An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial*

The RENAL Replacement Therapy Study Investigators

Objective: **To examine associations between mean daily fluid balance during intensive care unit study enrollment and clinical outcomes in patients enrolled in the Randomized Evaluation of Normal vs. Augmented Level (RENAL) replacement therapy study.**

Design: **Statistical analysis of data from multicenter, randomized, controlled trials.**

Setting: **Thirty-five intensive care units in Australia and New Zealand.**

Patients: **Cohort of 1453 patients enrolled in the RENAL study.**

Interventions: **We analyzed the association between daily fluid balance on clinical outcomes using multivariable logistic regression, Cox proportional hazards, time-dependent analysis, and repeated measure analysis models.**

Measurements and Main Results: **During intensive care unit stay, mean daily fluid balance among survivors was −234 mL/day compared with +560 mL/day among nonsurvivors ($p < .0001$). Mean cumulative fluid balance over the same period was −1941 vs. +1755 mL ($p = .0003$). A negative mean daily fluid balance during study treatment was independently associated with a decreased risk of death at 90 days (odds ratio 0.318; 95% confidence interval 0.24−0.43; $p < .000.1$) and with increased survival time ($p < .0001$). In addition, a negative mean daily fluid balance was associated with significantly increased renal replacement-free days ($p = .0017$), intensive care unit-free days ($p < .0001$), and hospital-free days ($p = .01$). These findings were unaltered after the application of different statistical models.**

Conclusions: **In the RENAL study, a negative mean daily fluid balance was consistently associated with improved clinical outcomes. Fluid balance may be a target for specific manipulation in future interventional trials of critically ill patients receiving renal replacement therapy. (Crit Care Med 2012; 40: 1753–1760)**

Key Words: acute kidney injury; continuous renal replacement therapy; hemodialysis; hemofiltration; intensive care; kidney

Fluid resuscitation is considered beneficial in critically ill patients at risk for or with acute kidney injury (AKI) (1), and intravenous fluids are commonly administered to maintain adequate renal perfusion (2–4). This practice paradigm appears common and perhaps dominant in intensive care units (ICUs) worldwide (5–7).

The concept that liberal fluid administration is good for the kidney has been recently challenged (1, 5). Observational studies of patients with AKI have linked a positive fluid balance (FB) before or during renal replacement therapy (RRT) with increased mortality (9–15). More recently, an analysis of AKI patients from the ARDS Network trial of liberal vs. conservative fluid management in acute lung injury patients identified an independent association between positive FB and mortality (16).

The Randomized Evaluation of Normal vs. Augmented Level (RENAL) study (17–20) offers a unique opportunity to explore the association between FB. Accordingly, we conducted a secondary

***See also p. 1970.**

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (http://www.ccmjournal.com).

This study was supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (grant 352550) and Health Research Council (HRC) of New Zealand (grant 06–357).

Professor Alan Cass was supported by a NHMRC Senior Research Fellowship; and received funding from the Australian National Health and Medical Research Council; and received grant support from Roche and Gambro. Professor Rinaldo Bellomo received consulting fees as an advisor for Gambro; and consulted for Gambro, Biosite, Abbott, and Philipps. Professor Simon Finfer has received travel support to present research results at scientific meetings from Eli Lilly, Cardinal Health, and CSL Bioplasma; and received funding from the Australian government. Dr. Gallagher received honoraria/speaking fees from Roche. Dr. Myburgh received funding from the NHMRC (Australia) and honoraria/speaking fees and grant support from Fresenius. Dr. Scheinkestel received funding from the NHMRC and Health Research Council of New Zealand. The remaining authors have not disclosed any potential conflicts of interest.

The George Institute for International Health, an independent not-for-profit institute affiliated with the University of Sydney, has received reimbursement for Professor Finfer's time as a steering committee member for studies sponsored by Eli Lilly and Eisai. The George Institute has received research funding from Servier, Novartis, Eisai, Merck, Sharp & Dohme, Pfizer Australia, Fresenius Kabi Deutschland GmbH, and Sanofi Aventis.

The Randomized Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the George Institute for International Health.

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DOI: 10.1097/CCM.0b013e318246b9c6

analysis of the RENAL study data focusing on the relationship between FB and primary and secondary predefined study outcomes.

MATERIALS AND METHODS

The RENAL study was a multicenter, randomized, controlled trial (RCT) of intensity of continuous renal replacement therapy (CRRT) in 1508 critically ill patients with AKI (17). The Human Research Ethics Committees of the University of Sydney and all participating institutions approved the study.

The methodologic details of the RENAL study were recently reported (17). In brief, patients were eligible for enrollment if they were critically ill adults with AKI, were deemed to require RRT by the treating clinician, and fulfilled predefined criteria (urine output <100 mL/6 hrs unresponsive to fluid resuscitation or a potassium level >6.5 mmol/L or a pH <7.2 or a urea concentration >25 mmol/L or a creatinine level >300 μmol/L or clinically significant organ edema, e.g., lung). The presence of clinically significant organ edema was defined by clinician opinion. This included radiologically confirmed pulmonary edema or visible or palpable organ edema (cardiac or gastrointestinal) at surgery. Eligible patients were randomly assigned to continuous veno-venous hemodiafiltration with effluent flow at 40 mL/kg/hr (higher intensity) or 25 mL/kg/hr (lower intensity). Study treatment was discontinued on death, discharge from ICU, or recovery of renal function. The primary study end point was death from any cause by day 90.

Fluid Balance. FB and cumulative FB data were obtained using data from each study day after randomization until the occurrence of death, ICU discharge, or completion of 28 days from study randomization, whichever occurred first.

No FB data were obtained before randomization. However, clinicians were asked to identify whether a patient did or did not have clinically significant organ edema as described. Daily FB was calculated as the difference between fluid administered (intravenous fluids + blood products + enteral fluids + dialysate + RRT replacement fluids) and fluid lost (dialysis effluent from CRRT [when applied] + urine output + blood losses + enteral losses + drain losses).

A negative FB was present when fluid loss was greater than fluid administered (indicated by a negative sign) and a positive FB was present when fluid removal was less than fluid administered (indicated by a positive sign).

Mean daily FB was calculated for each day during ICU study enrollment. Incomplete study days (day of randomization and day of discharge or death) were considered full data collection days. FB was adjusted for body weight and also calculated as cumulative FB over the period of observation. We also assessed the relationship between FB and the cardiovascular Sequential Organ Failure Assessment (SOFA) score, renal SOFA score, and both albumin levels and albumin therapy.

Statistical Analysis. Continuous variables were expressed as means with SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Comparisons were made using Student *t* test or the Mann-Whitney test when appropriate. Categorical variables were expressed as proportions and compared with the chi-square test or Fisher exact test as appropriate.

Mean daily FB-related variables and all baseline variables (biochemical, demographic, clinical, and illness severity-related) were used to create a multivariate logistic regression model using mortality at 90 days as the dependent variable. Such models included a propensity score. The propensity score was estimated

Table 1. Baseline characteristics and outcome of patient with a mean daily positive vs. negative fluid balance

Baseline Characteristics	Positive Mean Daily Fluid Balance, n = 705	Negative Mean Daily Fluid Balance, n = 748	*p*
Age	64.5 (14.7)	64.7 (14.9)	.85
Male	446/705 (63.3%)	491/748 (65.6%)	.34
Estimated glomerular filtration rate	57.9 (32.7)	55.2 (29.4)	.21
Mechanical ventilation	548/705 (77.7%)	523/748 (69.9%)	<.001
Severe sepsis at baseline	371/705 (52.6%)	348/748 (46.5%)	.02
Acute Physiology and Chronic Health Evaluation III score	106.8 (26.7)	98.2 (24.0)	<.0001
SOFA cardiovascular	3.0 (1.5)	2.7 (1.6)	<.001
SOFA respiration (score)	2.8 (1.0)	2.7 (0.9)	.03
SOFA coagulation (score)	1.0 (1.2)	0.9 (1.1)	.08
SOFA liver (score)	1.0 (1.2)	0.9 (1.2)	.60
Weight	79.9 (12.9)	81.4 (12.9)	.03
Source of admission			.
Accident and emergency department	194/658 (29.5%)	152/701 (21.7%)	<.01[a]
Hospital floor/ward	182/658 (27.7%)	203/701 (29.0%)	—
Transfer from another intensive care unit	58/658 (8.8%)	53/701 (7.6%)	—
Transfer from another hospital	73/658 (11.1%)	79/701 (11.3%)	—
Admitted from operating theater/recovery after emergency surgery	88/658 (13.4%)	115/701 (16.4%)	—
Admitted from operating theater/recovery after elective surgery	63/658 (9.6%)	99/701 (14.1%)	—
Nonoperative admission diagnosis			—
Cardiovascular	298/531 (56.1%)	230/511 (45.0%)	.01[a]
Genitourinary	94/531 (17.7%)	135/511(26.4%)	—
Gastrointestinal	35/531 (6.6%)	40/511 (7.8%)	—
Hematology	14/531 (2.6%)	8/511 (1.6%)	—
Metabolic/endocrine	12/531 (2.3%)	13/511 (2.5%)	—
Neurologic	7/531 (1.3%)	4/511 (0.8%)	—
Respiratory	67/531 (12.6%)	78/511 (15.3%)	—
Transplant	3/531 (0.6%)	2/511 (0.4%)	—
Trauma	1/531 (0.2%)	1/511 (0.2%)	—
Operative admission diagnosis			—
Cardiovascular	111/174 (63.8%)	156/237 (65.8%)	.1260[a]
Genitourinary	2/174 (1.1%)	2/237 (0.8%)	—
Gastrointestinal	44/174 (25.3%)	54/237 (22.8%)	—
Neurologic	5/174 (2.9%)	2/237 (0.8%)	—
Respiratory	3/174 (1.7%)	5/237 (2.1%)	—
Transplant	0/174 (0.0%)	9/237 (3.8%)	—
Trauma	9/174 (5.2%	9/237 (3.8%)	—
Plasma urea (mmol/L)	22.9 (12.8)	23.8 (12.3)	.1323
Creatinine at randomization (μmol/L)	326.7 (214)	346.6 (202)	.0684
pH	7.2 (0.1)	7.3 (0.1)	<.0001
Bicarbonate (mmol/L)	17.5 (6.2)	19.1 (5.4)	<.0001
Base excess (mmol/L)	−29.3 (7.4)	−27.3 (6.4)	<.0001
Outcomes			
Number of renal replacement therapy-free days	15.1 (11.6)	19.7 (8.9)	<.0001
Number of intensive care unit-free days	37.2 (39.5)	60.4 (34.4)	<.0001
Number of hospital-free days	23.5 (31.6)	40.8 (33.2)	<.0001
Mechanical ventilation-free days	37.7 (39.5)	59.8 (36.0)	<.0001
Number of deaths at 90 days	403/705 (57.2%)	241/747 (32.3%)	<.0001

SOFA, Sequential Organ Failure Assessment.

Continuous variables expressed as mean with SD in brackets.

Nominal variables expressed as number with percentage in brackets. All values obtained at randomization.

[a]Value for overall comparison.

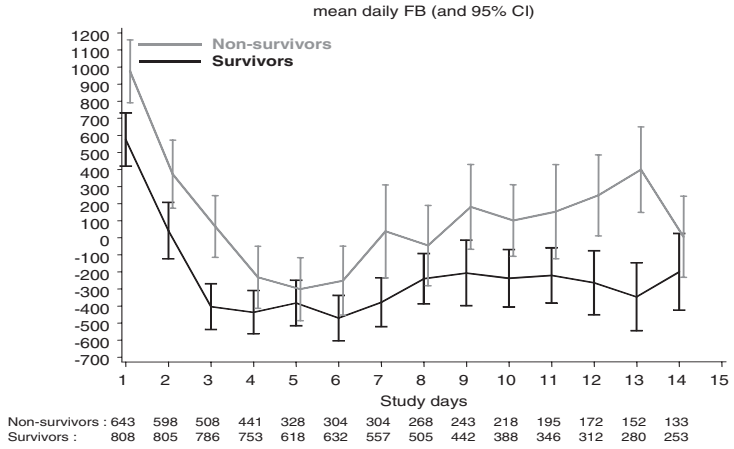

Figure 1. Graphic representation of mean daily fluid balance over the first 2 wks of observation after randomization according to survival status at 90 days (survivors = *continuous line*; nonsurvivors = *broken line*). The *y-axis* indicates mean daily fluid balance in mL/d. Mean daily FB during was significantly more positive in nonsurvivors. The *minus sign* indicates a negative fluid balance. For each study day on *x-axis*, the number of patients analyzed is also reported. The *vertical line* indicates the mean duration of renal replacement therapy at 6 days. *CI*, confidence interval.

by using a multivariate logistic regression of patients receiving positive mean daily fluid balance (MDFB) or not. The model included all available hospital characteristic variables in this study, such as country, region, and type of hospital. Patients are then divided into four strata based on the quartile of the estimated probabilities of receiving positive MDFB. This latter variable is included as covariate in the death at 90 days of analysis.

Multivariate linear regression analysis was used to assess the relationship between FB and mechanical ventilation-free days, RRT-free days, ICU-free days, and hospital-free days at 90-day follow-up as the dependent variables. Analysis of time to death within 90 days of randomization used the Kaplan-Meier product limit estimates and compared survival curves using the log-rank test.

To test the robustness of any association between mortality and FB, additional models were applied to data analysis. These models included time-dependent modeling, repeated measure modeling, and Cox proportional hazards modeling, all with adjustment with the following prespecified variables: treatment group, all Acute Physiology and Chronic Health Evaluation III diagnostic groups, daily use of CRRT, age, time from ICU to randomization, presence of sepsis, SOFA respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of nonrenal organ failure, international normalized ratio for prothrombin time, activated partial thromboplastin time, platelet count, serum creatinine, Pao_2/Fio_2 ratio, $Paco_2$, use of mechanical ventilation, and clinical diagnosis of significant edema at randomization.

A two-sided $p < .05$ was used to indicate statistical significance. Statistical analyses were performed and independently checked with the use of SAS software version 9.1.

RESULTS

Of the 1508 patients enrolled in the RENAL study, complete FB data to ICU discharge or 28 days or death (whichever occurred first) were available for 1453 (96.3%). During ICU stay, 705 (48.2%) patients had a positive MDFB and 748 (51.8%) a negative MDFB develop. The characteristics and outcomes of these patients are compared in Table 1. Patients with a negative MDFB had lower Acute Physiology and Chronic Health Evaluation III and cardiovascular SOFA scores at randomization and were less likely to have been admitted from the emergency department. Among patient with a negative MDFB, 241 (32.3%) had died by 90 days after randomization, compared with 403 (57.2%) in the positive MDFB group ($p < .0001$). Furthermore, survivors had a negative MDFB whereas nonsurvivors had a positive MDFB (Table 2).

The difference in MDFB between survivors and nonsurvivors was detectable on the day of randomization and persisted on subsequent days (Fig. 1). On day 1, both groups had a positive MDFB. However, survivors had a more negative MDFB, reached a near-neutral MDFB the next day (day 2), and had a negative MDFB every day thereafter. Nonsurvivors reached a slightly negative MDFB only by day 4, remained with a near-neutral MDFB for a few days, returned to a positive MDFB by day 9, and remained with a positive MDFB thereafter. Patients with organ edema, however, had a more negative MDFB (−26.3 vs. +230.8 mL; $p < .0001$) and cumulative FB (−1616 vs. 724.6 mL; $p < .0001$; see online Appendix for further details).

Patients with a negative MDFB had an average of 4.5 days of vasopressor therapy vs. 5.0 days for patients with a positive FB ($p = .07$). Patients who were receiving vasopressor therapy at randomization had more negative MDFB days than patients not receiving vasopressor support (5.5 vs. 4.8 days; $p = .01$) and, during treatment, there were more negative MDFB days when the cardiovascular SOFA score was 0-2 than when it was 3 or 4 (4.7 vs. 3.4

Table 2. Daily and cumulative fluid balance according to survival status at 90 days after randomization

Fluid Balance, No. of Patients, Mean, SD, Quartile 1 Median, Quartile 3 Days With Missing Data	Nonsurvivors	Survivors	p^a
Mean daily FB during time in ICU[a]	644	808	<.0001
	560.0 (1494)	−234 (852)	
	−274 305.2 1116	−738 −226 254.9	
	10	2	
Weight-adjusted mean daily FB during time in ICU	644	808	<.0001
	7.2 (19.1)	−2.7 (10.8)	
	−3.6, 4.0 14.3	−8.7 −2.6 3.1	
	10	2	
Mean cumulative FB during time in ICU	644	808	<.0001
	1755 (9061)	−1941 (11,000)	
	−2310, 1518, 5922	−6863, −1928, 2240	
	10	2	
Weight-adjusted mean cumulative FB during time in ICU	644	808	<.0001
	22.5 (119)	−22.3 (131)	
	−29.5, 18.8, 75.2	−85.0, −23.6, 28.4	
	10	2	

FB, fluid balance; ICU, intensive care unit.

[a]Refers to index admission to a maximum of 28 days.

Weight adjusted indicates FB in mL/patient weight in kg. Patient numbers add to 1452. Patient 1453 had missing outcome data.

days; $p < .0001$). In addition, in patients with an albumin level below the median at baseline, a negative MDFB was recorded on 5.4 days compared with 5.2 days in patients with an albumin level above the median ($p = .66$). Finally, a similar amount of albumin was administered to patients with a negative vs. positive MDFB (68.8 vs. 76.3 g; $p = .29$).

There was a more positive MDFB in patients with a renal SOFA score of 1 to 2 compared to patients with a score of 3 or 4 (Supplemental Digital Content 1, http://links.lww.com/CCM/A408). Finally, cessation of CRRT was associated with decreased ability to maintain a neutral MDFB. The MDFB was +20.9 mL/day during 4329 CRRT days but +402.2 mL ($p = .0035$) on the 1,150 days after CRRT was stopped (Supplemental Digital Content 1, (http://links.lww.com/CCM/A408).

On univariate analysis, all measures of FB considered and several baseline variables had a significant association with 90-day mortality (online Appendix). On multivariable logistic regression analysis, however, only a few of these variables remained independently associated with 90-day mortality (Table 3). Importantly, a negative MDFB was associated with a close to 70% reduction in the odds ratio for death at 90 days. Essentially identical findings were seen when the MDFB during study treatment was used in the model or when the model was applied to patients with significant organ edema (n = 639) or without clinically significant organ edema (n = 814) at randomization (online Appendix). These findings were not materially affected by the presence or absence of sepsis or by the inclusion of a propensity score (Supplemental Digital Content 1, http://links.lww.com/CCM/A408).

Survival plots were also compared according to the presence or absence of a positive MDFB in the first 2 days after randomization and from day 2 until the end of data collection during the index ICU admissions. Both analyses showed increased mortality in patients with early or late positive MDFB ($p < .0001$) (Figs. 2 and 3). These differences in outcome were confirmed by Cox proportional hazards modeling comparing quartiles of MDFB (Fig. 4). Assessment of quintiles of MDFB showed a progressive increase in mortality, with the greatest positive MDFB quintile having a five-fold increase in the risk of death compared to the first quintile (Fig. 5).

All measures of positive FB also showed an association with decreased RRT-free days at day 90 after randomization (online Appendix). On multivariable linear regression analysis, however, only a few of these variables remained independently associated with decreased RRT-free days at 90 days, including a positive MDFB ($p = .0017$). Similar findings were seen when the outcomes were mechanical ventilation-free days, ICU-free days, or hospital-free days (Supplemental Tables, Supplemental Digital Content 1, http://links.lww.com/CCM/A408).

When these associations was tested by means of additional univariate and sensitivity analyses, comparisons, time-dependent modeling, repeated measure modeling, and Cox proportional hazards modeling, the findings remained essentially unchanged (Supplemental Digital Content 1, http://links.lww.com/CCM/A408).

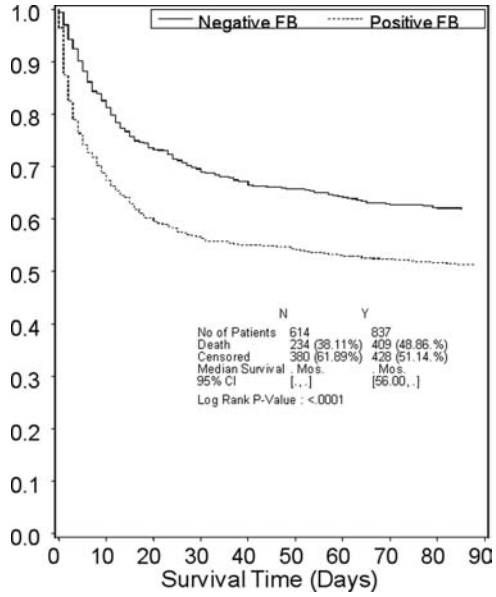

Figure 2. Kaplan Meier graph of survival plots from randomization to day 90 stratified by the presence or absence of a positive fluid balance (*FB*) from day 0 to day 2. The findings are similar to those seen when separating patients according to FB later during their time in intensive care unit. *CI*, confidence interval.

DISCUSSION

Statement of Key Findings

Using data from a large, multicenter RCT of the intensity of CRRT in critically ill patients with AKI, we assessed the association between FB from randomization until ICU discharge or 28 days or death (whichever occurred first) and outcome. We found that during the time of observation in ICU, a negative MDFB was associated with a significantly lower mortality than a positive MDFB and that whereas survivors had a negative MDFB, nonsurvivors had a positive MDFB. This key observation was true even when FB in the first 48 hrs only was considered. Furthermore, a negative MDFB was independently associated with a near 70% decrease in the odds ratio for mortality. This relationship was present in patients with or without the

Table 3. Multivariable logistic regression with death at 90 days after randomization as outcome[a]

Variable	Effect (Discrete Variable)	Odds Ratio	95% Confidence Interval	*p*
Negative mean daily fluid balance during index admission to intensive care unit[b]	No vs. yes	0.318	0.24-0.43	<.0001
Age		1.033	1.02-1.04	<.0001
Time from intensive care unit admission to randomization (d)		1.002	1.00-1.04	0.0065
Acute Physiology and Chronic Health Evaluation III score		1.012	1.01-1.02	0.0002
Sequential Organ Failure Assessment liver (score)		1.224	1.07-1.40	0.0033
International normalized ratio for prothrombin time		1.277	1.08-1.51	0.0047

[a]Only variables with $p < .05$ presented; [b]data collected to a maximum of 28 days.

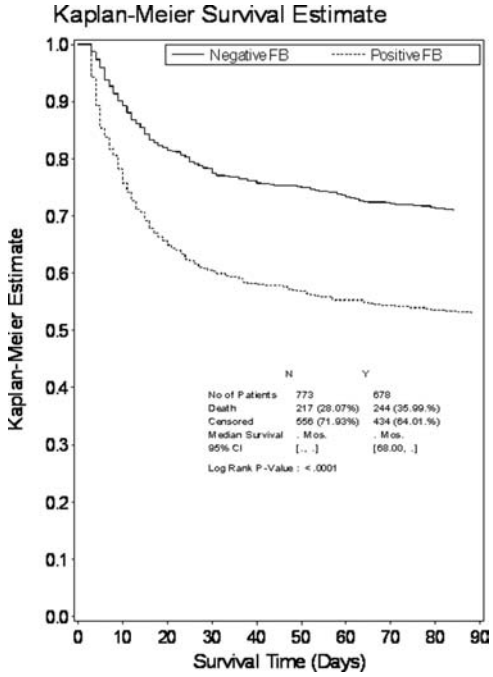

Figure 3. Kaplan Meier graph of survival time from randomization to day 90 stratified by the presence or absence of a positive fluid balance (*FB*) after the first 2 days of treatment had been removed and including all FB assessment over the index intensive care unit admission. The difference in outcome is similar in nature to that seen when separating patients according to FB in the first 2 days of management and is highly significant. *CI*, confidence interval.

clinical diagnosis of significant edema at randomization. A negative MDFB was also associated with better outcomes in terms of RRT-free days, mechanical ventilation-free days, ICU-free days, and hospital-free days. When we applied propensity analysis, time-dependent modeling, repeated measure modeling, and Cox proportional hazards modeling, our findings remained unchanged.

Comparison With Previous Studies

Our findings are in agreement with and expand those of previous observational studies (6–13). In all of these studies, the relationship between FB and outcome typically related to both before and during treatment with RRT. However, the relationship between timing of RRT and FB was not studied. In our patients, no numerical information was available to estimate the degree of fluid overload before RRT. However, 639 patients were assessed as having clinically significant vital organ edema at randomization. The cumulative FB difference between survivors and nonsurvivors was close to 5% of body weight (approximately 3.5 L in an average 80-kg person). This difference in cumulative FB has been previously associated with unfavorable outcome (10, 11).

Our data expand our understanding of the relationship between FB and outcome. They provide independently monitored and verified information with independent data verification and negligible missing data. They also provide such information in the setting of essentially exclusive CRRT use. This difference is important because intermittent hemodialysis may result in a more positive FB (11) and has limited ability to control volume status in patients with AKI (11). With CRRT, volume control is typically always possible. Thus, FB in this setting likely reflects therapeutic choices rather than technical limitations (22–24).

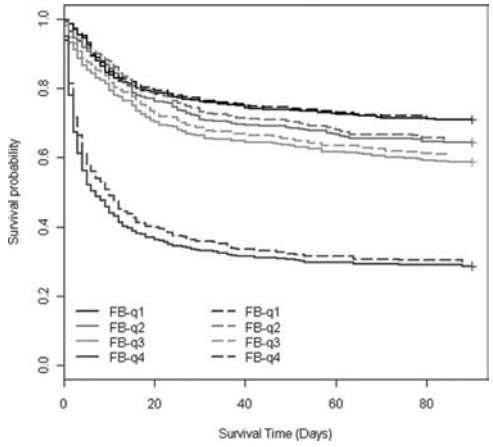

Figure 4. Cox proportional hazards survival plot with adjustment for treatment group, all Acute Physiology and Chronic Health Evaluation III diagnostic groups, daily use of continuous renal replacement therapy, age, time from intensive care unit to randomization, presence of sepsis, Sequential Organ Failure Assessment (SOFA) respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of nonrenal organ failure, international normalized ratio for prothrombin time, activate partial thromboplastin time, platelet count, serum creatinine, Pao_2/Fio_2 ratio, $Paco_2$ days, and clinical diagnosis of significant edema at randomization. The quartile 1 to quartile 4 refer to fluid balance (*FB*). The *broken line* refers to patients with a positive mean daily FB, whereas the *continuous line* refers to patients with a negative mean daily FB. In both groups of patients, there is a significant increase in mortality according to quartile of FB, such that the greater the mean daily FB, the greater the risk of death. *q*, quartile.

Significance of Study Findings

Our study provides additional evidence of an independent association between a negative FB and decreased 90-day mortality. It also raises the possibility that the pursuit of a positive FB is potentially deleterious.

The association between a positive FB and adverse outcome may simply represent the fact that a positive FB is a marker of illness severity, as suggested by higher Acute Physiology and Chronic Health Evaluation III and cardiovascular SOFA scores at randomization. However, the association remained after adjustment for propensity and all available markers of illness severity at randomization, suggesting that differences in illness severity may not fully account for our findings. The consistent association between a positive FB and unfavorable outcome suggests the need to exert prudence with fluid administration in patients with AKI (22). If a negative FB in considered unsafe because of patient instability, then our findings suggest the need to consider a negative FB as soon as it appears clinically safe to do so.

A positive FB may simultaneously act as a biomarker and mediator of illness

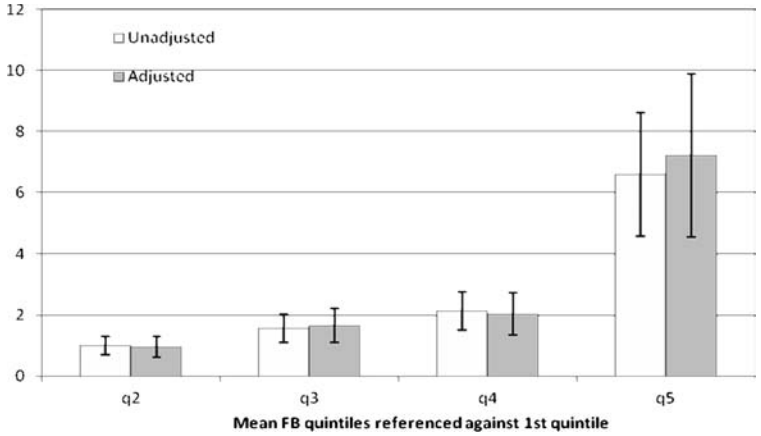

Figure 5. Changes in 90-day mortality according to quintiles of mean daily fluid balance (*FB*) during study observation period with or without adjustment for baseline characteristics.

severity, with each aspect occurring to a degree that cannot yet be quantified. Only RCTs can address these issues. However, such trials are only justified if observational studies such as ours support the need to test the hypothesis that the pursuit of a negative FB may improve outcomes. This hypothesis now seems to apply to FB management in AKI patients. This is similar to the field of acute lung injury, in which the hypothesis that a positive FB negatively impacts outcome was tested and confirmed true in RCT.

Study Strengths and Limitations

We cannot provide information on FB before treatment. However, although the definition of edema had a subjective component, close to 44% had edema at randomization, suggesting fluid overload. Their inclusion in multivariable analysis did not affect studies finding the association between a positive FB and outcome, and such patients behaved in relation to FB in the same way as those without edema at randomization. Despite such limitations, a relationship still emerged between FB and outcome, suggesting that FB may be an important physiologic variable and that its management may affect patient-centered outcomes. We reported the association of FB with a variety of intervention-free days-related outcomes. Such "intervention-free days" were chosen in preference to "duration of treatment days" because, although both outcome measures are confounded by the competing effect of mortality, free-days penalize mortality by allocating a value of 0 intervention free-days to patients who die while receiving treatment, whereas the "duration of treatment days" approach "rewards" mortality by allocating it a value of 0 treatment days.

Finally, as in all other observational studies, the relationship between FB and outcome may not be causal. We note, however, that our findings are analogous with an RCT in patients with acute lung injury (21) and observational studies in septic patients (25), and are suggestive of a functional relationship between an observed variable (FB in this case) and outcome (26). In addition, a possible causal relationship between a 2- and 3-kg fluid-induced gain in body weight (as seen in our patients) and outcome is supported by randomized controlled evidence (27) showing a progressive increase in complications (anastomotic breakdown, sepsis, bleeding, pulmonary edema, and arrhythmias), with increases from 0.5 to <2.5 to >2.5 kg in postoperative weight. Such complications appear biologically plausible because gut edema can weaken anastomotic strength (28) and function (29, 30), excessive fluid therapy can induce dilutional coagulopathy (31), pulmonary edema can cause hypoxemia, which, in turn, can predispose to arrhythmias, and cardiac edema can also contribute to such complications (29).

Table 4. Multivariable linear regression with renal replacement therapy-free days as outcome

Variable	Estimates	Standard Error	*p*
Intercept	−142.02968	80.90755	.0800
Positive mean daily fluid balance during index intensive care unit admission*	−4.29606	1.35909	.0017
Patients weight (kg)	0.07610	0.03859	.0493
Time from intensive care unit admission to randomization (days)	−0.01299	0.00485	.0077
Overall Sequential Organ Failure Assessment score (all nonmissing organ scores lumped together/5)	−3.68006	1.19039	.0021
Chloride (mmol/L)	0.35592	0.12614	.0050
pH	20.81819	10.26559	.0432

Only variables with $p < .05$ presented.

Future Investigations

Our study suggests that FB (a variable that can be manipulated during CRRT) may affect patient outcome in patients with AKI. Further investigations should now be directed at testing the feasibility of the conservative vs. liberal approaches of RCTs to FB in patients with or at high risk for AKI in a manner similar to studies conducted in patients with acute lung injury (21).

CONCLUSION

In the RENAL study, patients with a positive FB had higher mortality rate than those with a negative FB. After correction for multiple confounding variables and the application of different statistical modeling techniques, a negative FB was independently associated with a decreased risk of death at 90 days. These findings suggest the need for RCTs to test the hypothesis that a conservative FB can improve outcome in patients with AKI.

ACKNOWLEDGMENTS

We thank Professor Carol Pollock and Professor Peter Kerr for their assistance with protocol development, and Dr. Peter Stow for his assistance with APACHE III software application. We thank Gambro for providing discounted pricing for hemosol dialysate and replacement fluids, and the nurses in our intensive care units, our physician colleagues, and our patients and their families for the support of this trial.

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