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Influence of Daily Fluid Balance prior to Continuous Renal Replacement Therapy on Outcomes in Critically Ill Patients

Min Jee Han, Ki Hyun Park, Jung-ho Shin, and Su Hyun Kim

Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea

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Address for Correspondence:
Jung-ho Shin, MD
Department of Internal Medicine, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea
E-mail: junghoshin1982@gmail.com

Positive fluid balance is a risk factor for mortality in critically ill patients, especially those requiring continuous renal replacement therapy (CRRT). However, the association between daily fluid balance and various organ impairments remains unclear. This study investigated the impacts of daily fluid balance prior to CRRT on organ dysfunction, as well as mortality in critically ill patients. We identified daily fluid balance between intensive care unit (ICU) admission and CRRT initiation. According to daily fluid balance, the time to CRRT initiation and the rate of organ failure based on the sequential organ failure assessment (SOFA) score were assessed. We recruited 100 patients who experienced CRRT for acute kidney injury. CRRT was initiated within 2 [0, 4] days. The time to CRRT initiation was shortened in proportion to daily fluid balance, even after the adjustment for the renal SOFA score at ICU admission (HR 1.14, $P = 0.007$). Based on the SOFA score, positive daily fluid balance was associated with respiratory, cardiovascular, nervous, and coagulation failure, independent of each initial SOFA score at ICU admission (HR 1.36, 1.26, 1.24, and 2.26, all $P < 0.05$). Ultimately, we found that positive fluid balance was related with an increase in the rate of 28-day mortality (HR 1.14, $P = 0.012$). Positive daily fluid balance may accelerate the requirement for CRRT, moreover, it can be associated with an increased risk of multiple organ failure in critically ill patients.

Keywords: Continuous Renal Replacement Therapy; Critically Ill Patients; Daily Fluid Balance; Organ Failure

INTRODUCTION

Fluid therapy is essential for treating critically ill patients. A large amount of fluid may be needed to optimize hemodynamics, especially in patients with severe sepsis and septic shock (1). On the other hand, fluid is excessively administered in numerous cases, sometimes resulting in fluid accumulation, inducing tissue edema, which can predispose organ dysfunction (2). Studies have demonstrated that positive fluid balance is associated with worse outcomes, such as prolonged duration of mechanical ventilation and delayed recovery of kidney function, as well as increased mortality in critically ill patients (3-5). Thus, a conservative strategy of fluid management in critically ill patients is now being advocated rather than liberal fluid therapy.

Acute kidney injury (AKI) frequently occurs in critically ill patients (6-8), and fluid therapy is performed to maintain adequate renal perfusion in patients with or at risk of AKI (9,10). Due to the fact that the mortality rate of such patients is high, appropriate management is required for the treatment and prevention of AKI (8,11,12). However, liberal fluid therapy for kidney protection is now being challenged. Several studies have supported that liberal fluid therapy in critically ill patients with AKI might be associated with poor outcomes, so restrictive fluid therapy is suggested to improve the survival rate (3,13-15). Although previous studies have shown an increased mortality, there is a paucity of studies with respect to organ impairment depending on inadequate fluid balance in patients with AKI to date. In addition, most studies have focused on the respiratory system, thus, the impact of fluid balance on other organs remains uncertain.

In this study, we performed a retrospective study to investigate the influence of daily fluid balance prior to continuous renal replacement therapy (CRRT) on various organ outcomes in critically ill patients. The time to CRRT initiation and multiple organ impairment based on the sequential organ failure assessment (SOFA) score as well as mortality were evaluated according to daily fluid balance.

MATERIALS AND METHODS

Patients

Patients who underwent CRRT between April 2007 and August 2011 were recruited. A total of 140 adult patients who had received CRRT were identified. Of these, the study included AKI patients who were admitted for medical illness. Thus, we excluded 34 patients based on the following criteria: 6 were trau-

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ma admissions; 12 were postoperative admissions; and 16 had preexisting end-stage renal disease requiring dialysis. We additionally excluded 2 patients who had simultaneously received extracorporeal membrane oxygenation and 4 patients who had received a kidney transplant before admission. Ultimately, 100 patients treated with CRRT in the intensive care unit (ICU) were analyzed in the present study.

Continuous renal replacement therapy protocol

The initiation of CRRT was decided by the physician if the patients who could not bear intermittent hemodialysis due to unstable vital signs had refractory pulmonary edema, intractable hyperkalemia or metabolic acidosis, uremic symptoms including pericarditis and encephalopathy, or oliguria with progressive azotemia. A central venous catheter was inserted into the internal jugular or femoral vein. Continuous hemodiafiltration was carried out using the Prisma (Gambro, Lund, Sweden) or Prismaflex (Gambro) machines with high flux hemofilter (ST100, Gambro), and dialysate and replacement fluids (Hemosol B0, Gambro). Anticoagulation was conducted with nafamostat mesilate (SK chemicals, Seoul, Korea). The target dose of CRRT was 40 mL/kg/hour, which could be adjusted by the physician depending on the patient's condition.

Data collection

All data were collected from electronic medical records. Baseline demographic and clinical data at ICU admission included age, sex, comorbidities, and routes and causes of admission. The data at CRRT initiation included the reasons for AKI, the time to initiate CRRT, central venous pressure, chest radiograph to identify pulmonary edema, urine output and doses of diuretics. Urinary results for fractional excretion of sodium were also recorded. To calculate the SOFA score, related parameters were obtained both at ICU admission and at CRRT initiation (16). All available intake and output data between ICU admission and CRRT initiation were collected. Intake was composed of oral and parenteral fluid administered, and output included urine, gastrointestinal losses, and drains.

Definitions

Fluid balance was computed using total intake and output data. Cumulative fluid balance was defined as the difference between total intake and total output from ICU admission to CRRT initiation. Daily fluid balance was calculated by dividing the cumulative fluid balance by the day of CRRT initiation. Patients were classified into tertiles based on daily fluid balance: group 1 included patients with a fluid balance of < 1.5 L/day; group 2 included those with a fluid balance of 1.5 to 3.0 L/day; and group 3 included those with a fluid balance of ≥ 3.0 L/day.

Failure of organ systems was evaluated to elucidate the impact depending on daily fluid balance. Organ failure was assessed based on the SOFA score excluding renal system and was defined as each SOFA score of 4.

Outcome

We firstly evaluated the time to start CRRT from ICU admission according to daily fluid balance. Next, the prevalence of organ failure was compared between the groups and the probability of organ failure depending on daily fluid balance was determined. We also evaluated the 28-day mortality according to daily fluid balance. Lastly, recovery of renal function was assessed by dialysis independency at 90 days from ICU admission.

Statistical analysis

Continuous variables are expressed as the median [interquartile range], and were compared using the Wilcoxon rank sum test or ANOVA, followed by the Turkey-Kramer method for multiple comparison. Categorical variables are expressed as a number (percentage), and were analyzed using the χ^2 test. The Kaplan-Meier method was used to evaluate the CRRT implementation rate and the 28-day patient survival rate, and those were assessed by the log-rank test. Univariate and multivariate Cox regression analyses were performed to explore the hazard ratio (HR) for daily fluid balance. Multivariate analyses for the risk of organ failure were conducted with adjustment for age, sex and the SOFA score of each organ at ICU admission. On the other hand, the 28-day mortality was adjusted as follows: model 1 was adjusted for age and sex; model 2 was adjusted for the variables in model 1 plus the total SOFA score at ICU admission; and model 3 was adjusted for the variables in model 2 plus causes of AKI. All statistical analyses were performed using SPSS Statistics version 18 (IBM Corp., Armonk, NY, USA). A two-sided P value < 0.05 was considered to be significant.

Ethics statement

The study was approved by the institutional review board at Chung-Ang University Hospital, IRB number: C2013013(973). Since the study was retrospective and the subjects were de-identified, the board waived the need for written consent from patients.

RESULTS

Baseline characteristics at ICU admission according to daily fluid balance

Of the 100 included patients, there were 67 (67.0%) men and 33 (33.0%) women, and the median age was 65 [51, 73] years old. Those admitted to ICU were from either the emergency department (65.0%) or a general ward (35.0%). The most common reason for admission was infection (49.0%), followed by heart disease (17.0%).

According to daily fluid balance between ICU admission and

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CRRT initiation, there were 37 patients (37.0%) in group 1, 31 (31.0%) in group 2, and 32 (32.0%) in group 3. Baseline characteristics at ICU admission were compared between the groups (Table 1). The total SOFA scores at ICU admission were 9 [7, 12], 10 [6, 12] and 11 [9, 13] in group 1, 2, and 3, respectively (P = 0.251). The coagulation and renal SOFA scores differed at the time of ICU admission (P = 0.034 and 0.015, respectively).

Table 1. Baseline characteristics at ICU admission according to daily fluid balance

Parameters	Group 1 (n = 37)	Group 2 (n = 31)	Group 3 (n = 32)	*P* value
Age, yr	66 [52, 78]	66 [51, 74]	58 [50, 70]	0.295
Sex, M:F	24:13	21:10	22:10	0.938
Source of admission				
Emergency room	22 (59.5)	19 (61.3)	24 (75)	0.351
Comorbidities				
Hypertension	19 (51.4)	18 (58.1)	12 (37.5)	0.247
Congestive heart failure	6 (16.2)	4 (12.9)	2 (6.3)	0.439
Diabetes	11 (29.7)	11 (35.5)	10 (31.3)	0.874
Chronic kidney disease	7 (18.9)	1 (3.2)	4 (12.5)	0.139
Cancer	8 (21.6)	8 (25.8)	11 (34.4)	0.485
Reasons for admission				
Infection	16 (43.2)	18 (58.1)	15 (46.9)	0.457
Cardiovascular	9 (24.3)	4 (12.9)	4 (12.5)	0.327
Gastrointestinal	1 (2.7)	4 (12.9)	5 (15.6)	0.165
Renal	8 (21.6)	2 (6.5)	6 (18.8)	0.207
Others	3 (8.1)	3 (9.7)	2 (6.3)	0.882
SOFA score	9 [7, 12]	10 [6, 12]	11 [9, 13]	0.251
Respiratory	2 [2, 3]	3 [2, 3]	2 [0, 3]	0.102
Nervous	1 [0, 3]	1 [0, 3]	1 [1, 3]	0.465
Cardiovascular	2 [0, 3]	2 [0, 4]	3 [0, 4]	0.279
Liver	0 [0, 1]	0 [0, 2]	0 [0, 2]	0.228
Coagulation	0 [0, 1]	1 [0, 2]	2 [0, 3]	0.034
Renal	4 [2, 4]	2 [1, 3]	3 [2, 3]	0.015
28-day mortality	21 (56.8)	21 (67.7)	26 (81.3)	0.094

Data are expressed as the median [interquartile range] or number (percentage). Group 1 included patients with a fluid balance of < 1.5 L/day; group 2 included patients with a fluid balance of 1.5-3.0 L/day; and group 3 included patients with a fluid balance of ≥ 3.0 L/day.
SOFA, sequential organ failure assessment.

Timing of CRRT initiation from ICU admission according to daily fluid balance

The median time to start CRRT was 2 [0, 4] days, and the causes of AKI were septic (47.0%), cardiorenal (14.0%), ischemic (9.0%),

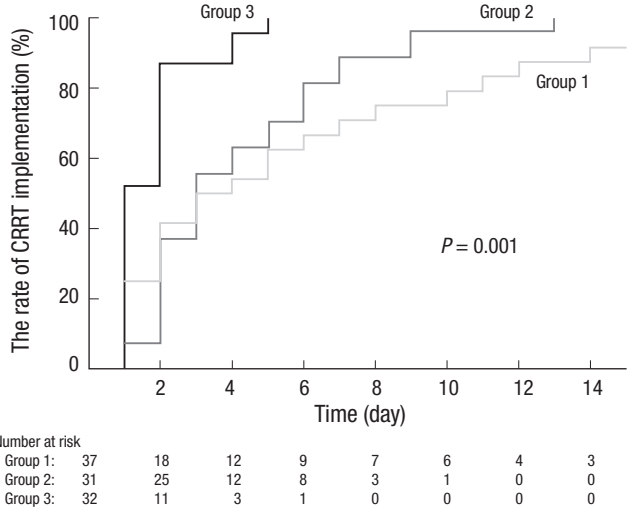

Fig. 1. Time to CRRT according to daily fluid balance in critically ill patients. The time to start CRRT was shortened from group 1 to group 3 (P = 0.001). On day 5, the rate of CRRT implementation was 54.2%, 63.0%, and 95.7% in group 1, 2, and 3, respectively. Group 1 included patients with a fluid balance of < 1.5 L/day; group 2 included patients with a fluid balance of 1.5-3.0 L/day; and group 3 included patients with a fluid balance of ≥ 3.0 L/day.
CRRT, continuous renal replacement therapy.

Table 2. Comparisons at CRRT initiation according to daily fluid balance

Clinical conditions	Group 1 (n = 37)	Group 2 (n = 31)	Group 3 (n = 32)	*P* value
Causes of AKI				0.359
Septic	14 (37.8)	17 (54.8)	16 (50.0)	
Cardiorenal	9 (24.3)	3 (9.7)	2 (6.3)	
Ischemic	4 (10.8)	3 (9.7)	2 (6.3)	
Hepatorenal	3 (8.1)	5 (16.1)	6 (18.8)	
Others	7 (18.9)	3 (9.7)	6 (18.8)	
Time to start CRRT, days	1 [0, 6]	3 [2, 6]	1 [0, 2]	0.003
Central venous pressure, cmH_2O	14 [13, 19]	16 [13, 19]	18 [16, 21]	0.249
Presence of pulmonary edema, No. (%)	21 (56.8)	21 (67.7)	24 (75.0)	0.272
Fractional excretion of sodium, %	5.4 [1.8, 7.3]	1.5 [0.6, 5.4]	1.4 [0.3, 2.8]	0.493
Urine output, mL/hr	10 [2, 32]	14 [6, 29]	11 [7, 22]	0.912
Use of diuretics, %	16 (43.2)	12 (38.7)	21 (65.6)	0.069
Doses of furosemide, mg/day	90 [80, 12]	100 [20, 300]	140 [90, 240]	0.195
SOFA score	11 [8, 14]	15 [12, 17]	17 [13, 18]	< 0.001
Respiratory	1 [0, 4]	3 [2, 3]	3 [2, 4]	0.047
Nervous	3 [2, 3]	3 [3, 4]	4 [3, 4]	< 0.001
Cardiovascular	2 [0, 3]	4 [0, 4]	4 [4, 4]	< 0.001
Liver	0 [0, 2]	1 [0, 2]	2 [0, 2]	0.120
Coagulation	1 [0, 2]	2 [1, 2]	2 [1, 3]	0.001

Data are expressed as the median [interquartile range] or number (percentage). Group 1 included patients with a fluid balance of < 1.5 L/day; group 2 included patients with a fluid balance of 1.5-3.0 L/day; and group 3 included patients with a fluid balance of ≥ 3.0 L/day.
SOFA, sequential organ failure assessment.

hepatorenal (14.0%), and others (16.0%) such as toxic, postrenal or unknown. Table 2 shows the comparison at CRRT initiation among three groups. The causes of AKI did not differ between the groups (P = 0.359, Table 2). The time to CRRT initiation was gradually shortened from group 1 to group 3 (P = 0.001, Fig. 1). Furthermore, positive daily fluid balance from ICU admission to CRRT initiation was related with the acceleration of the requirement of CRRT even after adjustment with age, sex, and the baseline renal SOFA score (HR 1.14, 95% confidence interval [CI] 1.04 to 1.25, P = 0.007).

Organ dysfunction depending on daily fluid balance

The prevalence of organ failure based on the SOFA score was compared between ICU admission and CRRT initiation (Fig. 2). The prevalence of respiratory failure was insignificantly decreased in group 1 but was increased in group 3 (P = 0.085 and 0.075, respectively). Cardiovascular failure became prevalent at CRRT initiation in group 2 and 3, in comparison with at ICU admission (P = 0.010 and 0.004). In addition, the prevalence of nervous failure was increased in group 3 (P = 0.004). However, increases in liver and coagulation failure were not significant (P = 1.000 and 0.196 in group 3).

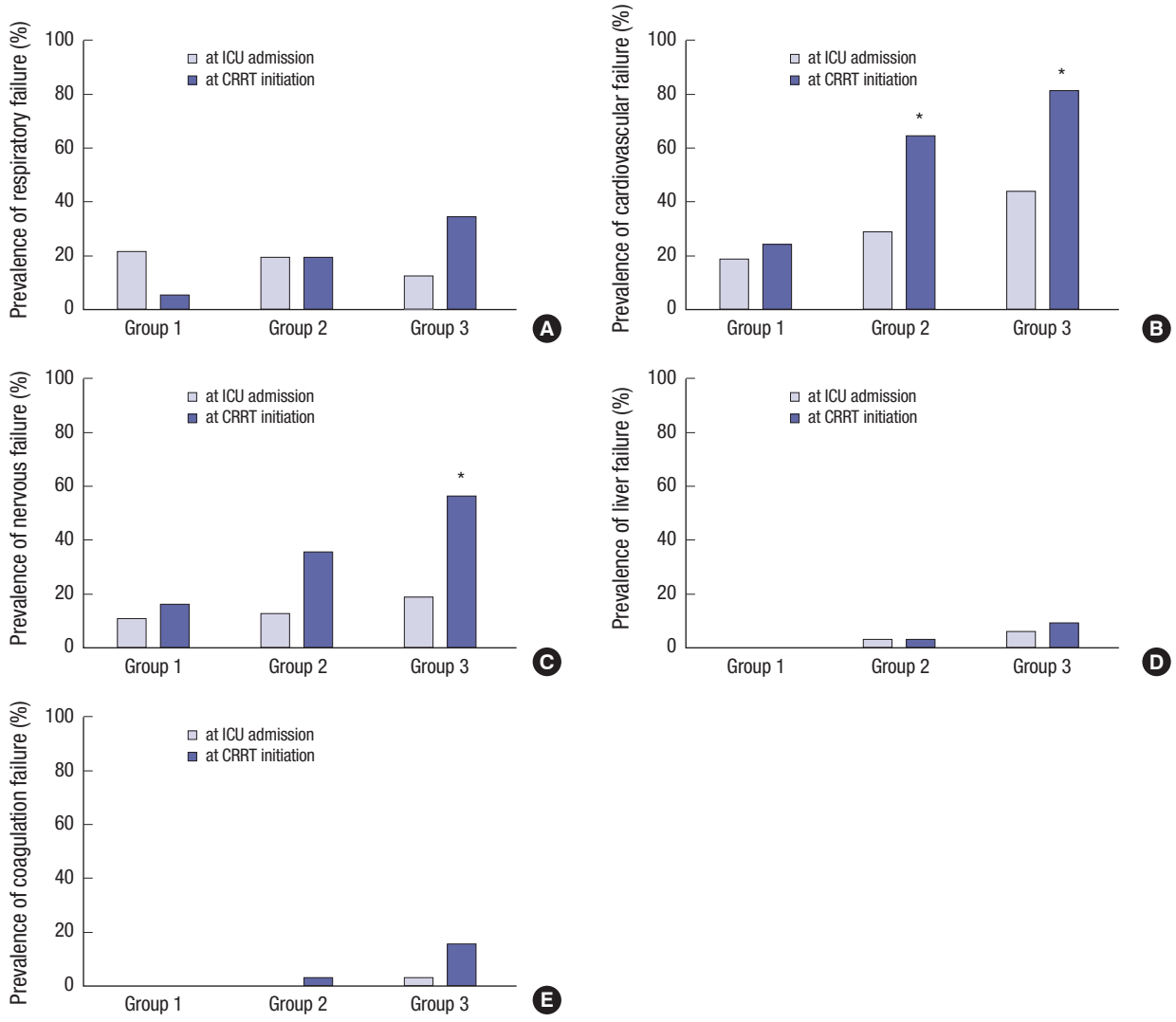

Fig. 2. The comparisons of the prevalence of organ failure between ICU admission and CRRT initiation. (**A**) Changes of the prevalence of respiratory failure did not statistically differ. But it was slightly decreased from 21.6% to 5.4% in group 1, but was increased from 12.5% to 34.4% in group 3 (P = 0.085 and 0.075, respectively). (**B**) Cardiovascular failure became prevalent at CRRT initiation in groups 2 and 3, compared with those at ICU admission (from 29.0% to 64.5% and from 43.8% to 81.3%, P = 0.010 and 0.004, in group 2 and 3, respectively). (**C**) The nervous failure also increased from 18.8% to 56.3% in group 3 (P = 0.004). (**D**) The prevalence of liver failure did not change between ICU admission and CRRT initiation (from 6.3% to 9.4%, P = 1.000 in group 3). (**E**) Although a slight increase in coagulation failure from 3.1% to 15.6% was seen in group 3, this was not statistically significant (P = 0.196). Group 1 included patients with a fluid balance of < 1.5 L/day; group 2 included patients with a fluid balance of 1.5-3.0 L/day; and group 3 included patients with a fluid balance of ≥ 3.0 L/day.
CRRT, continuous renal replacement therapy; ICU, intensive care unit.

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Table 3. Organ failure depending on daily fluid balance prior to CRRT in critically ill patients

Variables	Univariate HR [95% CI]	*P* value	Multivariate* HR [95% CI]	*P* value
Daily fluid balance, L				
Respiratory failure	1.31 [1.14, 1.52]	< 0.001	1.36 [1.15, 1.60]	< 0.001
Cardiovascular failure	1.26 [1.15, 1.38]	< 0.001	1.26 [1.14, 1.40]	< 0.001
Nervous failure	1.27 [1.13, 1.42]	< 0.001	1.24 [1.10, 1.40]	0.001
Liver failure	1.37 [1.02, 1.82]	0.035	1.29 [0.82, 2.04]	0.275
Coagulation failure	1.40 [1.11, 1.77]	0.005	2.26 [1.05, 4.86]	0.038

CI, confidence interval; CRRT, continuous renal replacement therapy; HR, hazard ratio; ICU, intensive care unit; SOFA, sequential organ failure assessment.
*Adjusted by age, sex, and the SOFA score of each organ at ICU admission.

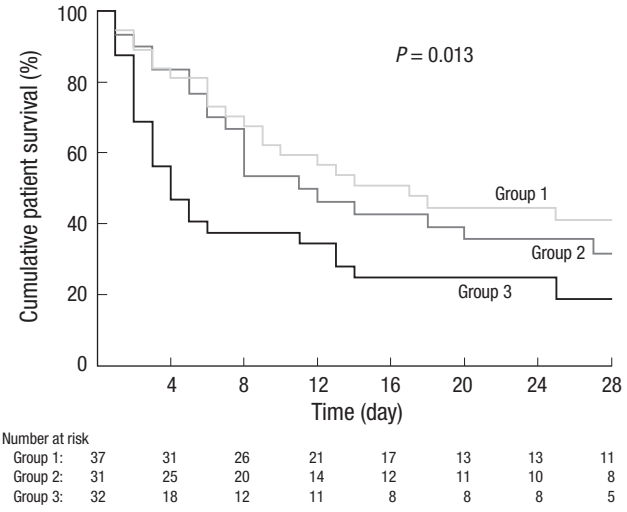

Fig. 3. Twenty-eight-day survival rate according to daily fluid balance prior to CRRT in critically ill patients. The cumulative survival rates differed between the groups (P = 0.013). The 28-day survival rates were 41.0% in group 1, 31.6% in group 2, and 18.8% in group 3. Group 1 included patients with a fluid balance of < 1.5 L/day; group 2 included patients with a fluid balance of 1.5-3.0 L/day; and group 3 included patients with a fluid balance of ≥ 3.0 L/day.
CRRT, continuous renal replacement therapy.

The HR for organ failure depending on daily fluid balance was determined (Table 3). The risk of respiratory failure was increased in proportion to daily fluid balance (HR 1.36, 95% CI 1.15 to 1.60, P < 0.001). We found that positive daily fluid balance was associated with an increase in the probability of cardiovascular failure, independently of age, sex, and the initial cardiovascular SOFA score at ICU admission (HR 1.26, 95% CI 1.14 to 1.40, P < 0.001). In addition, nervous and coagulation failure were related with positive daily fluid balance (HR 1.24 and 2.26, 95% CI 1.10 to 1.40 and 1.05 to 4.86, P = 0.001 and 0.038, respectively). Despite the association between liver failure and positive daily fluid balance in univariate analysis, this was not seen in multivariate analysis (P = 0.275).

Twenty-eight-day mortality rate according to daily fluid balance

Included patients were followed for a median of 10 [3, 26] days from ICU admission until hospital discharge. The median length of ICU stay was 7 [3, 16] days, and the 28-day mortality rate was 68.0%. The duration of ICU stay did not differ between the groups (7 [3, 14] days in group 1, 9 [5, 26] days in group 2 and 4 [2, 14] days in group 3, P = 0.110). However, as Fig. 3 shows, the cumulative survival rate was decreased from group 1 to group 3 (P = 0.013). The 28-day survival rates were 41.0%, 31.6% and 18.8% in group 1, 2, and 3, respectively. In Cox regression analysis, we found that positive daily fluid balance prior to CRRT was associated with an increase in the risk of death in critically ill patients, and this was independent of age, sex, the baseline SOFA score at the time of ICU admission, and causes of AKI (HR 1.14, 95% CI 1.03 to 1.26, P = 0.012, Table 4).

Table 4. Daily fluid balance prior to CRRT for 28-day mortality in critically ill patients

Daily fluid balance, L	HR [95% CI]	*P* value
Univariate	1.11 [1.02, 1.21]	0.014
Multivariate model 1*	1.12 [1.03, 1.22]	0.009
Multivariate model 2†	1.14 [1.04, 1.25]	0.007
Multivariate model 3‡	1.14 [1.03, 1.26]	0.012

CI, confidence interval; CRRT, continuous renal replacement therapy; HR, hazard ratio; ICU, intensive care unit; SOFA, sequential organ failure assessment.
*Model 1 was adjusted by age and sex; †Model 2 was adjusted by age, sex and the total SOFA score at ICU admission; ‡Model 3 was adjusted by age, sex, the total SOFA score at ICU admission and causes of AKI.

Recovery of renal function according to daily fluid balance

A total of 32 patients (16 in group 1, 10 in group 2 and 6 in group 3) who survived at 28 days were followed until 90 days to determine dialysis dependency. Of those, 13 patients (40.6%) successfully terminated CRRT and 19 patients (59.4%) were converted to intermittent hemodialysis. At 90 days from ICU admission, 18 (56.3%) had recovery of renal function, 9 (28.1%) were receiving chronic dialysis, and 5 (15.6%) had been transferred to another hospital with maintaining renal replacement therapy. The incidence of renal recovery did not differ between the groups (6 [37.5%] in group 1, 7 [70.0%] in group 2, and 5 [83.3%] in group 3, P = 0.089). The median duration of renal replacement therapy was 5 [4, 14] days in group 1, 3 [2, 11] days in group 2, and 3 [1, 11] days in group 3, respectively (P = 0.031).

DISCUSSION

We retrospectively investigated the outcomes affected by fluid accumulation in critically ill patients receiving CRRT. The present study found that the implementation of CRRT had been brought forward due to an increase in daily fluid overload prior to initiation of CRRT. Moreover, we found a significant relationship between organ failure including respiratory, nervous, cardiovascular, and coagulation systems, and daily fluid balance. The present study also confirmed that the 28-day mortality was increased in proportion to daily fluid balance prior to CRRT initiation in critically ill patients.

Since the landmark trial of early goal-directed therapy, several concerns regarding fluid accumulation have been raised, and numerous researches have dealt with the impacts of fluid balance on outcomes (4,17-19). Besides, fluid therapy is a major concern in patients with AKI, especially those requiring CRRT, and previous studies have demonstrated an association between fluid overload and mortality in patients who have undergone renal replacement therapy (3,15,20,21). Nevertheless, there is a lack of clinical research regarding the influence of fluid accumulation on various organ systems. Therefore, we evaluated the association between fluid balance and organ dysfunction in critically ill patient receiving CRRT and found that positive fluid balance prior to CRRT might relate the probability of organ failure at the time of CRRT initiation, although the study could not conclude whether fluid balance is a therapeutic target or just a biomarker.

The study showed that positive fluid balance shortened the time to CRRT commencement. Traditionally, liberal fluid therapy has been thought to be good for the kidneys (9,10). However, previous studies have demonstrated that positive fluid balance cannot protect the kidneys (22,23), further it may decrease the likelihood of renal recovery (3,14). Adverse effects of fluid accumulation on the kidneys may be explained by the renal compartment. Due to the fact that the kidney is an encapsulated organ, increases in renal venous pressure associated with volume expansion lead to a lower renal blood flow (24,25). This adverse effect of fluid accumulation on the kidneys has also been shown in patients with heart failure and sepsis (26,27).

Besides the kidneys, the lungs are the most affected organ by fluid overload (28). It is well-known that a conservative fluid strategy improves oxygenation and shortens the duration of mechanical ventilation in critically ill patients (4,5,29). Again, the present study emphasized the importance of restrictive fluid therapy for lung protection. As shown, the prevalence of respiratory failure between ICU admission and CRRT initiation was increased in patients with a fluid balance of ≥ 3.0 L/day, whereas it was decreased in those with a fluid balance of < 1.5 L/day. Due to the fact that mechanical ventilation is an independent risk factor of mortality (6), a conservative fluid strategy to prevent lung injury is required in critically ill patients, especially those requiring RRT.

It is noteworthy that positive fluid balance was associated with cardiovascular failure in the present study. In general, aggressive fluid therapy is performed to maintain blood pressure and to improve cardiovascular function in critically ill patients (1). However, we found that daily fluid balance was a risk factor of cardiac dysfunction. Increased venous return through vasodilation caused by fluid overload may cause cardiac chamber dilatation, increased ventricular wall stress, and functional atrioventricular valvular insufficiency (30). In another aspect, increases in intra-abdominal pressure by fluid overload may lead to reduced venous return, which results in hemodynamic deterioration (31). Because this study was retrospective, we could not conclude the causality, but the association between positive fluid balance and cardiovascular failure was independent of baseline cardiovascular dysfunction assessed by the SOFA score. Further prospective studies are needed to investigate whether positive fluid balance can aggravate the cardiovascular outcome in critically ill patients.

In the present study, there was an association between daily fluid balance and failure of the nervous system. This could be caused because the nervous SOFA score, based on the Glasgow coma scale, is influenced by intubation and use of sedation (32). Accordingly, the nervous SOFA score at the time of CRRT might be prominent in patients with excessive fluid accumulation.

In addition, the study showed increases in the failure of coagulation in patients with positive fluid balance. Although our results could not also exclude increases in platelet consumption in severely ill patients, this coagulopathy might be explained by dilutional coagulopathy, which refers to alterations in the coagulation system induced by aggressive fluid therapy in patients with shock (33). Thus, judicious uses for fluid therapy to prevent undesirable bleeding complications should be performed in critically ill patients requiring excessive fluid administration.

The present study also evaluated liver failure according to daily fluid balance. The risk of liver failure was increased in univariate analysis, but disappeared after adjustment. There are few reports regarding the association between fluid overload and hepatic failure. Since the liver is also an encapsulated organ like the kidney, liver function can be compromised by fluid overload (34). In animal models, increased intra-abdominal pressure caused impairment of hepatic perfusion and inflammatory changes (35,36). However, clinical research is required to confirm these findings.

The present study has several limitations that must be mentioned. Firstly, selection bias should be considered. Due to the fact that the study was not a randomized trial, more severe patients may need aggressive fluid management. Actually, organ failure at ICU admission, with the exception of kidneys and lungs, was more prevalent in patients administered excessive daily

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fluid. To find an independent impact of fluid accumulation on organ systems, we collected the severity score assessed by the SOFA score at ICU admission, and those were used to adjust the data. Consequently, we found the relationship between fluid overload and organ dysfunction, independent of the baseline severity at the time of ICU admission. Secondly, present study did not handle the data after CRRT initiation, such as doses and fluid removal of CRRT. This could influence survival rates. However, this study intended to investigate whether fluid balance prior to CRRT affects the organ dysfunction at the time of CRRT. We deduced that adverse outcomes of organ systems at the time of CRRT initiation may consequently result in worse survival rates in patients receiving CRRT. Thirdly, our small sample size limits the power of the results. However, we demonstrated significant impact of daily fluid balance on various organs, and our results give clinical implications for the treatment of critically ill patients despite a small sample size.

In conclusion, this retrospective study investigated the influence of daily fluid balance prior to CRRT on outcomes including organ failure and 28-day mortality in critically ill patients. Positive daily fluid balance may accelerate the requirement of RRT and may relate unfavorable impacts on various organs. Furthermore, these can influence poor patient survival. Therefore, judicious fluid therapy is necessary in critically ill patients prior to CRRT initiation. Further prospective controlled research is needed, to investigate whether the modification of daily fluid balance can have a beneficial effect on organ dysfunction as well as on patient survival.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Design of the study: Shin J, Kim SH. Collection of data: Han MJ, Park KH, Shin J. Analysis and interpretation of data: Shin J. Drafting the manuscript: Han MJ, Shin J. Critical revision of the manuscript: Shin J. Manuscript approval: all authors.

ORCID

Min Jee Han http://orcid.org/0000-0002-8712-6292
Ki Hyun Park http://orcid.org/0000-0003-0142-027X
Jung-ho Shin http://orcid.org/0000-0001-9755-3100
Su Hyun Kim http://orcid.org/0000-0003-3382-528X

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