Severe acute kidney injury not treated with renal replacement therapy: characteristics and outcome

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Abstract
Background. Only a proportion of critically ill patients with severe [RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria, class-F] acute kidney injury (AKI) appear to receive renal replacement therapy (RRT). The aim of this study was to study the characteristics and outcome of patients with severe (RIFLE-F) AKI who did not receive RRT.

Methods. We identified all consecutive patients admitted to our institution that developed RIFLE-F AKI by creatinine criteria over a 3-year period and did not receive RRT, and compared their characteristics and outcomes with those of RIFLE-F RRT-treated patients.

Results. Within the study period, 20,126 patients were admitted to our institution for >24 h. Among them, 2,949 were admitted to the intensive care unit (ICU) and 195 developed RIFLE-F AKI. Of these, 90 received RRT (RRT patients) and 105 did not (no-RRT patients). Compared with RRT patients, no-RRT patients were similar in terms of age, gender and ward of origin. However, they had a shorter median ICU stay (2.7 versus 7.9 days; P < 0.001), required less mechanical ventilation (56.2 versus 70%; P < 0.05) and had a lower mean Acute Physiology and Chronic Health Evaluation III score (82.7 versus 86.7; P < 0.05). The two main reasons these patients did not receive RRT were limitations of medical therapy (LOMT) orders in 41 (39%) cases and expected renal functional improvement in 59 (56.2%). Mortality in no-RRT patients was 58.1% compared with 55.5% in the RRT group (P = 0.72). After exclusion of LOMT patients, the mortality of the no-RRT group, although lower than that of the RRT group, remained high (30.5 versus 55%; P < 0.001). Most of these deaths occurred after ICU discharge and appeared secondary to underlying chronic diseases or recurrence of the initial insult.

Conclusions. After exclusion of LOMT patients, about a third of critically ill patients with severe (RIFLE-F) AKI did not receive RRT. A third of these patients died in hospital. The timing of the deaths and their underlying causes do not suggest that a broader application of RRT would have changed patient outcomes.

Keywords: acute kidney injury; epidemiology; renal replacement therapy; RIFLE score

Introduction
Acute kidney injury (AKI) in critically ill patients is common and associated with morbidity and mortality [1]. When severe, it is often associated with major physiological derangements and may require control by means of renal replacement therapy (RRT). However, outside of life-threatening hyperkalemia, it is still unclear which AKI patients should receive RRT.

RRT is associated with complications, high costs, great complexity of care and an increased workload for the nursing staff. Thus, the question of which patients should be treated with RRT and at what levels of azotemia has important implications. Despite several studies [2–4] suggesting that early intervention might improve outcome, there is insufficient evidence to guide practice. Although the Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria has never been validated as a trigger to initiate therapy, one might expect that a significant proportion of patients with the highest severity of functional loss (RIFLE-F criteria) would receive RRT [5–10]. Instead, as shown by Hoste et al. [9], only a minority do receive this therapy. Little is known about these ‘untreated’ patients, their characteristics and their outcome. Accordingly, we performed a retrospective study in our institution in order to characterize such patients, understand why they did not receive RRT and describe their outcome.

Materials and methods
The need for informed consent was waived because the study required no intervention and was not in breach of privacy or anonymity. The study was approved by the Austin Hospital Human Research Ethics Committee.

Hospital
The Austin health is an 800-bed teaching hospital including 400 acute beds. The intensive care unit (ICU) contains 20 beds and operates according to a closed model, where only ICU physicians can prescribe therapy.
Renal replacement therapy

In our institution, continuous renal replacement therapy (CRRT) is the preferred option in acutely ill patients and the only initial treatment option. However, intermittent hemodialysis is available for patients in the recovery phase of AKI especially after discharge from the ICU. For the purpose of this study, all forms of RRT were considered. During the study period, there were no pre-specified criteria for RRT and the decision for treatment initiation was left to the treating medical team.

Data collection and database construction

Database construction. We used a database designed to assess the prevalence and outcome of AKI according to RIFLE criteria in our institution. The characteristics and methodology for such a database have been previously described [8]. In brief, patients were excluded if they were <15 years old, if they were on chronic dialysis, had kidney transplant or if their length of hospital stay was <24 h. Demographic information was collected from the database (age, gender, type of admission, ICU admission, use of mechanical ventilation, admission units and hospital mortality). If a patient had more than one admission during the study period, only the last admission was included in the study.

Patients selection—RIFLE F. In this study, as previously described [8], we used the glomerular filtration rate (GFR) or creatinine criteria of the RIFLE classification only. The highest RIFLE category reached during hospital admission was chosen from the Risk, Injury or Failure categories and assigned to each patient for analysis. To classify patients into one of the RIFLE criteria, peak and baseline creatinine values were collected from the computerized laboratory database. The peak creatinine was defined as the highest creatinine level during hospital admission. The baseline creatinine was defined in two ways. For patients who had more than one admission during the study period, the baseline creatinine was defined as that measured at hospital discharge from the previous admission. For patients with only one admission, the baseline creatinine was estimated using the Modification of Diet in Renal Disease (MDRD) equation [11], as recommended by the Acute Dialysis Quality Initiative (ADQI) workgroup (assuming an average GFR of 75 mL/min in this age group). Only patients fulfilling the RIFLE-F criteria were included in this analysis.

Detailed review of medical records. To confirm the RIFLE-F status, detailed medical record review was performed for the patients deemed to fulfill the RIFLE-F criteria. We then obtained data from our ICU database with regards to ICU admission, need for endotracheal intubation and RRT administration. We included patients that fulfilled the creatinine criteria for RIFLE-F but did not receive RRT as well as all patients that received RRT during the study period as controls.

Cause of AKI. On chart review, the major trigger for AKI was evaluated by an intensive care physician (A.S.) and categorized into 10 classes: sepsis, Cause of AKI.

Reason for no RRT. Similarly, on chart review, the researcher classified the reason why no RRT was undertaken. Five a priori categories were defined: limitations of medical therapy (LOMT), recovery of renal function, transfer to another hospital, death before initiation of RRT and other. The ‘recovery of renal function’ category referred to cases where the clinicians estimated that the patient’s condition was not sufficient to trigger RRT and/or they presented signs of renal recovery (increased urinary output, improved hemodynamic status), which justified continued observation without the application of RRT.

Creatinine over baseline ratio. To allow for comparison of azotemia over time between patients with different baseline creatinine, we calculated a ‘creatinine over baseline ratio’ for each patient. This ratio was calculated by dividing the daily serum creatinine concentration by the baseline creatinine concentration.

Statistical analysis. Descriptive statistics are presented with mean and SD or median as appropriate, ordinal data are presented with number and percentage. Comparisons of nominal data were by means of the chi-square test or Fisher’s exact test where indicated. The Wilcoxon rank-sum test was used for comparisons of numerical data. Kaplan–Meier analysis and log-rank comparison were performed to assess survival after ICU admission for the patients that received RRT and those that did not. Additionally, binary logistic regression was performed to identify baseline variables, which were independently associated with in-hospital mortality for the two groups. Variables entered in the model were demographic and illness severity data, type of admission (elective versus emergency and medical versus surgical) and AKI etiology. Significance was set at P <0.05. Data were analyzed using PASW/SPSS™ software, version 18 (IBM Inc., Chicago, IL).

Results

Between January 2000 and December 2002, 20 126 patients were admitted to our hospital for >24 h and of which 2949 were admitted to the ICU (Figure 1). Among these ICU patients, 236 initially fulfilled the RIFLE-F criteria. After manual medical record review, however, 6 patients were re-classified as RIFLE-R, 29 as RIFLE-I, and 4 as RIFLE-E. Finally, sufficient data could not be retrieved in two patients. Thus, 195 patients were included in the study. Of these, 90 (46.2%) received RRT during their ICU stay and 105 (53.8%) did not.

The baseline characteristics of the study patients are presented in Table 1. In comparison with the RRT group, patients in the no-RRT group were less often admitted electively, had lower Acute Physiology and Chronic Health Evaluation (APACHE) scores, shorter ICU stay and a trend towards a shorter hospital stay. Their in-hospital mortality was 58.1% compared with 55.5% in the RRT group (P =
Survival. 53 patients (58.1%) of the no-RRT patients and 61 (58.1%) of the RRT group survived to hospital discharge compared with 61 (58.1%) of the no-RRT patients (P = 0.72). After exclusion of LOMT orders (Table 1), no-RRT patients were comparable to RRT patients for most baseline characteristics except for a lower APACHE II (20.2 versus 23.3, P < 0.001) and III score (74.8 versus 86.7, P < 0.001). Their ICU length of stay was shorter (3.4 versus 7.9 days, P < 0.001), and they were less likely to require mechanical ventilation (50 versus 70%, P = 0.013).

AKI triggers

As presented in Table 2, the main triggers for AKI were sepsis, cardiogenic shock, major non-cardiac surgeries and hepato-renal syndrome. Primary renal etiologies were less frequent in the no-RRT group and sepsis was more frequent. Only one patient had a renal biopsy, which revealed acute crescentic glomerulonephritis.

Survival. Overall, 50 (55.5%) of the RRT patients did not survive to hospital discharge compared with 61 (58.1%) of the no-RRT patients (P = 0.72). After exclusion of LOMT orders, 18 (30.5%) died in hospital in the no-RRT group compared with 50 (55.5%) in the RRT group (P = 0.002). As illustrated in Figure 2, deaths in the no-RRT patients occurred more than a week after ICU admission, three occurred after ICU discharge and two during a second ICU admission.

Causes of death. On chart review, the cause of death was determined for the 18 patients in the no-RRT group who survived from AKI but eventually died. Eight had terminal disease and LOMT orders were later documented on ICU discharge in five for terminal heart failure, two for small cell lung cancer and one for severe vascular disease with recurrent limb ischemia. Five patients died of complications of their underlying disease (recurrence of variceal bleeding, hematologic malignancy, multiple trauma in an 88-year-old and mesenteric ischemia). Three had recurrent sepsis >1 week after the initial event. Finally, the two remaining patients died without clear explanation (asystolic cardiac arrest) but both had experienced full renal recovery before their death.

Predictors of death. On binary logistic regression, in the no-RRT group, a medical admission [odds ratio (OR) 5, P = 0.02] and a higher APACHE III score (OR 1.074, P < 0.001) were independently associated with an increased risk of death. None of the different etiologies for AKI reached statistical significance.

Similarly, in the RRT group, a higher APACHE III score (OR 1.028, P = 0.01) and a diagnosis of hepato-renal syndrome (OR 6.3, P = 0.048) were independently associated with an increased risk of death, while a diagnosis of sepsis was associated with a trend toward increased risk (P = 0.089, OR 2.8).

Recovery of renal function. Among the no-RRT patients who survived, the creatinine concentration at hospital discharge was back to within 20% of baseline in 23/41 (56%) patients and back to within 40% of baseline for 29/41 (70.1%). Only two patients had a persistent marked elevation of their creatinine at discharge (2.5 and 3.9 times the baseline value).

Discussion

Key findings

We conducted a retrospective study of critically ill patients who developed RIFLE-F AKI and did not receive RRT. Our objective was to understand their characteristics, the reasons why they did not receive RRT and to study their hospital outcome. We found that these patients were similar in numbers to those treated with RRT but had slightly lower...
APACHE III scores and required less mechanical ventilation. As expected, on average, they did better than RRT-treated patients in terms of ICU length of stay and, after exclusion of LOMT patients, in terms of in-hospital mortality. These patients did not receive RRT because of LOMT orders or because, despite the important increase in serum creatinine concentration, their metabolic disturbances were not considered sufficient to require RRT and/or recovery was expected to occur within hours or days. Although a majority of these patients eventually regained their renal function, 30% of them did not survive to hospital discharge. All these deaths, however, occurred >7 days after ICU admission and were not directly related to complications of AKI.

Comparison with previous studies

To the best of our knowledge, no previous publication has studied the characteristics and outcome of patients with severe AKI that did not receive RRT.

We report a very high mortality rate (56.9% overall and 55.5% for RRT patients) overall which is consistent with the mortality reported in the major recently published trials of RRT [12, 13] and epidemiological studies [1, 14]. In the data presented by Hoste et al. [15], the overall mortality for RIFLE-F patients was 26.3%. However, the patients included in their study were younger (62.1 versus 66 years old in the present study) had a lower average APACHE III score (56 versus 84.6 in this study) and were mainly surgical (63.9 versus 42.1% in our series). These three factors are known to be associated with decreased in-hospital mortality. Finally, only 14.2% of the patients reported in their study received RRT versus 46.4% in our study, suggesting a combination of different selection criteria for RRT and different levels of illness severity.

Clinical significance

This study describes, for the first time, characteristics, reasons for non-treatment and outcome of a significant subpopulation of critically ill patients with AKI. As compared with patients treated with RRT, these patients had very similar baseline characteristics and were very similar in number. Thus, they represented 3% of all ICU admissions. However, these patients were not a uniform group and could be divided into two major categories: (1) those considered likely to achieve early recovery and (2) those with LOMT orders. While it is very difficult to evaluate the appropriateness of LOMT orders in this setting, a comparison can be made between the RRT group and no-RRT group for patients assessed as requiring active treatment (but not RRT).

As expected, the patients not requiring RRT had a lower mortality, a shorter ICU stay and, in most cases, recovered their renal function to a creatinine concentration within 40% of their baseline. Despite being a less severely ill group, they had a high in-hospital mortality raising the question of whether a more aggressive approach (possibly including the use of RRT) would have changed their outcome. However, the fact that most deaths occurred after recovery of renal function, after ICU discharge and mostly appeared secondary to underlying chronic diseases or recurrence of the initial insult suggests that RRT would not have changed their prognosis. This finding is consistent with the findings of

| Table 2. Clinical conditions triggering AKI |

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>RRT</th>
<th>All no-RRT</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No-RRT without LOMT</th>
<th>p&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>n</td>
<td>195</td>
<td>90</td>
<td>105</td>
<td></td>
<td>60</td>
<td></td>
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<tr>
<td>Sepsis</td>
<td>75</td>
<td>26 (28.9%)</td>
<td>49 (46.7%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.01</td>
<td>26 (43.3%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.07</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>30</td>
<td>9 (10.0%)</td>
<td>21 (20.0%)</td>
<td>0.06</td>
<td>8 (13.3%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.53</td>
</tr>
<tr>
<td>Major non-cardiac surgeries</td>
<td>18</td>
<td>8 (8.9%)</td>
<td>10 (9.5%)</td>
<td>0.89</td>
<td>9 (15%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.24</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>15</td>
<td>10 (11.1%)</td>
<td>5 (4.8%)</td>
<td>0.16</td>
<td>5 (8.3%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.58</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>4</td>
<td>2 (2.2%)</td>
<td>2 (1.9%)</td>
<td>0.87</td>
<td>2 (3.3%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.68</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>18</td>
<td>12 (13.3%)</td>
<td>6 (5.7%)</td>
<td>0.06</td>
<td>1 (1.7%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.01</td>
</tr>
<tr>
<td>Obstructive</td>
<td>3</td>
<td>0 (0%)</td>
<td>3 (2.9%)</td>
<td>0.11</td>
<td>3 (5.0%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.06</td>
</tr>
<tr>
<td>Primary renal</td>
<td>10</td>
<td>9 (10%)</td>
<td>1 (1.0%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.004</td>
<td>0 (0%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.01</td>
</tr>
<tr>
<td>Drugs/toxins/metabolic</td>
<td>7</td>
<td>3 (3.3%)</td>
<td>4 (3.8%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.59</td>
<td>4 (6.7%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.29</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
<td>11 (12.2%)</td>
<td>4 (3.8%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.03</td>
<td>2 (3.3%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.06</td>
</tr>
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<sup>a</sup>Chi-square of Fisher exact test as appropriate.

<sup>b</sup>P for the comparison with the RRT group.

<sup>c</sup>P for the comparison with the RRT group.
a recently published trial [16, 17], where equal number of patients within the different RIFLE categories were started on dialysis. Although only a properly designed randomized control trial could provide a definitive answer for this question, it seems unlikely that a creatinine-based trigger for RRT would have any significant impact on mortality.

Strengths and limitations

This study is, to the best of our knowledge, the first to present the characteristics and outcome of patients with severe AKI who do not receive RRT. We confirmed their RIFLE-F status by chart review and the reason for no-RRT was established independently according to pre-determined criteria. Thus, we believe that our classification is accurate and provides important information on the characteristics, clinical course and outcome of a cohort, which represents -1 every 30 ICU admissions in a general academic ICU. However, the RIFLE score has never been validated as a tool to trigger the initiation of RRT making our choice of the RIFLE-F selection criteria subjective. However, we reasoned that such patients have advanced AKI and would at least be considered as potential candidates for RRT. And that understanding their overall prognosis, their cause of death and the variables associated with a greater risk of death would help clinicians make more informed decisions.

Our study is retrospective in nature with the limitations of such studies. However, chart review was conducted in a structured way with pre-defined criteria and all numeric variables were collected prospectively. The study design also did not allow us to reliably determine the criteria used to start RRT. We used clinical judgment to determine why RRT was not applied. This evaluation, however, was performed in a standardized way to minimize interpretation bias. Similarly, we were not able to determine the value of different physiological and clinical parameters at the time of peak creatinine level and were limited to comparing baseline characteristics. Patient selection was limited to those with an increase in creatinine and we were not able to classify patients according to urine output criteria and had to use the MDRD equation to estimate baseline GFR. These factors may have been responsible for a degree of under-diagnosis of RIFLE-F patients. This approach, however, has been common in the literature [18–20] and shown to select sicker patients [21]. We consider that this misclassification is unlikely to have caused outcome bias since it should have affected both groups equally. Finally, the data were generated in a single center, limiting its external validity. However, our ICU has all the typical features of a tertiary ICU in a developed country and it is likely that our findings would apply to similar ICUs.

Future studies

Other epidemiological studies in different countries or health care systems appear desirable to confirm or refute our findings.

Conclusions

Some critically ill patients with severe (RIFLE-F) AKI do not receive RRT. These patients are either deemed inappropriate for such active treatment or likely to recover without it. The latter group of patients, however, still have a substantial mortality rate, particularly for medical admissions and in the presence of high APACHE scores. However, these deaths appear related mostly to the underlying disease or recurrence of the original acute condition rather than the direct effects of AKI itself and it seems unlikely that a broader application of RRT would have any significant impact on mortality.

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Conflict of interest statement. None declared.

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