Association of Rhabdomyolysis With Renal Outcomes and Mortality in Burn Patients

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The contribution of rhabdomyolysis to acute kidney injury (AKI) in the context of burn injury is poorly studied. We sought to determine the impact of rhabdomyolysis on AKI (defined by the AKI Network classification), renal replacement therapy (RRT), and death. Patients admitted to the burn unit at our institution were examined. Information on sex, age, presence of inhalation injury, electrical burn, percentage TBSA burned, percentage of full-thickness burns, Injury Severity Score, and peak creatine kinase (CK) were recorded. These variables were examined via multivariate logistic regression analysis against AKI Network stage, RRT, and death. Of 1973 consecutive admissions meeting the inclusion criteria, 525 met our eligibility criteria. Log peak CK was found to be correlated with any stage of AKI (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.36–2.16; $P < .0001$), moderate to severe AKI (OR, 2.09; 95% CI, 1.40–3.11; $P = .0003$), need for RRT (OR, 1.67; 95% CI, 1.16–2.40; $P = .0057$), and mortality (OR, 1.49; 95% CI, 1.01–2.20; $P = .0441$), after adjustment. Each 10-fold increase in peak CK was associated with a 70% increase in the odds of AKI, more than a 100% increase in the odds of moderate to severe AKI, a nearly 70% increase in the odds of RRT, and an almost 50% increase in the odds of mortality in patients with burn injury. (J Burn Care Res 2013;34:318–325)

Rhabdomyolysis is a process by which the cellular contents are released into circulation after damage to skeletal muscle. Their release can result in profound effects on renal function. As recently reviewed by Bosch et al,[1] the major causative factors in renal damage are intrarenal vasoconstriction and toxicity of myoglobin. Vasoconstriction is the result of fluid sequestration in the damaged muscle with resultant up-regulation of the sympathetic nervous system, renin–angiotensin–aldosterone system, and arginine vasopressin. Additional factors that promote vasoconstriction, such as F_2-isoprostanes, endothelin-1, thromboxane A_2, tumor necrosis factor α, and nitric oxide deficiency have also been implicated in this process. Myoglobin is postulated to have deleterious effects in the kidney as a result of oxygen-free radical production and precipitation with Tamm–Horsfall protein in the tubule. Although burn patients have been reported to have rhabdomyolysis as a complication of their injuries, risk factors for the development of rhabdomyolysis and its subsequent effect on acute kidney injury (AKI) and mortality are not well understood.[2]

Although prior estimates of rates of AKI in the burn population widely varied, in part because of differences in both definitions of AKI and inclusion criteria, recent studies using the risk, injury, failure, loss, and end-stage (RIFLE) criteria[3] have estimated

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the incidence at approximately 25%.[4–6] These studies consistently demonstrated high rates of mortality in burn patients with AKI with increasing risk of death at higher RIFLE stage. Patients in the "failure" category had a risk of death of 60 to 83% compared to rates of 6 to 8% in those without AKI. These mortality rates in the burn population with RIFLE class failure are seemingly higher than the rate of 33.2 to 56.8% seen in the intensive care unit (ICU) population as a whole.[7,8] In addition to increased mortality, AKI has been associated with increased morbidity in the form of longer time in the hospital, time in the ICU, and time on mechanical ventilation.[4]

Numerous studies have attempted to identify factors associated with the development of AKI and with the morbidity and mortality that result from renal injury in burn patients. Factors that have been correlated with the development of AKI in the burn population include inhalation injury, age, percentage burned of TBSA, extent of full-thickness burns, catheter infection, and sepsis.[2,4–6,9] In the AKI setting, factors shown to increase the risk of death are TBSA, higher abbreviated burn severity index scores, inhalation injury, flame burn, and rhabdomyolysis.[2] Given the implications of AKI in burn patients, identification of factors involved could guide research to improve outcomes in this high-risk population.

Little is currently known about the potential role of rhabdomyolysis in the development of AKI and subsequent mortality in the burn population. We sought, in a retrospective fashion, to establish an association of rhabdomyolysis with AKI, renal replacement therapy (RRT), and mortality in a population of burn patients. Additionally, we attempted to establish a level of creatine kinase (CK) that is associated with poor outcomes.

METHODS

After approval from the institutional review board, we retrospectively reviewed all admissions to our institution from January 2003 to November 2008. Patients were included if they were hospitalized for more than 24 hours, had a measured serum creatinine, and did not have end-stage renal disease. Patients were excluded from the analysis if they did not have a measured CK, if they did not have complete data, or if the elevation of CK could be secondary to myocardial infarction (defined for study purposes as those with a recorded diagnosis of myocardial infarction on review of the medical record). Baseline creatinine was determined by using the lowest value of creatinine during the first week of hospital admission. AKI Network-1 (AKIN-1) was defined as a 1.5-fold to <2-fold increase in creatinine (or an absolute increase of >0.3 mg/dl), AKIN-2 as a 2-fold to <3-fold increase, and AKIN-3 as a >3-fold increase from baseline (or an increase of 0.5 mg/dl when the baseline was more than 4 mg/dl).[10] By definition, all patients requiring RRT were classified as AKIN-3. We did not have data on urine output; therefore, it was not used to classify AKIN stage. If a patient had only one creatinine measured in the course of his or her hospitalization or if the creatinine continued to rise in the course of the first 7 days, a baseline creatinine was estimated by solving the modification of diet in renal disease study equation assuming an estimated glomerular filtration rate (GFR) of 75 ml/min/1.73 m^2. In determining the AKIN stage, the highest creatinine was compared with the baseline. Therefore, AKIN stage is reported as the highest stage during the subject's hospitalization.

At our institution, patients admitted with >20% TBSA burns are resuscitated using the modified Brooke formula to derive the initial fluid rate. Fluid rates are then titrated using a compilation of end points centered on a urine output target between 30 and 50 ml/hr for standard burns and 50 to 100 ml/hr for electrical burns. As we have not seen different renal outcomes with this approach,[11] there were no differences in how patients with and without AKI were resuscitated.

All pertinent data were analyzed using descriptive and correlational statistics as appropriate to compare those patients who developed rhabdomyolysis and those who did not. Overall, standard descriptive statistical methods were used to analyze other data; categorical variables from each group were compared via χ^2 analysis, whereas continuous variables were compared via Student's *t*-test or Wilcoxon's test as appropriate. A multiple logistic regression analysis was performed to analyze the relationship between independent variables of age, sex, TBSA, full-thickness burn, inhalation injury, Injury Severity Score (ISS), electrical burn, and logarithm of the peak CK during admission (log peak CK) against dependent variables of AKI (by AKIN criteria), RRT, and death. The AKIN classification was added to the death model. Factors that were deemed insignificant ($P > .1$) were removed from the model via backward elimination. Although a peak CK was recorded for all patients, we used a log base 10 transformation in the data analysis to normalize the peak CK values. Peak CK values were highly right-skewed with a skew factor of +10.56. Log base 10 transformation was used to normalize the peak CK values bringing the skewness factor down to +0.52. This value was

still statistically significant, but these results were much more manageable, and reliance of the central limit theorem was markedly improved using the log transformation.

To establish a CK level that is associated with poor outcomes, we examined a composite end point of AKIN-2, AKIN-3 (which includes RRT by definition), and death. The CK value associated with a >50% chance of the composite end point was then calculated.

RESULTS

Of 1973 admissions that met the inclusion criteria, 1442 did not have a measured CK, 5 were diagnosed with myocardial infarctions, and 1 had incomplete data, leaving 525 patients for analysis. Characteristics of the patients studied are summarized in Table 1. Patients who had a CK measured were significantly different from patients who did not have a CK measured on all variables examined. In general, patients with a CK measured were older, more acutely ill and more likely to have electrical injury. The majority of patients included for analysis were male (83.4%), with an average age of 43.8 years. Mean value for TBSA and full-thickness TBSA with SD were 27.9 ± 24.2% and 15.6 ± 22.8%, respectively. Average ISS was 18.3. Sixteen percent of patients had electrical burns, and 28.8% had inhalation injury. The median number of days on mechanical ventilation, in ICU, and in the hospital (± SD) were 12.5 ± 29.5, 20.5 ± 35.3, and 35.5 ± 46.4, respectively. Median peak CK was 5042 U/L with an SD of 19,565 U/L. AKI, defined by the AKIN criteria, was present in 63% of patients, with 29.9% having AKIN-2 or AKIN-3. Mean day of AKI was 3.9. The majority of patients (55.3%) met AKIN criteria on the first hospital day, whereas 33.8 and 10.9% met AKIN criteria on hospital days 2 to 7 and day 8 or later, respectively (Figure 1). The overall mortality of the cohort was 24%, and 11.1% of patients required RRT. The average blood urea nitrogen and creatinine prior to RRT initiation was 44.1 ± 26.91 and 2.67 ± 1.92, respectively. The mean hospital day that RRT was started was 13 ± 18.3 days. The mortality in the group that received RRT was 70.1%. Of the patients requiring RRT who survived to discharge, only one required maintenance hemodialysis. The prevalence of AKIN-2 or AKIN-3, death, and RRT increased with each 10-fold increase in CK (Figure 2).

Table 1. Characteristics of patient cohort

Variables	Patients With CK Measured	Patients Without CK Measured	*P*
Male (%)	83.4	87.5	.0215
Age (yr)	43.8 ± 19.1	33.5 ± 14.2	<.0001
Peak CK (units/L)	5042 ± 19565	—	—
Ventilator days	12.5 ± 29.5	1.5 ± 6.9	<.0001
ICU days	20.5 ± 35.3	4.0 ± 17.0	<.0001
Hospital days	35.5 ± 46.4	14.4 ± 29.1	<.0001
ISS	18.3 ± 15.1	7.3 ± 9.2	<.0001
Electrical burn (%)	16.0	1.3	<.0001
TBSA (%)	27.9 ± 24.2	11.3 ± 12.7	<.0001
Full-thickness TBSA (%)	15.6 ± 22.8	3.9 ± 10.6	<.0001
Inhalation injury (%)	28.8	6.7	<.0001
AKI* (%)	63.0	21.4	<.0001
AKIN-2 or AKIN-3 (%)	29.9	3.9	<.0001
Day of AKI* (hospital day)	3.9 ± 10.7	2.8 ± 4.6	<.0001
Renal replacement therapy (%)	11.1	0.8	<.0001
Mortality (%)	24.0	1.0	<.0001

CK, creatine kinase; *ICU*, intensive care unit; *ISS*, Injury Severity Score; *AKI*, acute kidney injury; *AKIN*, AKI Network criteria.
Data expressed as an average ± SD where appropriate.
*By AKIN criteria.

For patients with rhabdomyolysis (defined as peak CK ≥ 3925 U/L, as below), CK was first checked on average hospital day 1.5 ± 1.7. Hospital day of first CK meeting the threshold of 3925 U/L was 2.5 ± 5.8. Hospital day of peak CK was 2.8 ± 5.8. Peak CK occurred with the first measurement for the majority of patients (68.8%). In patients with both rhabdomyolysis and AKI (N = 83), the rise in CK occurred before AKI in 25.3% and concurrently with AKI in 37.3%. AKI occurred before rhabdomyolysis in 18.1%. In 19.3% of patients, CKs were only checked after the development of AKI.

For the outcome of AKI (Table 2), log peak CK (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.36–2.16; $P < .0001$), age (OR, 1.02; 95% CI, 1.01–1.03; $P = .0012$), and TBSA (OR, 1.04; 95% CI, 1.03–1.05; $P < .0001$) were significant. Electrical burn was associated with less AKI in the model (OR, 0.43; 95% CI, 0.25–0.75; $P = .0026$). Log peak CK was also correlated with AKIN-2 to AKIN-3 (OR, 2.09; 95% CI, 1.40–3.11; $P = .0003$) after adjustment (Table 3). Age (OR, 1.02; 95% CI, 1.01–1.04; $P = .0103$), inhalation injury (OR, 2.34; 95% CI, 1.17–4.66; $P = .0160$), and TBSA (OR, 1.06; 95% CI, 1.04–1.08; $P < .0001$) were also correlated with AKIN-2 to AKIN-3, whereas electrical burn was again associated with less AKI (OR, 0.28; 95% CI, 0.11–0.68; $P = .0052$).

For RRT, only log peak CK (OR, 1.67; 95% CI, 1.16–2.40; $P = .0057$), TBSA (OR, 1.02; 95% CI, 1.01–1.04; $P = .0003$), and inhalation injury (OR,

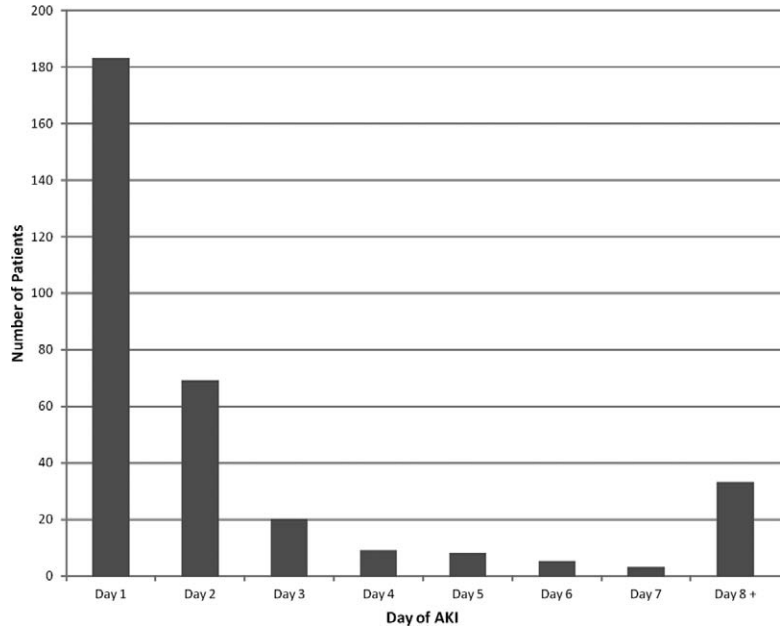

Figure 1. Hospital day of the diagnosis of acute kidney injury (AKI), by the AKI Network criteria.

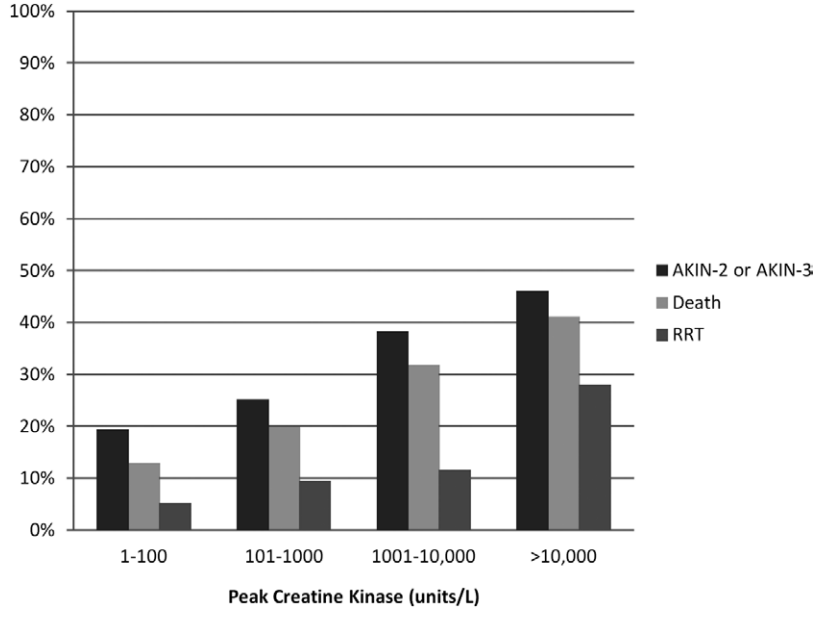

Figure 2. Incidence of Acute Kidney Injury Network (AKIN)-2 or AKIN-3, death, and renal replacement therapy (RRT) stratified by creatine kinase.

1.83; 95% CI, 0.99–3.40; $P = .0548$) had a $P < .1$, which was our criterion for inclusion in the final model (Table 4).

Log peak CK was also significantly associated with mortality (OR, 1.49; 95% CI, 1.01–2.20; $P = .0441$) in the multivariate regression (Table 5). Age (OR, 1.07; 95% CI, 1.05–1.09; $P < .0001$), ISS (OR, 1.07; 95% CI, 1.04–1.11; $P < .0001$), TBSA (OR, 1.04; 95% CI, 1.02–1.06; $P = .0002$), and all AKIN stages were also associated with death. Male sex was associated with less mortality in this model (OR, 0.32; 95% CI, 0.15–0.68; $P = .0029$).

We found that the peak CK associated with a >50% chance of a composite of AKIN-2, AKIN-3 (which includes RRT), and death was 3925 U/L. This represented 20.2% of the patients studied (N = 106).

On the assumption that injury severity alone could predict rhabdomyolysis and subsequent outcomes,

Table 2. Multivariate logistic regression analysis for the outcome of AKIN stages 1 to 3

Variables	OR (95% CI)	*P*
Age	1.02 (1.01–1.03)	.0012
Electrical injury	0.43 (0.25–0.75)	.0026
TBSA burned	1.04 (1.03–1.05)	<.0001
Inhalation injury	1.56 (1.06–2.31)	.0249
Log of creatine kinase	1.71 (1.36–2.16)	<.0001

OR, odds ratio; *CI*, confidence interval; *AKIN*, Acute Kidney Injury Network criteria.

we did a subgroup analysis of patients with an ISS >25 (N = 338). In the multivariate models for this subset, log peak CK was no longer significant. However, when the variable was dichotomized to a peak CK cutoff of 3925, it was significant for mortality (OR, 2.74; 95% CI, 1.34–5.58; *P* = .0056) and AKIN-2 to AKIN-3 (OR, 2.14; 95% CI, 1.20–3.82; *P* = .0098), after adjustment.

DISCUSSION

We report an association of rhabdomyolysis with mortality, AKI, and RRT in the burn population. Our results show that after adjustment, for every 10-fold increase in peak CK, the odds of AKI by AKIN criteria increased by more than 70%, the odds of RRT increased by 67%, and the odds of death increased by nearly 50%. Similarly, the odds of moderate to severe AKI (AKIN-2 or AKIN-3) more than doubled.

Although the incidence and risk for the development of AKI in the setting of rhabdomyolysis are not well understood in the burn population specifically, a body of evidence does exist in other clinical conditions. In the largest study to date of trauma patients (N = 2083), 85% were found to have an elevated CK, and 10% of patients had AKI (defined as serum creatinine > 2 mg/dl).[12] A CK level of 5000 U/L was the lowest level associated with a risk of AKI above that of the population as a whole. The group with high CK was also noted to have higher peak blood urea nitrogen, creatinine, and longer ICU stay. Another high-risk group, patients undergoing cardiac surgery, is known to be at risk for AKI and have poor outcomes.[13] One study that examined patients undergoing coronary artery bypass grafting found that patients with elevations in myoglobin (>465 μg/ml) were more likely to develop AKI after adjustment.[14] Although CK was also correlated with this outcome, serum myoglobin was found to have better receiver operator characteristics.

Though little research has been published about rhabdomyolysis specific to the burn population, previous work suggests that it is associated with increased AKI and morbidity. Ward[15] reported a study that included eight burn patients and demonstrated that rhabdomyolysis had an increased risk of AKI with an OR of 6.95. In a study of 238 burn patients, Mustonen and Vuola [2] reported the incidence of rhabdomyolysis (defined as CK > 5000 U/L) was 17.2% in those with AKI. In this subset, renal dysfunction occurred earlier (5.2 vs 9.7 days) and required RRT more often (75 vs 40.3%). A significant limitation in these articles is their small sample size. To our knowledge, our study is the largest to date examining the incidence and outcomes of rhabdomyolysis in the burn population. Our findings confirm the prior data, as we demonstrated that each 10-fold increase in peak CK is associated with a 70% increase in the odds of

Table 3. Multivariate logistic regression analysis for the outcome of AKIN stages 2 to 3

Variables	OR (95% CI)	*P*
Age	1.02 (1.01–1.04)	.0103
Electrical injury	0.28 (0.11–0.68)	.0052
TBSA burned	1.06 (1.04–1.08)	<.0001
Inhalation injury	2.34 (1.17–4.66)	.0160
Log of creatine kinase	2.09 (1.40–3.11)	.0003

OR, odds ratio; *CI*, confidence interval; *AKIN*, Acute Kidney Injury Network criteria.

Table 4. Multivariate logistic regression analysis for the outcome of renal replacement therapy

Variables	OR (95% CI)	*P*
TBSA	1.02 (1.01–1.04)	.0003
Inhalation injury	1.83 (0.99–3.40)	.0548
Log of peak creatine kinase	1.67 (1.16–2.40)	.0057

OR, odds ratio; *CI*, confidence interval.

Table 5. Multivariate logistic regression analysis for the outcome of in-hospital mortality

Variable	OR (95% CI)	*P*
Male sex	0.32 (0.15–0.68)	.0029
Age	1.07 (1.05–1.09)	<.0001
ISS	1.07 (1.04–1.11)	<.0001
TBSA	1.04 (1.02–1.06)	.0002
AKIN-1*	3.21 (1.08–9.51)	.0352
AKIN-2*	3.69 (1.02–13.41)	.0473
AKIN-3*	21.42 (7.03–65.31)	<.0001
Log of peak creatine kinase	1.49 (1.01–2.20)	.0441

OR, odds ratio; *CI*, confidence interval; *ISS*, Injury Severity Score; *AKIN*, Acute Kidney Injury Network criteria.
*Compared to no AKI by AKIN criteria.

AKI, more than a 100% increase in the odds of moderate to severe AKI, and nearly 70% in need of RRT.

As with morbidity, little is known about the contribution of rhabdomyolysis to mortality in the burn population. In a prior series of AKI in burn patients, 16 had rhabdomyolysis (defined as CK > 5000 U/L). In this subset of patients, mortality was 56.3% with nonsurvivors having greater TBSA, more inhalation injury, and higher abbreviated burn severity index scores.[2] Other studies have noted an increase in mortality in patients who develop AKI in the setting of rhabdomyolysis in the ICU[15] and a general hospital population as a whole.[16] Myoglobinemia has also been associated with full-thickness burns and correlated with risk of early death in one small study of severely burned patients.[16] Only one of the patients in this group, however, developed renal failure, and CK was not found to be associated with the extent of burn or mortality. Our study supports the hypothesis that rhabdomyolysis is associated with mortality as we found that the odds of mortality increased by nearly 50% with each 10-fold increase in peak CK.

We found that age, TBSA, and AKI were significantly correlated with mortality, which is similar to prior published work.[4] Notably, however, we also found that male sex was negatively correlated with mortality, and ISS was positively correlated with mortality. Although the correlation of ISS is readily biologically plausible, the reason for negative correlation with male sex is less clear. It is possible that differences in muscle mass, which could affect both AKI classification (which is based on creatinine) and CK release, could explain these findings. It is also possible that this finding is a false-positive and represents a type I error.

The absolute value of CK that was associated with a >50% chance of a composite of AKIN-2, AKIN-3 (which includes RRT), and death was 3925 U/L. This number differs from the value of 5000 U/L arrived at in the article by Brown et al.[12] This disparity could be because of the differences in the population studied, differences in laboratory measurement, or differences in the statistical methods used to arrive at the cutoff. Differing definitions of AKI could also have contributed to this disparity. Brown et al used a creatinine of >2 mg/dl, which is a less-sensitive method than the AKIN criteria, but it is somewhat analogous to our end point of AKIN-2 to AKIN-3. Of the 1973 patients in the full cohort that we examined, 5.4% had a CK level above 3925 U/L. This level likely represents a lower limit of the incidence of rhabdomyolysis in this population as CK was checked in a minority of patients (26.9%). Additionally, we found that the degree of CK elevation was associated with a risk of AKI, RRT, and mortality. Other studies have found a similar correlation,[15,17,18] but it has been seen less so or not at all in others.[19,20] It has also been suggested that blood myoglobin levels may be a better predictor of AKI than CK.[21] Unfortunately, serum myoglobins were checked in a minority of our patients with elevated CKs and very rarely assessed in patients with lower CK values. Therefore, this could not be included in the study.

Patients with electrical injury comprised 16% of the cohort who had a CK checked. However, patients with an electrical injury only made up 5.3% of the full database used for the present study, which is more in line with prior estimates of the incidence of electrical injury in burn centers.[22] This implies that more patients with electrical injuries had a CK checked compared to patients without electrical injuries, likely as a result of the known association of electrical injury with rhabdomyolysis.[23] Indeed, we found that 81.9% of patients in our database with electrical injury had a CK checked compared to 19.2% of patients without electrical injury. This tendency to check CKs in patients with electrical injury, regardless of burn size and severity of illness, may explain why electrical injury was associated with less AKI in our model. The more aggressive fluid resuscitation given to patients with electrical injury may have contributed to this difference as well.

Our study has several limitations. First, its retrospective design makes it susceptible to all the limitations and biases inherent to this type of study. One possible source of selection bias is that we relied on CKs drawn at the discretion of the physicians caring for the patients. Indeed, as shown in Table 1, patients with a CK measured were older and more acutely ill. Our results need to be placed in this context. We also do not have data on how these patients were treated, and thus cannot comment on how different treatment regimens might have influenced outcomes. Additionally, the baseline creatinine was not known in our patient population, and the lowest value obtained during the first week of hospitalization was preferentially used as the baseline to establish AKIN criteria. Although this method has proven to be superior to backcalculating creatinine, assuming an estimated GFR of 75 ml/min/1.73 m^2 by the modification of diet in renal disease equation (a method we also used for some patients), it still overestimates AKIN-1 and underestimates AKIN-2 and AKIN-3.[24] Furthermore, AKIN and RIFLE also classify patients on the basis of urine output, which was not available to us. Our method to exclude increased CK potentially secondary to myocardial infarction was to review the medical record for this diagnosis. It is

possible that this method was not sufficiently sensitive to exclude these patients who would likely have higher rates of AKI and death. It is also worthwhile to note that the muscle injury that induced the elevation in CK could also have resulted in an increased creatinine level irrespective of changes in GFR, thus artificially increasing the risk of AKI by the AKIN criteria. Because AKIN-1 can be diagnosed with as little as a 0.3 mg/dl rise in creatinine, we did a separate analysis that only included AKIN-2 and AKIN-3 (which requires at least a 2-fold increase in creatinine) and examined the hard end point of mortality. That said, there is some work demonstrating that the RIFLE classification system,[3] which is similar to the AKIN criteria, has prognostic value in the setting of rhabdomyolysis.[25] Last, the results from a cohort of burn patients may not be generalizable to the population as a whole. Although studying a critically injured burn population may make the results less generalizable, there are advantages to studying AKI in this setting. Because mortality rates in this population are quite high, it is theoretically easier to find associations in retrospective studies and differences in treatment protocols in prospective studies. Results in this population could serve to generate hypotheses that could later be tested in other cohorts of patients.

In summary, we found that elevations in CK were significantly associated with the risk of AKI, RRT, and death. A prospectively designed trial measuring CK in all critically injured burn patients would be required to establish a true prevalence of rhabdomyolysis in this population and to verify the link with morbidity and mortality. Although mannitol and bicarbonate therapy have not shown promise in treating this disorder,[12] future randomized trials could examine the therapeutic benefits of newer therapies such as fenoldopam[26] or RRT.[27,28]

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