

# Renal Replacement Therapy in Severe Burns: A Multicenter Observational Study

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Acute kidney injury (AKI) after severe burns is historically associated with a high mortality. Over the past two decades, various modes of renal replacement therapy (RRT) have been used in this population. The purpose of this multicenter study was to evaluate demographic, treatment, and outcomes data among severe burn patients treated with RRT collectively at various burn centers around the United States. After institutional review board approval, a multicenter observational study was conducted. All adult patients aged 18 or older, admitted with severe burns who were placed on RRT for acute indications but not randomized into a concurrently enrolling interventional trial, were included. Across eight participating burn centers, 171 subjects were enrolled during a 4-year period. Complete data were available in 170 subjects with a mean age of  $51 \pm 17$ , percent total body surface area burn of  $38 \pm 26\%$  and injury severity score of  $27 \pm 21$ . Eighty percent of subjects were male and 34% were diagnosed with smoke inhalation injury. The preferred mode of therapy was continuous venovenous hemofiltration at a mean delivered dose of  $37 \pm 19$  (ml/kg/hour) and a treatment duration of  $13 \pm 24$  days. Overall, in hospital, mortality was 50%. Among survivors, 21% required RRT on discharge from the hospital while 9% continued to require RRT 6 months after discharge. This is the first multicenter cohort of burn patients who underwent RRT reported to date. Overall mortality is comparable to other critically ill populations who undergo RRT. Most patients who survive to discharge eventually recover renal function. (J Burn Care Res 2018;39:1017–1021)

Acute kidney injury (AKI) is relatively common among hospitalized burn patients and when severe, it is historically associated with an exceedingly high mortality of 80% to 100%.<sup>1,2</sup> A recent comprehensive review determined that AKI occurred in 25% of patients among burn patients and was associated with a median mortality of 35%.<sup>1</sup> Among those requiring renal replacement therapy (RRT), mortality was reported as 80%.<sup>1</sup> A more recent study also reported a mortality of 81.5% among 216 burn patients from one center managed with RRT over a span of 7 years.<sup>3</sup> Over the past two decades, various modes of RRT have been used at a number of burn centers to manage severe metabolic and fluid balance derangements observed in these patients. Wide

practice variation currently exists in critical care in general with regards to the optimal mode, dose, and timing of RRT initiation due to the lack of consensus. Recent studies in this area have improved the general understanding of the practice patterns that exist among nonburn ICUs.<sup>4–7</sup> However, very little information exists with regards to the contemporary practice of RRT application in critically ill burn patients. To date, only single center RRT experience has been reported.<sup>3,8</sup> Hence, it is difficult to understand overall practice patterns and characterize RRT-related outcomes. The purpose of this multicenter observational study was to evaluate the various RRT practice patterns and their associated outcomes among severe burn patients treated in burn centers around the United States.

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## MATERIALS AND METHODS

After multilevel institutional review board approval, a multicenter observational study was conducted; concurrent with the American Burn Association's Randomized controlled Evaluation of high-volume hemofiltration in adult burn patients with Septic shock and acute kidney injury (RESCUE) trial, Clinicaltrials.gov Registration Number: NCT01213914. All adult patients aged 18 or older, admitted with severe burns placed on RRT for acute indications during their hospitalization but not randomized into the RESCUE trial, were included. Patients already on dialysis for end-stage renal disease (ESRD) at the time of admission were excluded. As the RESCUE trial was already enrolling subjects when this protocol was written, patients placed on RRT before approval of this protocol were identified retrospectively. On approval of the study at each study site, patients were prospectively enrolled after obtaining informed consent from either the patient or the legal authorized representative when patients were not able to give their own consent.

Demographic data, injury characteristics, physiological and laboratory data around the period of RRT initiation, and various outcomes data were captured and entered into a web-based electronic data management portal (Velos, Inc., Fremont, CA). Specifically, the following information related to RRT was recorded: AKI stage at the time of RRT initiation, as defined by the KDIGO criteria<sup>9</sup>; mode of RRT; prescribed and delivered dose of therapy; the type of prescribing provider (nephrologist vs non-nephrologist); and method of regional anticoagulation used. Additionally, need for RRT on hospital discharge among survivors was captured. Among those who survived to be discharged on RRT, a follow-up audit was performed to determine whether survivors remained on RRT at 6-months post-hospitalization.

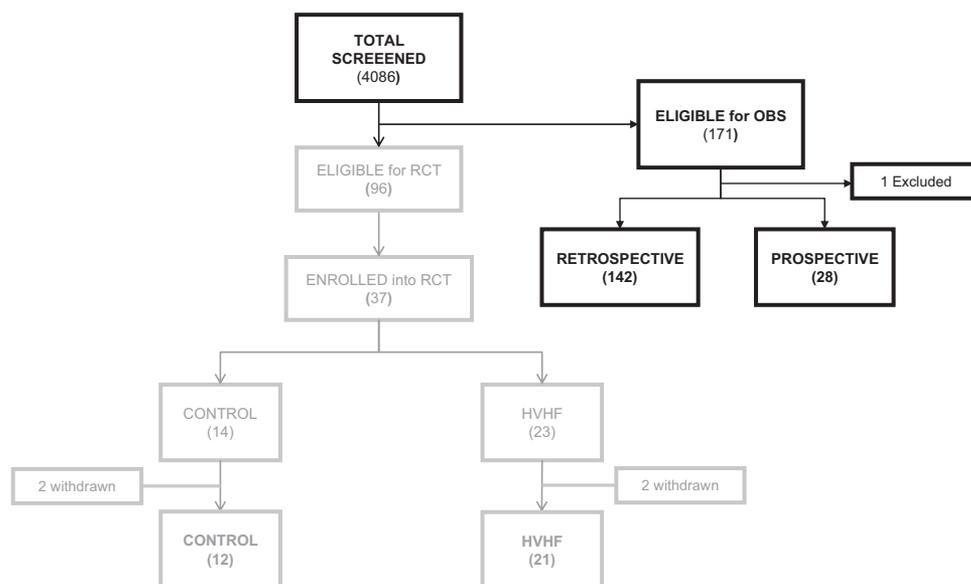
Baseline, physiological, and laboratory data were summarized using basic descriptive statistics. Continuous variables were reported in means with standard deviations. Categorical

variables were reported in proportions and analyzed using chi-squared tests or Fisher's exact test as appropriate. Significance for results was established when *P*-values were less than .05. All statistical analyses were performed using SPSS v22.0.

## RESULTS

Across eight participating burn centers, 171 subjects were enrolled during a 4-year period, 143 retrospectively and 28 prospectively. One retrospectively identified patient was excluded due to incomplete data, leaving us with a final sample size of 170 subjects for the study. Figure 1 depicts the CONSORT diagram that illustrates breakdown of those enrolled into the randomized controlled trial vs the observational study. Patient demographics are depicted in Table 1. On average ( $\pm$ SD), patients were initiated on RRT  $12 \pm 17$  days after admission. At the time of RRT initiation, 54% had stage 3 AKI, 18% stage 2, and 22% with stage 1 via KDIGO criteria. Ten patients (6%) did not meet criteria for AKI. The vast majority of patients (94%) also required mechanical ventilation with 61% diagnosed with acute respiratory distress syndrome (ARDS) on initiation of RRT. Patients had an average positive fluid balance of  $6.5 \pm 6.6$  l in the 24 hours before RRT initiation. Additionally, almost half the patients (46%) were in shock, requiring vasopressor support. Other clinical diagnoses and various laboratory data at the time of RRT initiation are presented in Table 2.

RRT prescription characteristics for those enrolled are characterized in Table 3. All but three patients (2%) received continuous RRT (CRRT). Continuous venovenous hemofiltration (CVVH) was the preferred mode of therapy in this population. Prescribing physicians, most of whom were CRRT-credentialed burn surgeons, prescribed a relatively high average blood flow with a relatively high dose of therapy among patients whom data were available ( $n = 99$ ). On average, patients remained on RRT for  $13 \pm 24$  days and most were regionally anticoagulated on either heparin or citrate.



**Figure 1.** CONSORT diagram. This figure illustrates the breakdown of patients in both the interventional trial and the observational study. Legend: RCT, randomized controlled trial; OBS, observational study; HVHF, high-volume hemofiltration.

**Table 1.** Baseline demographics (mean ± SD)

Variable	(n = 170)
Age	51 ± 17
Gender (% male)	80%
Height (cm)	173 ± 10
Weight (kg)	88 ± 26
%TBSA	38 ± 26
% FT	24 ± 25
Inhalation	34%
ISS	27 ± 21
APACHE II	26 ± 9

TBSA, total body surface area; FT, full thickness; ISS, injury severity score; APACHE, acute physiology and chronic health evaluation; RRT, renal replacement therapy.

**Table 2.** Characteristics on the day of RRT initiation (mean ± SD)

Variable	(n = 170)
Day of RRT initiation	12 ± 17
KDIGO AKI stage	
Stage 1	22%
Stage 2	18%
Stage 3	54%
No AKI	6%
Mechanical ventilation	94%
ARDS	61%
Pneumonia	36%
Bacteremia	22%
Urinary tract infection	10%
Wound infection	15%
Vasopressors	46%
Preceding 24-hr fluid balance (l)	6.5 ± 6.6
Sodium (mmol/l)	142 ± 6
Potassium (mmol/l)	4.5 ± 0.8
Chloride (mmol/l)	107 ± 7
HCO <sub>3</sub> (mEq/l)	22 ± 6
BUN (mg/dl)	52 ± 34
Magnesium (mg/dl)	2.2 ± 0.7
Phosphate (mg/dl)	4.4 ± 1.9
Ionized calcium (mmol/l)	1.0 ± 0.3
Arterial pH	7.32 ± 0.11
Arterial PaCO <sub>2</sub> (mmHg)	44 ± 12
Arterial PaO <sub>2</sub> (mmHg)	141 ± 79
FiO <sub>2</sub>	60 ± 20
PFR	265 ± 157
Heart rate	105 ± 22
Systolic (mmHg)	120 ± 22
Mean arterial pressure (mmHg)	78 ± 15

RRT, renal replacement therapy; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; PFR, partial pressure of oxygen to fraction of inspired oxygen ratio; MAP, mean arterial pressure.

Aggregate and cohort outcomes data are presented in [Table 4](#). Overall, in hospital, mortality was 50%. No significant differences in mortality were noted when comparing modes of RRT, AKI stage at time of initiation, prescribing physician, or

**Table 3.** Renal replacement therapy characteristics

Variable	(n = 170)
Initial mode	
CVVH	54%
CVVHDF	30%
CVVHD	14%
IHD/SLED	2%
Prescribing physician	
Burn Surgeon	67%
Nephrologist	21%
Nonsurgical intensivist	10%
Other	2%
Blood flow (ml/min)	240 ± 84
Prescribed dose (ml/kg/hr)	42 ± 16 (n = 99)
Delivered dose (ml/kg/hr)	37 ± 19 (n = 77)
Day of RRT initiation	12 ± 17
Treatment duration	13 ± 24
Anticoagulation	
Heparin	26%
Citrate	36%
None	35%
Other	3%
First 24-hr fluid balance (L)	3.1 ± 8.2
In-hospital mortality	50%
RRT at time of discharge	21%
RRT after 6 months	9%

Abbreviations: CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; CVVHD, continuous veno-venous hemodialysis; IHD, intermittent hemodialysis; SLED, sustained low efficiency dialysis.

anticoagulation strategy. Among survivors, 21% required RRT on discharge from the hospital while 9% continued to require RRT 6 months after discharge.

## DISCUSSION

To date, this is the largest multicenter observational study assessing the characteristics of RRT and resultant outcomes as applied to the critically ill burn population. A number of key findings deserve to be emphasized from our study. First, the preferred RRT mode in this population was CVVH, with more than half receiving this mode of therapy. Although there are obvious theoretical benefits of leveraging convective clearance for a better metabolic control, previous studies have not demonstrated a difference in clinical outcomes.<sup>10,11</sup> Additionally, there is no convincing evidence to date that continuous therapies are superior to intermittent therapies in terms of biochemical efficacy and mortality rate.<sup>12</sup> Still, there is general agreement in the nephrology and critical care community that continuous therapies are better tolerated and thus more desirable and patients who are hemodynamically unstable.<sup>9</sup> In this cohort, nearly half the patients were in shock and required vasopressor support. Thus, it reasonably justifies the approach taken in these patients with that vast majority being placed on continuous modalities. Furthermore, we have found previously that CVVH is well tolerated in this population and may even be therapeutic in the form of shock reversal based on a recent randomized controlled trial.<sup>8,13</sup>

**Table 4.** Outcomes

Variable	(n = 170)	P
In-hospital mortality	50%	
Mortality based on cohort		
Mode of RRT		
CVVH, (n = 92)	44%	0.15
CVVHD, (n = 24)	70%	
CVVHDF, (n = 51)	50%	
IHD/SLED, (n = 3)	67%	
AKI subgroup		
No AKI, (n = 10)	60%	0.28
AKI Stage 1, (n = 37)	62%	
AKI Stage 2, (n = 30)	47%	
AKI Stage 3, (n = 92)	45%	
Prescribing physician		
Burn surgeon, (n = 114)	48%	0.79
Nephrologist, (n = 34)	50%	
Non-surgeon intensivist, (n = 18)	61%	
Regional anticoagulation		
Heparin, (n = 44)	44%	0.50
Citrate, (n = 62)	52%	
None, (n = 60)	53%	
RRT at time of discharge	21%	
RRT after 6 mo	9%	

RRT, renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; CVVHD, continuous veno-venous hemodialysis; IHD, intermittent hemodialysis; SLED, sustained low efficiency dialysis; AKI, acute kidney injury.

The second important finding is that the average dose of therapy, both prescribed and delivered, was relatively high compared with what is typically recommended based on high quality evidence.<sup>14,15</sup> Although this information was not reliably available in all patients, it provides important insight into current practice patterns within the burn critical care community. The profound and sustained hypercatabolic states observed in the severely burned have been well documented.<sup>16</sup> This predisposes these patients to profound metabolic disturbances that may benefit from a relatively higher dose of therapy. Interestingly, Yoon et al recently reported an overall mortality of 81% in this population treating primarily with continuous veno-venous hemodiafiltration (CVVHDF) at prescribed doses around 30 ml/kg/hour.

The third point of emphasis centers on the timing of RRT initiation. Based on the breakdown of AKI stage at the time of RRT initiation, there is suggestion that most of these patients were put on relatively early. In the management of burn patients with severe AKI, a traditional approach of waiting for classic triggers for initiation of RRT (such as acidosis, severe electrolyte abnormalities, intractable fluid overload, and uremic complications) may result in an unacceptably high mortality. An aggressive approach of initiating RRT with early AKI combined with metabolic derangements led us to an absolute reduction in mortality by 30% when compared with historical controls, most of whom never met classic criteria for renal replacement and thus were not offered RRT.<sup>8</sup> One recent single center randomized control trial validated a similarly aggressive approach.<sup>7</sup> Unfortunately, another multicenter study did not show a difference in outcome.<sup>17</sup> A recent

meta-analysis suggests no added benefit of early initiation of RRT.<sup>18</sup>

The fourth intriguing finding for our study was that the mortality rate observed is the lowest ever reported in this population. Overall, hospital mortality among thousands of critically ill patients who develop AKI in a multinational study was 60%.<sup>19</sup> Mortality as high as 80% has been reported among those requiring RRT.<sup>10</sup> Hence, this relatively low mortality rate of 50% in the severely burned is quite remarkable. It could be argued that some of these patients may have been placed on RRT when they would have otherwise recovered their renal function without it. However, it could be that the combination of early initiation along with a relatively high intensity of therapy that was individualized may explain this low mortality. In a recent meta-analysis, the only subgroup that seemed to benefit from high intensity RRT was patients with post-surgical AKI.<sup>20</sup>

Finally, the majority of survivors experienced renal recovery as evidenced by being off of RRT at discharge and at a minimum 6-month follow-up post-discharge. In fact, a 90% recovery rate amongst survivors is similar to what has been reported in the past from other studies.<sup>21,22</sup>

This study is not without some limitations. The vast majority of data collection occurred retrospectively, although some of these patients were identified prospectively. Additionally, this observational study ran concurrent with a prospective interventional trial.<sup>13</sup> Thus, those that met inclusion and exclusion criteria for that study were not included into this one. The overall in-hospital mortality in that interventional trial (n = 37) was 62%. The relatively low mortality of 50% must be interpreted in that context. Finally, there is inherent bias that could be present due to the fact that all participating centers had an existing RRT program with a preference towards continuous modes. This bias must be taken into consideration when interpreting our findings.

## CONCLUSION

This is the largest multicenter cohort of critically ill burn patients who underwent RRT reported to date. Most patients who survived to discharge eventually recovered renal function. Timely initiation of RRT with an individualized preference towards continuous modes at relatively higher than recommended doses has become standard practice in critically ill burns with AKI and is associated with a historically low mortality

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