharge was examined in quartiles and as a continuous variable; the lowest quartile was used as the reference for all analyses. We tested for non-linearity by the inclusion of a quadratic term in the adjusted model ($P > 0.5$). The proportional hazard assumption was tested by visual inspection of a plot of the integrated hazard versus time.

In subgroup analyses, we examined *a priori* whether underlying heart failure or renal disease modified the effect of fluid balance on mortality. Sensitivity analyses were performed in three groups: (i) patients with CHF as determined by International Classification of Diseases, Ninth Revision codes at discharge; (ii) patients with AKI, as determined by a 100% increase in peak serum creatinine compared with the levels at either ICU admission or discharge; and (iii) those with an eGFR of <60 mL min^{-1} at discharge. We created an indicator variable for the presence of any one of these three clinical risk factors (CHF, AKI or eGFR <60 mL min^{-1}) to test the interaction between fluid balance in patients with none versus one or more of these factors. Analyses were also stratified by severity of renal disease, according to the fold change in creatinine level during the ICU stay (1.5 to <2, ≥2 to <3 and ≥3).

In a sensitivity analysis, we determined whether restoration of fluid balance prior to ICU discharge in those with the highest peak fluid balance was associated with improved survival. Those in the highest quartile of peak fluid balance were stratified by the threshold for the highest discharge fluid balance quartile (4.5 L), and the adjusted effect of fluid balance on 90-day survival was determined.

As fluid balance includes both oral intake and hypotonic fluids, we then assessed whether isotonic fluid balance was associated with survival. Weight at both admission and discharge was recorded in only 44% of patients, precluding the use of body weight changes as a meaningful additional exposure. Next, to assess the presence of survival bias, logistic regression analysis, including 1582 individuals who died during the ICU stay and were not included in the original analysis, was performed to determine whether fluid balance was associated with in-ICU mortality. Finally, because fluid balance is unlikely to affect mortality beyond 90 days from discharge, we explored the association between fluid balance and mortality in those patients who survived the first 90 days after ICU discharge as an internal model control. All analyses were performed using JMP Pro (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

In the 15 395 critically ill patients included in this study, mean (±SD) total fluid balance was 2.6 (±5.2) L and differed significantly according to ICU type [cardiac 0.1 (±3.4), cardiothoracic 2.2 (±3.9), medical 3.0 (±5.3) and surgical 3.8 (±6.0) L; $P < 0.001$]. As shown in Table 1, although patients in the highest quartile of total fluid balance tended to have longer ICU stays with greater severity of illness and a higher admission creatinine concentration, they also tended to be younger, with fewer comorbidities and a lower serum creatinine level at the time of discharge.

Total fluid balance and 90-day mortality

During the 90 days after ICU discharge, there were 1827 deaths (cumulative incidence of 11.9%). Of these deaths, 33% occurred prior to hospital discharge. Higher quartiles of fluid balance at discharge were associated with higher unadjusted mortality (Table 2). Adjusting for demographic characteristics, comorbidities, ICU type, severity and length of illness, AKI, renal function at discharge, total administered isotonic fluids and peak fluid balance slightly attenuated the association,

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Table 1 *Baseline characteristics stratified by quartiles of fluid balance at discharge*

	Quartiles of fluid balance				
	1	2	3	4	
	n = 3848	n = 3848	n = 3848	n = 3851	P-value
Median fluid balance (IQR)	−1.5 (−3.1, −0.7)	0.7 (0.3, 1.1)	2.8 (2.2, 3.6)	7.6 (5.7, 10.8)	
Demographic characteristics					
Age, mean (SD) and years	64.1 (17.0)	63.3 (18.5)	63.4 (17.4)	62.7 (18.0)	0.009
Female, n (%)	1711 (44.5)	1706 (44.3)	1535 (39.9)	1661 (43.1)	<0.001
Race, n (%)					
Asian	81 (2.1)	82 (2.1)	87 (2.3)	87 (2.3)	0.004
Black/African	241 (6.3)	277 (7.2)	248 (6.4)	286 (7.4)	
Hispanic/Latino	120 (3.1)	109 (2.8)	111 (2.9)	102 (2.7)	
Other	93 (2.4)	93 (2.4)	99 (2.6)	101 (2.6)	
Unknown/Unspecified	631 (16.4)	552 (14.4)	548 (14.2)	473 (12.3)	
White people	2682 (69.7)	2735 (71.1)	2755 (71.6)	2802 (72.8)	
Medical history, n (%)					
Congestive heart failure	998 (25.9)	660 (17.2)	594 (15.4)	712 (18.5)	<0.001
Cardiac arrhythmias	700 (18.2)	724 (18.8)	723 (18.8)	814 (21.1)	0.006
Chronic pulmonary disease	766 (19.9)	634 (16.5)	578 (15.0)	597 (15.5)	<0.001
Hypertension	1210 (31.4)	1382 (35.9)	1352 (35.1)	1290 (33.5)	<0.001
Diabetes	985 (25.6)	833 (21.7)	857 (22.3)	852 (22.1)	0.001
ICU type, n (%)					
Cardiac	1102 (28.6)	759 (19.7)	419 (10.9)	155 (4.0)	<0.001
Cardiothoracic	658 (17.1)	735 (19.1)	1216 (31.6)	714 (18.5)	
Medical	1207 (31.4)	1353 (35.2)	1197 (31.1)	1504 (39.1)	
Surgical	881 (22.9)	1001 (26.0)	1016 (26.4)	1478 (38.4)	
ICU values[a]					
Admission SAPS, points	12.6 (4.9)	12.0 (4.9)	13.8 (5.0)	15.4 (4.9)	<0.001
Total SAPS, points	50.1 (67.2)	29.3 (40.8)	40.1 (53.2)	90.1 (115.2)	<0.001
Peak SAPS, points	13.6 (4.9)	12.7 (5.0)	14.6 (4.8)	16.7 (4.7)	<0.001
Intravenous fluid (LOS), L	2.6 (7.3)	2.0 (3.1)	3.2 (4.5)	6.5 (7.2)	<0.001
ICU admission creatinine, mg dL^{-1}	1.17 (0.9)	1.10 (0.8)	1.10 (0.8)	1.24 (1.0)	<0.001
ICU discharge creatinine, mg dL^{-1}	1.05 (0.7)	0.99 (0.7)	0.98 (0.7)	0.99 (0.8)	<0.001
Vasopressor, n (%)	1142 (29.7)	928 (24.1)	1586 (41.2)	1823 (47.3)	<0.001
Mechanical ventilator, n (%)	1863 (48.4)	1524 (39.6)	2232 (58.0)	2760 (71.7)	<0.001
Peak fluid balance, mean (SD)	0.62 (2.9)	1.67 (1.8)	4.08 (2.4)	11.11 (6.7)	<0.001
ICU length of stay (days)	4.7 (5.5)	2.9 (8.8)	3.5 (4.1)	7.3 (8.8)	<0.001

IQR, interquartile range; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; LOS, length of stay.
[a]Values are presented as mean (SD), unless otherwise stated.

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Table 2 *Association between fluid balance at discharge and survival*

	Hazard ratio 90-day mortality per total fluid balance			
	Quartiles of fluid balance			
	1	2	3	4
Deaths, *n* (%)	404 (10.5)	410 (10.7)	391 (10.2)	622 (16.2)
Unadjusted	1.00 (Ref.)	1.02 (0.89–1.17) $P = 0.78$	0.97 (0.85–1.12) $P = 0.70$	1.60 (1.41–1.81) $P < 0.001$
Adjusted[a]	1.00 (Ref.)	1.09 (0.94–1.26) $P = 0.25$	1.07 (0.92–1.25) $P = 0.35$	1.35 (1.13–1.61) $P = 0.001$

Ref., reference.
Hazard Ratios (95% confidence intervals) provided.
[a]Adjusted for age, sex, race, ICU type, length of stay, mechanical ventilation, vasopressor use, admission Simplified Acute Physiology Score (SAPS), total SAPS, peak SAPS, total intravenous isotonic fluid, all 30 Elixhauser comorbidities, admission, peak and discharge creatinine levels and peak fluid balance.

but discharge fluid balance remained a significant predictor of 90-day mortality.

We considered *a priori* three categories of patients to be at higher risk of acute fluid retention: those with (i) CHF or (ii) AKI during the ICU stay or (iii) impaired renal function at the time of discharge. In all three high-risk groups, the effect of fluid balance on mortality was increased compared with individuals without these comorbidities, with positive fluid balance strongly predicting mortality after ICU discharge (Table 3). In addition, there was a trend towards improved mortality with negative total fluid balance in patients with CHF or AKI. We then compared whether the presence of CHF, AKI or an eGFR <60 mL min^{-1} at discharge, versus none of these comorbidities, affected the association between fluid balance and outcome (multiplicative interaction term $P = 0.03$). There were 1111 (18.8%) postdischarge deaths in the group with CHF, AKI or eGFR <60 mL min^{-1}, compared with 716 (7.6%) in those without any of these comorbidities. The highest quartile of total fluid balance in the former group (with CHF, AKI or eGFR <60 mL min^{-1}) was associated with a 55% [95% (CI) 1.24–1.95] increased risk of 90-day mortality. Total fluid balance was not significantly associated with outcome in patients without these comorbidities.

In analyses of patients with renal injury, serum creatinine level increased by 1.5- to <2-fold in 13% ($n = 1987$), by 2- to <3-fold in 7% ($n = 998$) and by three-fold or more in 2% ($n = 344$). Within each increasing category of renal dysfunction, the highest quartile of fluid balance was associated with an adjusted risk of mortality of 1.79 (95% CI 1.18–2.77, $P = 0.006$), 2.11 (95% CI 1.20–3.77, $P = 0.008$) and 1.35 (95% CI 0.47–4.11, $P = 0.57$), respectively.

Restoration of discharge fluid balance and mortality in patients with the highest peak fluid balance

In the quartile with the highest peak fluid balance ($n = 3851$), the mean (±SD) peak fluid balance and fluid balance at discharge were 11.9 (±6.4) and 8.5 (±6.1) L, respectively. Only 18% of patients in this quartile reached a discharge fluid balance of < 4.5 L and, despite a tendency towards a greater severity of illness on ICU admission, higher rates of mechanical ventilation and vasopressor use and longer ICU stays (Table 4), were more likely to survive 90 days after ICU discharge than those in whom total fluid balance remained more positive (Table 5).

Isotonic fluid balance and 90-day mortality

Given that total fluid balance is a composite of all types of physiological inputs, we then evaluated whether isotonic fluid balance was associated with outcome. The median (interquartile range) values for administered isotonic fluid and urine output during the period of ICU stay were 2.2 (0.7–4.3) and 5.5 (3.2–10.5) L, respectively. In an adjusted analysis, each 1 L of positive isotonic fluid balance was associated with a hazard ratio (HR) of 1.04 (95% CI 1.03–1.05, $P < 0.001$) for risk of dying within 90 days of ICU discharge.

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Table 3 *Association between fluid balance at discharge and survival stratified by comorbidities*

	Hazard ratio 90-day mortality stratified by presence of cardiac or renal disease[a]			
	Quartiles of fluid balance			
	1	2	3	4
CHF	(*n* = 166, 16%)	(*n* = 137, 21%)	(*n* = 120, 20%)	(*n* = 202, 28%)
	1.00 (Ref.)	1.15 (0.91–1.47) *P* = 0.24	1.18 (0.91–1.54) *P* = 0.21	1.83 (1.33–2.51) *P* < 0.001
AKI	(*n* = 36, 13%)	(*n* = 23, 16%)	(*n* = 34, 14%)	(*n* = 142, 20%)
	1.00 (Ref.)	1.29 (0.74–2.23) *P* = 0.36	1.33 (0.80–2.21) *P* = 0.27	1.99 (1.24–3.27) *P* = 0.004
eGFR<60 mL min^{-1}	(*n* = 176, 18%)	(*n* = 153, 19%)	(*n* = 138, 19%)	(*n* = 215, 26%)
	1.00 (Ref.)	0.96 (0.76–1.21) *P* = 0.74	1.07 (0.83–1.39) *P* = 0.58	1.40 (1.02–1.92) *P* = 0.04
CHF, AKI or eGFR<60 mL min^{-1}[b]	(*n* = 260, 16%)	(*n* = 232, 18%)	(*n* = 211, 17%)	(*n* = 408, 24%)
	1.00 (Ref.)	1.07 (0.89–1.29) *P* = 0.46	1.11 (0.91–1.35) *P* = 0.31	1.55 (1.24–1.95) Verschuren F *P* < 0.001
Neither CHF, AKI, and eGFR ≥60 mL min^{-1}	(*n* = 144, 7%)	(*n* = 178, 7%)	(*n* = 180, 7%)	(*n* = 214, 10%)
	1.00 (Ref.)	1.12 (0.89–1.41) *P* = 0.33	1.05 (0.82–1.33) *P* = 0.72	1.11 (0.82–1.52) *P* = 0.50

Ref., reference.
Data are presented as number of deaths and percentage within each quartile of fluid balance.
[a]Hazard ratios generated from adjusted model; [b]multiplicative interaction between 4th quartile and congestive heart failure (CHF)/acute kidney injury (AKI)/estimated glomerular filtration rate (eGFR) at discharge<60 mL min^{-1} = 0.03.

Total fluid balance and ICU outcome

Although ICU outcome was not an *a priori* end-point of this study, we performed a sensitivity analysis including within-ICU deaths (*n* = 1582). In an adjusted analysis, each 1 L of positive fluid balance was associated with an HR of 1.07 (95% CI 1.06–1.08) for risk of within-ICU death, confirming that the higher risk of death following ICU discharge was not related to survivorship bias during the ICU stay.

Fluid balance and survival in patients who survived 90 days from ICU discharge

Because the effect of fluid balance on mortality is likely to be time dependent, we examined the association between fluid balance and outcome in patients who survived 90 days from ICU discharge as an internal model control (*n* = 13 408). Each 1 L of positive fluid balance was associated with an HR of 1.00 for risk of mortality (95% CI 0.99–1.01, *P* = 0.69) in this group, suggesting that the association between fluid balance and 90-day outcome was not due to residual confounding.

Discussion

In this large single-centre study of critically ill patients, those with a positive fluid balance during critical illness had a significantly greater risk of dying within 90 days of ICU discharge. This association was particularly strong amongst patients at

Table 4 *Baseline characteristics of highest peak fluid balance quartile stratified by fluid balance quartile at discharge*

	Fluid balance at discharge (L)		
	≤4.5	>4.5	
	n = 690	*n* = 3161	*P*-value
Demographic characteristics			
Age, mean (SD), years	63.6 (16.6)	62.3 (18.0)	0.096
Female, *n* (%)	303 (43.9)	1356 (42.9)	0.640
Race, *n* (%)			
Asian	15 (2.2)	78 (2.5)	0.273
Black/African	48 (7.0)	235 (7.4)	
Hispanic/Latino	18 (2.6)	83 (2.6)	
Other	18 (2.6)	84 (2.7)	
Unknown/Unspecified	109 (15.8)	386 (12.2)	
White people	482 (69.9)	2295 (72.6)	
Medical history, *n* (%)			
Congestive heart failure	160 (23.2)	603 (19.1)	0.02
Cardiac arrhythmias	137 (19.9)	667 (21.1)	0.46
Chronic pulmonary disease	122 (17.7)	491 (15.5)	0.16
Hypertension	186 (27.0)	1053 (33.3)	0.001
Diabetes	149 (21.6)	694 (22.0)	0.83
ICU type, *n* (%)			
Cardiac	78 (11.3)	111 (3.5)	<0.0001
Cardiothoracic	197 (28.6)	482 (15.3)	<0.0001
Medical	196 (28.4)	1262 (39.9)	<0.0001
Surgical	219 (31.7)	1306 (41.3)	<0.0001
ICU values[a]			
Admission SAPS, points	16.8 (4.9)	15.6 (4.9)	<0.0001
Total Intravenous fluid, L	7.8 (9.3)	7.2 (7.7)	0.10
ICU admission creatinine, mg dL^{-1}	1.20 (1.0)	1.25 (1.0)	0.24
ICU discharge creatinine, mg dL^{-1}	0.98 (0.7)	0.98 (0.8)	0.98
Vasopressor, *n* (%)	464 (67.3)	1518(48.0)	<0.0001
Mechanical ventilator, *n* (%)	612 (88.7)	2349 (74.3)	<0.0001
ICU length of stay (days)	11.2 (9.2)	8.3 (4.4)	<0.0001
Discharge fluid balance, L	1.04 (3.6)	10.17 (0.1)	<0.0001
Peak fluid balance, L	9.44 (4.1)	12.39 (6.7)	<0.0001
ICU day of peak fluid balance	3.98 (3.8)	6.17 (7.5)	<0.0001

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; LOS, length of stay.
[a]Values are presented as mean (SD), unless otherwise stated.

risk of chronic fluid retention, namely those with CHF, AKI and renal insufficiency at the time of ICU discharge.

Positive fluid balance was common amongst ICU patients, particularly those with a tendency towards fluid retention. As no data regarding post-ICU care are available, it is not possible to determine whether diuresis occurred after the resolution of critical illness. Although it is likely that diuresis occurs spontaneously to some degree in most healthy individuals [12], it is plausible that those with underlying cardiac and renal disease had a positive fluid balance that persisted into the

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Table 5 *Association between fluid balance at discharge and survival in highest quartile of peak fluid balance*

	Hazard ratio 90-day mortality	
	Fluid balance at discharge (L)	
	≤4.5	>4.5
Deaths, *n* (%)	75 (10.9)	544 (17.2)
Unadjusted	1.00 (Ref.)	1.71 (1.33–2.22) $P < 0.001$
Adjusted[a]	1.00 (Ref.)	1.54 (1.20–2.01) $P = 0.001$

Ref., reference.
Hazard Ratio (95% Confidence Intervals) provided.
[a]Adjusted for age, sex, race, type of intensive care unit, length of stay, mechanical ventilation use, vasopressor use, admission Simplified Acute Physiology Score (SAPS), total SAPS, peak SAPS, total intravenous isotonic fluid, all 30 Elixhauser comorbidities, admission, peak and discharge creatinine levels and peak fluid balance.

outpatient setting. This state of perpetual volume overload could increase the risk of hypertension, arrhythmia and CHF. In addition, whereas positive fluid balance was associated with increased mortality, a negative fluid balance was associated with a trend towards improved survival in those with CHF and AKI.

The association between positive fluid balance at ICU discharge and increased mortality was independent of the peak fluid balance that occurred during the ICU stay. Furthermore, in those with the highest peak fluid balance during the ICU stay, restoration of fluid balance at discharge was associated with improved survival. Whether this restoration was achieved spontaneously or pharmacologically is not known.

Our analysis adds to a growing awareness of the potential negative sequelae of net fluid accumulation. In sepsis, early positive fluid balance predicts both ICU [23] and 28-day mortality [24]. Observational studies have demonstrated an association between fluid overload and increased morbidity and mortality in other ICU populations, including patients with cancer [25], intracranial haemorrhage [26] and lung injury [27, 28]. The results of small randomized controlled studies have suggested that fluid restriction strategies can lead to improved outcomes [29, 30].

Our analysis, which represents the largest study to date, suggests a similar deleterious effect of excessive volume, particularly in those with an underlying state of fluid retention. Furthermore, because most re-admissions within 90 days of a hospital discharge are due to CHF [31], our results suggest that iatrogenic fluid accumulation might be a modifiable risk factor to reduce rehospitalizations. Our findings are not intended to limit the use of aggressive fluid resuscitation in the appropriate clinical setting. Instead, if the associations presented herein underlie a true causal relationship between fluid overload and mortality, one might expect a survival benefit from re-establishing body weight after the resolution of critical illness.

This study has several important limitations. Most notably, the cross-sectional nature of the data prevents any causal conclusions. In addition, as fluid balance was only assessed within the ICU, our findings cannot be generalized to patients with noncritical illness. Furthermore, as we did not have access to data regarding post-ICU care prior to hospital discharge, we may not have accounted for other factors that could influence 90-day survival. Although we included many predictors of illness severity, it is possible that residual confounding remains, particularly as positive fluid balance was associated with severity of illness. However, positive fluid balance was not associated with poor outcome in an adjusted analysis of patients without a predisposition towards fluid retention, and fluid balance was not associated with outcome in those who survived beyond 90 days from ICU discharge. These findings suggest that fluid balance is not simply a marker of illness severity.

In addition, ICU admission and discharge weight was only recorded in 44% of patients, suggesting that close surveillance of changes in body weight was not part of routine critical care in our institution. Information regarding diuretic use during the ICU stay was not available, and thus, whether positive fluid balance reflected diuretic resistance cannot be determined. The use of serum creatinine level to define kidney injury in critical illness has important limitations [32] and probably does not accurately reflect the dynamic changes of glomerular filtration that occur in this setting. Furthermore, pre-illness measures of renal function were not available, and therefore, we used change in serum creatinine concentration during critical illness to determine acuity. Finally, although dialysis patients, due to their anuric state, are perhaps

most vulnerable to complications of positive fluid balance, they were not included in this analysis due to an inability to accurately capture fluid balance.

In conclusion, we found that positive fluid balance is associated with postdischarge mortality, particularly amongst those patients most vulnerable to fluid retention. Our findings raise the possibility that careful attention to fluid balance at the time of hospital discharge may improve outcomes.

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Conflict of interest statement

No conflicts of interest to declare.

References

1 Selewski DT, Cornell TT, Lombel RM *et al.* Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. *Intensive Care Med* 2011; **37:** 1166–73.
2 Chaney E, Shaw A. Pathophysiology of fluid retention in heart failure. *Contrib Nephrol* 2010; **164:** 46–53.
3 Kalantar-Zadeh K, Regidor DL, Kovesdy CP *et al.* Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation* 2009; **119:** 671–9.
4 Wabel P, Moissl U, Chamney P *et al.* Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload. *Nephrol Dial Transplant* 2008; **23:** 2965–71.
5 Slagman MC, Waanders F, Hemmelder MH *et al.* Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011; **343:** d4366.
6 Francis GS, Benedict C, Johnstone DE *et al.* Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation* 1990; **82:** 1724–9.
7 Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987; **57:** 17–22.
8 Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002; **82:** 149–58.
9 Felker GM, O'Connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? *Circ Heart Fail* 2009; **2:** 56–62.
10 Ahmed A, Aronow WS, Fleg JL. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *Am Heart J* 2006; **151:** 444–50.
11 Rivers E, Nguyen B, Havstad S *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345:** 1368–77.
12 Srinivasa S, Tan ST. Postoperative fluid management in major elective plastic surgery. *J Plast Reconstr Aesthet Surg* 2010; **63:** 992–5.
13 Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. *Chest* 2000; **117:** 1749–54.
14 Bouchard J, Soroko SB, Chertow GM *et al.* Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; **76:** 422–7.
15 Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; **12:** R74.
16 Upadya A, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA. Fluid balance and weaning outcomes. *Intensive Care Med* 2005; **31:** 1643–7.
17 Sutherland SM, Zappitelli M, Alexander SR *et al.* Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *Am J Kidney Dis* 2010; **55:** 316–25.
18 Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock: the effect of increasing fluid balance on mortality. *J Intensive Care Med* 2013 [Epub ahead of print].
19 Kleespies A, Thiel M, Jauch KW, Hartl WH. Perioperative fluid retention and clinical outcome in elective, high-risk colorectal surgery. *Int J Colorectal Dis* 2009; **24:** 699–709.
20 Saeed M, Villarroel M, Reisner AT *et al.* Multiparameter Intelligent Monitoring in Intensive Care II: a public-access intensive care unit database. *Crit Care Med* 2011; **39:** 952–60.
21 Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998; **36:** 8–27.
22 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130:** 461–70.
23 Vincent JL, Sakr Y, Sprung CL *et al.* Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34:** 344–53.
24 Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; **39:** 259–65.

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25 de Almeida JP, Palomba H, Galas FR *et al.* Positive fluid balance is associated with reduced survival in critically ill patients with cancer. *Acta Anaesthesiol Scand* 2012; **56:** 712–7.
26 Martini RP, Deem S, Brown M *et al.* The association between fluid balance and outcomes after subarachnoid hemorrhage. *Neurocrit Care* 2012; **17:** 191–8.
27 Valentine SL, Sapru A, Higgerson RA *et al.* Fluid balance in critically ill children with acute lung injury. *Crit Care Med* 2012; **40:** 2883–9.
28 Flori HR, Church G, Liu KD, Gildengorin G, Matthay MA. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. *Crit Care Res Pract* 2011; **2011:** 854142.
29 McArdle GT, McAuley DF, McKinley A, Blair P, Hoper M, Harkin DW. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. *Ann Surg* 2009; **250:** 28–34.
30 Belba M, Aleksi A, Nezha I, Tafaj S, Shtylla M, Belba G. Net fluid accumulation and outcome. A randomized clinical trial. *Ann Burns Fire Disasters* 2009; **22:** 16–21.
31 Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009; **360:** 1418–28.
32 Mandelbaum T, Lee J, Scott DJ *et al.* Empirical relationships among oliguria, creatinine, mortality, and renal replacement therapy in the critically ill. *Intensive Care Med* 2013; **39:** 414–9.

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