Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury

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Summary

Background and objectives Management of volume status in patients with acute kidney injury (AKI) is complex, and the role of diuretics is controversial. The primary objective was to elucidate the association between fluid balance, diuretic use, and short-term mortality after AKI in critically ill patients.

Design, setting, participants, & measurements Using data from the Fluid and Catheter Treatment Trial (FACTT), a multicenter, randomized controlled trial evaluating a conservative versus liberal fluid-management strategy in 1000 patients with acute lung injury (ALI), we evaluated the association of post-renal injury fluid balance and diuretic use with 60-day mortality in patients who developed AKI, as defined by the AKI Network criteria.

Results 306 patients developed AKI in the first 2 study days and were included in our analysis. There were 137 in the fluid-liberal arm and 169 in the fluid-conservative arm ($P = 0.04$). Baseline characteristics were similar between groups. Post-AKI fluid balance was significantly associated with mortality in both crude and adjusted analysis. Higher post-AKI furosemide doses had a protective effect on mortality but no significant effect after adjustment for post-AKI fluid balance. There was no threshold dose of furosemide above which mortality increased.

Conclusions A positive fluid balance after AKI was strongly associated with mortality. Post-AKI diuretic therapy was associated with 60-day patient survival in FACTT patients with ALI; this effect may be mediated by fluid balance.

Introduciton

Optimal fluid management in acute kidney injury (AKI) is controversial. Traditionally, aggressive fluid resuscitation has been prescribed in AKI to avoid additional prerenal or hemodynamic insults during ongoing renal dysfunction (1–3). More recently, however, observational studies have demonstrated an association between a positive fluid balance, renal non-recovery, and mortality in children and adults with AKI (4–7).

Interpretation of studies evaluating the relationship between fluid balance and mortality is complex. Worsening renal function and associated oliguria may drive fluid accumulation rather than vice versa. Sicker patients may receive more intravenous fluids, either intentionally through a strategy of aggressive volume expansion or secondarily as carriers for vasopressors, antibiotics, and nutrition. A positive fluid balance may simply be a marker of poor health rather than a cause of mortality, especially in observational studies.

Diuretics further complicate the fluid accumulation-mortality association. Once considered a therapy for oliguria, diuretics are clearly ineffective in preventing or treating AKI (8,9). Moreover, some observational studies have demonstrated associations between diuretics and death and renal non-recovery in AKI (1,10). Many clinicians thus avoid diuretics in AKI because of concern that they may induce intravascular hypovolemia as well as exacerbate renal dysfunction and electrolyte abnormalities (11,12).

To date, no randomized controlled trial has evaluated different protocols of fluid management as therapy for AKI. In contrast, there have been several randomized controlled trials evaluating fluid-management strategies in mechanically-ventilated patients in intensive care units (ICUs) (13–16). Each of these trials demonstrated improved oxygenation or shorter mechanical ventilation requirements with a more restrictive fluid-management strategy, and none of the trials found a clinically relevant difference in renal function between the groups. However, these restrictive strategies relied on higher doses of diuretics to achieve and maintain diuresis.
The Fluid and Catheter Treatment Trial (FACTT) was the largest and only multicenter trial of a fluid-restrictive management strategy for the treatment of acute lung injury (ALI) (16). Although there was no demonstrated mortality benefit, the fluid-restrictive management strategy was associated with an increased number of ventilator-free days and a trend toward a reduced requirement for renal replacement therapy. The relationship between daily fluid balance and outcomes in the cohort of participants who experienced AKI has not been described. Because fluid and diuretic management were determined primarily by randomization and hemodynamic measures, data from the FACTT trial present a unique opportunity to analyze the relationship between fluid status, diuretics, and outcomes in critically ill patients with AKI, while minimizing the potential confounding by indication seen in an observational study. We hypothesized that positive fluid balance and diuretic therapy after AKI are independently associated with mortality in patients with ALI.

Study Population and Methods

Original Trial: Brief Description of Protocol and Outcomes

The FACTT trial evaluated two fluid-management strategies in patients with ALI, randomizing 1000 ventilated patients in a two-by-two factorial design to either conservative or liberal fluid management and a pulmonary-artery or a central venous catheter for hemodynamic monitoring (16,17). The study protocols were approved by the institutional review board at each participating center, and the patients or their surrogates consented to study participation. The study design and results have been previously published (16).

Fluid management was directed for up to 7 days by a prespecified algorithm on the basis of on-study hemodynamic measurements. Intravascular pressure, measures of circulatory adequacy, and hourly urine-output measurements were used to determine administration of a fluid bolus or a diuretic, with lower intravascular pressures directing diuresis in the conservative arm compared with the liberal arm (16). The primary outcome of the original FACTT study was death by day 60. Secondary outcomes included renal failure within 7 and 28 days defined by the Brussels criteria, and dialysis requirement before day 60. Included renal failure within 7 and 28 days defined by the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) criteria (19), and using Cox proportional hazards models. Given the large number of potential covariates relative to the number of outcomes, we limited the number of covariates in the “final model,” choosing the following for face validity, consistency with previous studies, or suspected strong confounding: age, gender, race, fluid and catheter randomization group, log-APACHE III score, study day of AKI, mean daily presence of shock, and mean daily CVP. We did not include fluid balance or furosemide dose in the final models evaluating the furosemide dose-mortality and fluid balance-mortality relationships, respectively, because of concern that these covariates were causal intermediates. The final model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test across deciles of risk.

Sensitivity analyses utilized the following prespecified subgroups: gender, fluid-management group, the presence of oliguria in the first 7 days (“early oliguria”), and maximum achieved serum creatinine in the first 7 days. Additional sensitivity analyses were performed excluding patients who died before receiving the full 7 days of protocolized therapy, defining AKI by the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) criteria (19), and using Cox proportional hazards models. Data analysis was conducted using Stata 11.0/SE (StataCorp, College Station, TX).

Study Population and Methods

Inclusion Criteria and Data Definitions of This Study

In this study, only patients developing AKI within 2 days on-study were included (n = 306). The time limit for AKI was designed to limit heterogeneity in the duration of fluid-management intervention relative to the duration of AKI and to match the Acute Kidney Injury Network (AKIN) stage 1 criteria (a 50% or 0.3 mg/dl increase in serum creatinine from baseline, occurring over 48 hours or less) (18). This differs from the parent trial, where renal failure was defined as a serum creatinine greater than 2 mg/dl using the Brussels criteria. Baseline serum creatinine was estimated by averaging up to three measures collected in the 24 hours prerandomization. Hourly urine-output data were not available in the FACTT study, so we did not use the AKIN urine-output criteria (18).

The primary outcome of our study was 60-day mortality after randomization. Fluid balance was calculated as the mean daily difference between fluid intake and fluid output from the development of AKI until study day 7, death, or withdrawal from study, whichever was earliest. Fluid output included all body fluids, including urine and, if applicable, dialysis ultrafiltrate. Mean daily furosemide dose was captured over the same period. Baseline severity of illness was estimated by the enrollment APACHE III score. Shock was defined as mean systemic arterial pressure below 60 mmHg or the need for a vasopressor. Baseline central venous pressure (CVP) was defined as the measured intravascular pressure on study day 1. Because fluid output measured during the trial did not distinguish urine from other body fluid losses, oliguria was defined conservatively as a daily fluid output less than 0.5 L.

Data Analyses

We estimated the association of post-AKI mean fluid balance and furosemide dose with 60-day mortality using logistic regression models. Lowess smoothed non-parametric regressions were used to visualize the relationship between predictors and mortality. Baseline APACHE III scores were log-transformed to achieve a more normal distribution. We assessed the robustness of the associations by the stepwise addition of potential confounders (resulting in the “full model”). Given the large number of potential covariates relative to the number of outcomes, we limited the number of covariates in the “final model,” choosing the following for face validity, consistency with previous studies, or suspected strong confounding: age, gender, race, fluid and catheter randomization group, log-APACHE III score, study day of AKI, mean daily presence of shock, and mean daily CVP. We did not include fluid balance or furosemide dose in the final models evaluating the furosemide dose-mortality and fluid balance-mortality relationships, respectively, because of concern that these covariates were causal intermediates. The final model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test across deciles of risk.

Sensitivity analyses utilized the following prespecified subgroups: gender, fluid-management group, the presence of oliguria in the first 7 days (“early oliguria”), and maximum achieved serum creatinine in the first 7 days. Additional sensitivity analyses were performed excluding patients who died before receiving the full 7 days of protocolized therapy, defining AKI by the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) criteria (19), and using Cox proportional hazards models. Data analysis was conducted using Stata 11.0/SE (StataCorp, College Station, TX).
Results

Characteristics of Participants Experiencing AKI

Of the 1000 FACTT participants, 306 developed stage 1 or worse AKI within 2 study days of enrollment. Slightly more participants were in the fluid-conservative arm than the fluid-liberal arm (169 versus 137, or 33.8% versus 27.4% of the original groups, $P = 0.04$). Most (59.2%) developed stage 1 AKI. Baseline and on-study characteristics of included participants, stratified by fluid-management strategy, are shown in Table 1. The groups were similar with the exception of baseline albumin levels, fluid balance in the 24 hours prerandomization, and proportion with aspiration as an etiology of ALI. There was no significant difference in mortality rate or time to death between the two groups.

Fluid and Furosemide Exposure in the Study Population

On average, participants with AKI assigned to the fluid-conservative group received more furosemide (80 mg/d versus 23 mg/d in the fluid-liberal group, $P = 0.001$) and had less fluid accumulation (0.9 L/d versus 2.2 L/d in the fluid-liberal group, $P < 0.001$). The mean cumulative fluid balance over a participant’s protocolized study period (mean, 6.0 days, SD, 1.8 days) was 3.7 L in the fluid-conservative arm and 10.2 L in the fluid-liberal arm ($P < 0.001$). Similarly, the mean cumulative dose of furosemide over the study period was 562 mg in the restrictive strategy group and 159 mg in the liberal strategy group ($P < 0.001$). Within groups, however, there was a large degree of overlap. At day 7, 37% of the patients in the fluid-conservative arm had a cumulative fluid balance above the median cumulative fluid balance in the fluid-liberal arm. Figures 1 and 2 depict the median and interquartile range of cumulative fluid balance and furosemide dose by study day and fluid-management group.

Univariate Associations with Mortality

In univariate analysis of the AKI population, several baseline factors were significantly associated with 60-day mortality (Table 2). Older age, higher baseline

<table>
<thead>
<tr>
<th>FACTT Participants with AKI</th>
<th>Liberal Fluid Strategy</th>
<th>Restrictive Fluid Strategy</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>137</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>% of total study ($n = 500$ in each arm)</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>60.6</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>39.4</td>
<td>44.4</td>
<td>0.38</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>51.8</td>
<td>62.1</td>
<td>0.18</td>
</tr>
<tr>
<td>black</td>
<td>32.8</td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>15.3</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Age (mean, years)</td>
<td>49.2</td>
<td>50.6</td>
<td>0.48</td>
</tr>
<tr>
<td>Time in ICU pre-enrollment (mean, days)</td>
<td>1.6</td>
<td>1.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Fluid balance 24 hours pre-enrollment (mean, L)</td>
<td>4.1</td>
<td>3.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline APACHE III score (mean)</td>
<td>108.4</td>
<td>102.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Baseline creatinine (mean, mg/dl)</td>
<td>1.7</td>
<td>1.6</td>
<td>0.14</td>
</tr>
<tr>
<td>Baseline albumin (mean, mg/dl)</td>
<td>2.1</td>
<td>2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline CVP (mean, mmHg)</td>
<td>13.3</td>
<td>13.0</td>
<td>0.72</td>
</tr>
<tr>
<td>Baseline shock (%)</td>
<td>40.9</td>
<td>40.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Contributing etiology of ALI (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trauma</td>
<td>8.0</td>
<td>6.5</td>
<td>0.61</td>
</tr>
<tr>
<td>sepsis</td>
<td>56.2</td>
<td>46.7</td>
<td>0.10</td>
</tr>
<tr>
<td>multiple transfusions</td>
<td>5.8</td>
<td>2.4</td>
<td>0.12</td>
</tr>
<tr>
<td>aspiration</td>
<td>9.5</td>
<td>17.2</td>
<td>0.05</td>
</tr>
<tr>
<td>pneumonia</td>
<td>67.9</td>
<td>65.1</td>
<td>0.61</td>
</tr>
<tr>
<td>Catheter group (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>central venous catheter</td>
<td>44.5</td>
<td>45.6</td>
<td>0.86</td>
</tr>
<tr>
<td>pulmonary-artery catheter</td>
<td>55.5</td>
<td>54.4</td>
<td></td>
</tr>
<tr>
<td>Day of AKI onset (mean)</td>
<td>1.1</td>
<td>1.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Stage of AKI (% during the first two study days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>57.7</td>
<td>60.4</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>13.1</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29.2</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td>7-day maximum creatinine (mean, mg/dl)</td>
<td>3.3</td>
<td>3.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Dialysis within the first 7 days (%)</td>
<td>32.1</td>
<td>26.6</td>
<td>0.29</td>
</tr>
<tr>
<td>60-day mortality (%)</td>
<td>40.9</td>
<td>37.9</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean study day of death</td>
<td>16.4</td>
<td>13.7</td>
<td>0.39</td>
</tr>
</tbody>
</table>

$^a$Participants were assigned up to two contributing etiologies for their acute lung injury.
APACHE III score, sepsis as an etiology for ALI, shock, lower platelets, higher potassium, higher blood urea nitrogen (BUN), lower bicarbonate, lower albumin, lower systolic BP, and a higher CVP at study day 1 were all associated with 60-day mortality. Diuretic use in the 24 hours before study randomization and trauma as an etiology for ALI were associated with lower mortality. The fluid-management and catheter-randomization arms were nonsignificant, as was the day of AKI diagnosis and 24 hours prerandomization fluid balance. On-study factors associated with mortality included stage of AKI, mean CVP, mean daily fluid balance, early oliguria, and dialysis requirement. Higher mean furosemide dose was negatively associated with mortality. Mean furosemide dose was plotted against mortality using smoothed nonparametric regressions, and it showed a relatively linear relationship, with no threshold effect visible (Supplementary Appendix 1).

In multiple logistic regression, 19 potential confounding covariates were added to regressions on post-AKI mean fluid balance or furosemide dose (Table 3, full model). A positive fluid balance remained significantly associated with 60-day mortality after adjustment for all covariates (adjusted odd ratio (OR) 1.61 per L/d, 95% confidence interval (CI): 1.29 to 2.00, \(P < 0.001\)). The association was unaffected by the addition of mean post-AKI furosemide dose. Mean post-AKI furosemide dose was significantly associated with decreased mortality in the full model; however, the association was NS after adjustment for post-AKI fluid balance. A more parsimonious final model resulted in similar adjusted odds ratios compared with the full model (post-AKI fluid balance: adjusted OR 1.61 per L/d, 95% CI: 1.32 to 1.96, \(P < 0.001\); post-AKI furosemide dose: adjusted OR 0.48 per 100 mg/d, 95% CI: 0.28 to 0.81, \(P = 0.007\)). Final model covariates included age, race, sex, fluid- and catheter-randomization arms, log-APACHE III score, day of AKI, mean daily presence of shock, and mean daily CVP.

### Subgroup and Sensitivity Analyses

Using the final model of covariates, associations with post-AKI mean fluid balance and furosemide dose were evaluated in the four predefined subgroups (Table 4). A positive fluid balance remained a significant risk factor for mortality in all subgroups. The protective association between furosemide dose and mortality was significant only in women, the fluid-conservative arm, and patients with oliguria during the first 7 study days. Interaction terms were tested for each subgroup–risk-factor combination, and both fluid balance-genre and furosemide dose-genre resulted in \(P\) values of <0.1.

In sensitivity analyses, participants who died during the initial 7 days on-study were excluded (\(n = 56\)). The adjusted OR for post-AKI fluid balance was similar (1.42 per L/d, 95% CI: 1.12 to 1.81, \(P = 0.004\)), although post-AKI furosemide dose was no longer significant (adjusted OR 0.61 per 100 mg/d, 95% CI: 0.35 to 1.07, \(P = 0.087\)). Next, we defined AKI using the RIFLE criteria, with similar results (\(n = 213\): adjusted OR for post-AKI fluid balance, 1.60 per L/d, 95% CI: 1.27 to 2.02, \(P < 0.001\), adjusted OR for post-AKI furosemide dose, 0.54 per 100 mg/d, 95% CI: 0.31 to 0.94, \(P = 0.029\)). Finally, models using Cox proportional hazard regression yielded similar results (post-AKI fluid balance: adjusted HR 1.30 per L/d, 95% CI: 1.22 to 1.38, \(P < 0.001\); post-AKI furosemide dose: adjusted HR 0.50 per 100 mg/d, 95% CI: 0.31 to 0.79, \(P = 0.003\)).

### Discussion

Using a unique data source to address optimal fluid and diuretic management in critically-ill patients with AKI, this study offers insight into the complex interplay between fluid management, fluid balance, and mortality. Clearly, and consistently across every subgroup we tested, a positive fluid balance after AKI was associated with 60-day mortality in patients with ALI. In this study, the risk of death was approximately 1.6-fold higher per L/d of fluid accumulated. Diuretic use was associated with decreased mortality, with no apparent threshold above which mortality increased. Both effects appeared stronger in women than men.

The observed independent association of post-AKI fluid accumulation and mortality is consistent with previous reports (2,4–7,20,21). In a retrospective study of pediatric bone marrow transplant recipients with dialysis-requiring...
AKI, a weight gain of ≥10% of baseline body weight at dialysis initiation was associated with subsequent death (7). The observational cohort Program to Improve Care in Acute Renal Disease (PICARD) (6) found a significant association between a 10% weight gain at AKI diagnosis and mortality in nondialyzed critically ill adults. The Sepsis Occurrence in Acutely Ill Patients (5) cohort demonstrated an increased relative hazard of mortality associated with post-AKI fluid balance in critically ill patients with serum creatinine greater than 3.5 mg/dl or oliguria. Our study extends this continuous association of post-AKI fluid balance and death to critically ill adults meeting the two most current definitions for AKI (RIFLE and AKIN).

In our analysis, post-AKI furosemide use had a protective effect on 60-day mortality, except when adjusted for fluid balance. This attenuation of effect with adjustment may simply signify that fluid balance is a causal intermediate in the association between diuretics and mortality. In other words, the benefit of furosemide in critically ill patients is derived from the resultant reduction in fluid balance. In this hypothesized biologic pathway, it may not be appropriate to include fluid balance in a regression model with furosemide dose.

Our observed protective effect of diuretics on 60-day mortality contrasts with results from the PICARD study (1) and, in part, the Beginning and Ending Supportive Ther-
apy for the Kidney (BEST Kidney) trial (10). In these observational cohorts, diuretic use was positively associated with mortality: significantly so in PICARD and significant only in the univariate analysis in BEST Kidney. Several factors could contribute to this difference. We model the continuous association of diuretic dose with mortality, rather than the ever/never categorization used in both the PICARD and BEST Kidney trials. Furthermore, the FACTT study involved protocolized administration of fluids and diuretics. Adjusting for the management strategy and drivers of diuretic use such as shock and CVP should dramatically decrease confounding by indication, i.e., the possibility that diuretic use is driven by severity of illness.

This study is unique in the depth of the data on fluid and diuretic management and the rigor of the fluid-management algorithm; however, some limitations must be considered. First, the population of patients is extremely specific: critically ill patients with ALI requiring ventilatory support who developed in-hospital AKI within 2 days on-study and were eligible for enrollment in a randomized

### Table 3. Relative odds of death by FACTT study day 60 associated with average daily fluid balance and furosemide dose following AKI

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Fluid Balance (Post-AKI, in Mean L/Day)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Furosemide Dose (Post-AKI, in Mean 100 mg/Day)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (univariate)</td>
<td></td>
<td>1.73 (1.47 to 2.03)</td>
<td>&lt;0.001</td>
<td>0.38 (0.23 to 0.63)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Full model*</td>
<td></td>
<td>1.61 (1.29 to 2.00)</td>
<td>&lt;0.001</td>
<td>0.54 (0.31 to 0.94)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>+Post-AKI fluid balance</td>
<td></td>
<td>1.56 (1.25 to 1.95)</td>
<td>&lt;0.001</td>
<td>0.73 (0.42 to 1.26)</td>
<td>0.255</td>
<td></td>
</tr>
<tr>
<td>+Post-AKI furosemide dose</td>
<td></td>
<td>1.61 (1.32 to 1.96)</td>
<td>&lt;0.001</td>
<td>0.48 (0.28 to 0.81)</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

*Full model includes adjustment for the following covariates: age, sex, race, fluid-strategy randomization group, catheter randomization group, day first diagnosed with AKI, fluid balance in the 24 hours prior to randomization, enrollment APACHE III score, sepsis as an etiology for ALI, trauma as an etiology for ALI, pneumonia as an etiology for ALI, multiple transfusions as an etiology for ALI, other etiology for ALI, baseline CVP, baseline presence or absence of shock, use of diuretics in the 24 hours prior to randomization, stage of AKI within 2 study days of randomization (AKIN creatinine-based criteria), mean daily CVP, and mean daily presence or absence of shock. The statistically significant covariates in the full model were race, age, day first diagnosed with AKI, and fluid-strategy randomization group.

*Final model includes adjustment for the following covariates: age, race, sex, fluid-strategy randomization arm, catheter randomization arm, enrollment APACHE III score, day first diagnosed with AKI, mean daily CVP, and mean daily presence or absence of shock. The statistically significant covariates in the final model were race, age, day first diagnosed with AKI (with mean fluid balance only), fluid-strategy randomization group (with mean fluid balance only), enrollment APACHE III score, mean daily CVP (with mean furosemide dose only), and mean daily presence or absence of shock.

### Table 4. Adjusted odds ratio of 60-day mortality associated with fluid balance and furosemide dose, by subgroup

<table>
<thead>
<tr>
<th>Subgroup*</th>
<th>n</th>
<th>Fluid balance (Post-AKI, in Mean L/Day)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>177</td>
<td>1.42 (1.13 to 1.78)</td>
<td>0.003</td>
<td>0.69 (0.36 to 1.31)</td>
</tr>
<tr>
<td>female</td>
<td>129</td>
<td>2.80 (1.73 to 4.54)</td>
<td>&lt;0.001</td>
<td>0.13 (0.03 to 0.63)</td>
</tr>
<tr>
<td>Fluid strategy</td>
<td></td>
<td>1.83 (1.29 to 2.60)</td>
<td>&lt;0.001</td>
<td>0.29 (0.06 to 1.32)</td>
</tr>
<tr>
<td>liberal</td>
<td>137</td>
<td>1.54 (1.16 to 2.03)</td>
<td>0.002</td>
<td>0.51 (0.28 to 0.90)</td>
</tr>
<tr>
<td>restrictive</td>
<td>169</td>
<td>1.77 (1.27 to 2.45)</td>
<td>&lt;0.001</td>
<td>0.25 (0.06 to 0.96)</td>
</tr>
<tr>
<td>Oliguria in initial 7 days</td>
<td></td>
<td>1.61 (1.20 to 2.15)</td>
<td>0.001</td>
<td>0.60 (0.33 to 1.07)</td>
</tr>
<tr>
<td>yes</td>
<td>114</td>
<td>1.55 (1.19 to 2.01)</td>
<td>0.001</td>
<td>0.51 (0.25 to 1.04)</td>
</tr>
<tr>
<td>no</td>
<td>192</td>
<td>1.91 (1.34 to 2.71)</td>
<td>&lt;0.001</td>
<td>0.46 (0.21 to 1.03)</td>
</tr>
</tbody>
</table>

The values are adjusted for covariates included in the final model of Table 3: age, race, sex, fluid-strategy randomization arm, catheter randomization arm, enrollment APACHE III score, day first diagnosed with AKI, mean daily CVP, and mean daily presence or absence of shock.

*All of the interaction terms between subgroup and post-AKI fluid balance and subgroup and post-AKI furosemide dose had P values >0.1, with the exception of post-AKI fluid balance and gender (P = 0.088) and post-AKI furosemide dose and gender (P = 0.064).
clinical trial. As such, the results of our study may not be
generalizable to patients different from the FACTT study
population or who develop AKI earlier or later in their
hospital stay. On the other hand, a frequent etiology of AKI
is sepsis (22), similar to that in our study, and the associ-
ations between mortality and positive fluid balance were
consistent across multiple subgroups and after adjustment
for many meticulously measured potential confounders.
Second, inclusion criteria were met after randomization,
precluding inferences regarding fluid strategy as a cause of
mortality. Our results, although less affected by confound-
ing by indication than observational studies, do not sub-
stitute for a randomized controlled trial of fluid-manage-
ment strategies in AKI. Finally, baseline creatinine was
estimated using an average of up to three creatinine values
measured in-hospital and within 24 hours before random-
ization, because these were the data available. Observa-
tional studies of AKI have varied widely in the selection
of baseline creatinine. If anything, the sensitivity of our def-
ingition may be low, but the positive predictive value
should be high, potentially resulting in a number of missed
cases but few false positives (23). Furthermore, the lack of
premorbid renal function is a common issue among hos-
pitalized patients (23). Our approach is likely preferable to
the use of an estimated creatinine from the Modification of
Diet in Renal Disease equation, which others have shown
may be flawed (24). Because the primary focus of our analy-
sis was post-AKI fluid balance and furosemide dose,
selection of participants enrolled with ongoing AKI may be
even preferable, allowing for an assessment of the effect of
fluid management including the protocolized administra-
tion of diuretics on AKI itself.

Conclusions

In this post-hoc analysis, a positive fluid balance after
in-hospital AKI carried a strong and consistent association
with mortality in patients with ALI, independent of liberal
or conservative fluid management. Higher diuretic dose
after AKI onset had a protective effect on survival, with no
observed threshold dose above which mortality increased;
this relationship appeared to be mediated by post-AKI
fluid balance. With the caveat that these data were ob-
erved in a study of patients with ALI, clinicians may be
reassured that, in the appropriate pa-
tient, diuretics may not be contraindicated. Future ran-
donized clinical trials focused on diuretic administration
and fluid balance in critically ill patients with AKI are
clearly warranted.

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