

Association of AKI with Adverse Outcomes in Burned Military Casualties

Ian J. Stewart,* Molly A. Tilley,* Casey L. Cotant,* James K. Aden,[†] Christopher Gisler,[‡] Hana K. Kwan,* Jeffery McCorcle,[†] Evan M. Renz,[†] and Kevin K. Chung[†]

Summary

Background and objectives Although associated with increased morbidity and mortality, AKI has not been systematically examined in military personnel injured from combat operations in Iraq and Afghanistan.

Design, settings, participants, & measurements Patients evacuated from Iraq and Afghanistan to a burn unit were examined. AKI was classified by the Acute Kidney Injury Network (AKIN) and Risk-Injury-Failure-Loss-End Stage (RIFLE) schemas. Age, sex, percentage of total body surface area burned (TBSA), percentage of full-thickness burn, inhalation injury, and injury severity score were recorded. Additional data that could be associated with poor outcomes were recorded for patients with TBSA \geq 20%. Multivariate logistic regression analyses were performed to determine factors associated with morbidity and mortality.

Results AKI prevalence rates by the RIFLE and AKIN criteria were 23.8% and 29.9%, respectively. After logistic regression, RIFLE categories of risk (odds ratio [OR], 15.34; 95% confidence interval [CI], 1.75–134; $P=0.01$), injury (OR, 46.28; 95% CI, 5.02–427; $P<0.001$), and failure (OR, 126; 95% CI, 13.39–>999; $P<0.001$); AKIN-2 (OR, 23.70; 95% CI, 2.32–242; $P=0.008$); and AKIN-3 (OR, 130; 95% CI, 13.38–>999; $P<0.001$) were significantly associated with death. AKIN-3, injury, and failure remained significant in the subset of patients with \geq 20% TBSA. There was also a strong interaction between TBSA and the stage of AKI with respect to ventilator and intensive care unit days.

Conclusions AKI is prevalent in military casualties with burn injury and is independently associated with morbidity and mortality after adjustment for factors associated with injury severity.

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Introduction

AKI has been associated with an increase in morbidity and mortality in a wide range of patient populations. Progress in the field of AKI research, however, was hindered by differing definitions. To standardize results, the Acute Dialysis Quality Initiative put forth the Risk-Injury-Failure-Loss-End Stage (RIFLE) criteria (1). These criteria were later modified by the Acute Kidney Injury Network (AKIN) (2) to reflect the fact that even small changes in serum creatinine portend a worse prognosis (3,4).

In two large cohort studies of intensive care (ICU) patients that used the RIFLE criteria, AKI had a prevalence of approximately 36% and was significantly associated with increased mortality (5,6). Similar results have been observed in the hospitalized population as a whole (7), patients undergoing cardiac surgery (8), and burn patients (9–11).

To our knowledge, the incidence of AKI and its effect on morbidity and mortality in patients injured in support of combat operations in Iraq and Afghanistan has not been examined. These patients are, however, subject to many potential risk factors for AKI, including hypoperfusion (12), sepsis (6), nephrotoxins (13),

intra-abdominal hypertension (14), transfusions (15), exposure to iodinated contrast material (16), burns (9–11), and trauma (15). We sought to determine the incidence of AKI, as well as its effect on morbidity and mortality in military casualties.

Materials and Methods

After permission was obtained from the Institutional Review Board, admissions to the US Army Institute of Surgical Research Burn Center from January 2003 to November 2008 were screened. Patients were included if they were military personnel burned in Iraq or Afghanistan. Patients were excluded if they were evacuated from a location other than Iraq or Afghanistan, did not have a recorded creatinine, or were hospitalized $<$ 24 hours. Only a patient's first admission was considered.

Serum creatinine levels were used to classify the stage of AKI based on the AKIN (2) and RIFLE (1) criteria. Because the military does not measure creatinine as part of routine physical examinations, a known baseline was not available. Therefore, the lowest creatinine value in the first 7 days was used to

*San Antonio Military Medical Center, Fort Sam Houston, Texas; [†]US Army Institute of Surgical Research, Fort Sam Houston, Texas; and [‡]University of Texas Health Science Center at San Antonio, San Antonio, Texas

Correspondence:

Dr. Ian J. Stewart, San Antonio Military Medical Center, ATTN: Nephrology, 3551 Roger Brooke Drive, Fort Sam Houston, TX 78234. Email: ian.stewart@us.af.mil

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determine whether the patient had AKI at admission. If the patient did not have AKI at admission, a 0.3-mg/dl increase within 48 hours was required to diagnose AKI by the AKIN criteria. The maximum creatinine level was then compared with this baseline to determine AKIN stage. Patients who had renal replacement therapy were classified as AKIN-3. RIFLE stage was determined in a similar manner, except that there was no time requirement for the increase in creatinine, a 50% increase in creatinine was required to diagnose AKI, and RRT did not automatically place the patient in the most severe category. If a patient did not have serial creatinine measurements, or if it increased over 7 days, it was compared with a baseline derived by solving the Modification of Diet in Renal Disease (MDRD) study equation assuming an estimated GFR of 75 ml/min per 1.73 m² (1,2).

Age, sex, percentage of total body surface area burned (TBSA), percentage of full-thickness burn (FT TBSA), and presence of inhalation injury were retrospectively collected for all patients. Injury severity score (ISS) (17) was taken from a prospectively collected database. To assess other factors potentially associated with mortality, we examined additional variables for patients with $\geq 20\%$ TBSA, including the total units of packed red blood cells (PRBCs), traumatic brain injury (TBI), sepsis, and acute respiratory distress syndrome or acute lung injury. PRBCs were quantified using data from our blood bank. Patients were considered to have sepsis if they had positive blood cultures and had the diagnosis of sepsis listed in their medical record. Patients were considered to have TBI, acute respiratory distress syndrome, or acute lung injury if these diagnoses were listed in the medical record.

Multivariate logistic regression analyses were done with independent variables of age, sex, TBSA, FT TBSA, inhalation injury, ISS, and AKIN stage and with dependent variables of in-hospital death, days on mechanical ventilation, days in the ICU, and days in the hospital. Factors that were not significant ($P > 0.1$) were removed from the model via backward elimination. The same analyses were also done for the RIFLE criteria and were repeated with the additional variables collected for the patients with $\geq 20\%$ TBSA. Receiver-operating characteristic curves were performed to examine the discriminating power of the models for the outcome of death.

Results

We identified 744 patients. Of these, 28 did not have a measured creatinine level, 3 were not injured in Iraq or Afghanistan, 12 did not have burns, 1 died en route, 1 was being readmitted, and 7 were hospitalized for <24 hours (Figure 1). This left 692 patients for analysis. Patient characteristics are summarized in Table 1. Most of our patients were male (97.5%), and 7.9% were African American. The patients had an average age \pm SD of 25.5 \pm 5.9 years. Median values were as follows: ISS, 9 (interquartile range [IQR], 1–24); TBSA, 9 (IQR, 4–24); and FT TBSA, 1 (IQR, 0–13.75). Inhalation injury was diagnosed in 16.6% of patients. Mortality for the cohort was 5.9%. The median durations of ventilator support, ICU days, and hospital days were 0 (IQR, 0–4), 0 (IQR, 0–10.5), and 12 (IQR, 6–35.5), respectively. The average creatinine and estimated GFR,

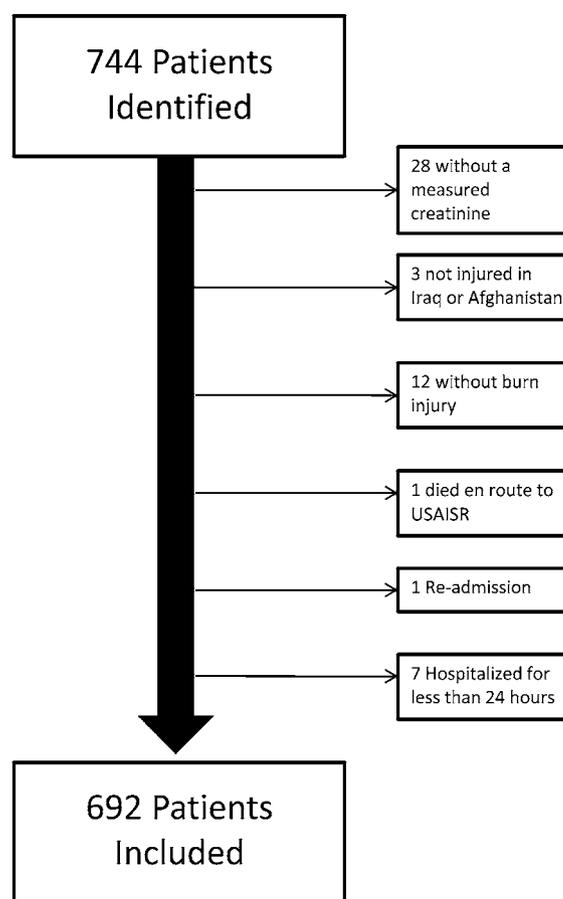


Figure 1. | Flow diagram of patients screened and reasons for exclusion. USAISR, US Army Institute of Surgical Research

by the Chronic Kidney Disease Epidemiology Collaboration equation, at admission for patients who developed AKI (by the AKIN criteria) were 1.24 mg/dl and 97 ml/min per 1.73 m², compared with 0.89 mg/dl and 116 ml/min per 1.73 m² for those without AKI. Peak creatinine levels for patients with no AKI and those with AKIN-1, -2, or 3 were 0.94, 1.20, 1.98, and 3.70 mg/dl, respectively. Nearly 6% of patients required renal replacement therapy. The characteristics of the patients with $\geq 20\%$ TBSA are summarized in Table 2.

The prevalence rates of AKI by RIFLE criteria were 14.0% for risk, 5.2% for injury, and 4.6% for failure, with mortality rates of 8.3%, 33.3%, and 62.5%, respectively (Figure 2). Patients without AKI by RIFLE had a mortality rate of 0.2%. Similar results were seen for the AKIN criteria, with an AKI prevalence of 19.7% for AKIN-1, 4.0% for AKIN-2, and 6.2% for AKIN-3. Mortality rates for AKIN-1, -2, and -3 were 4.4%, 21.4%, and 65.1%, respectively, compared with 0.2% for patients without AKI (Figure 3). The baseline creatinine levels were determined by back-calculating the MDRD calculation for 23.6% of patients. More patients in the no-AKI group (by AKIN) had their baseline creatinine levels determined by this method (31.6%) than did the AKI group (4.8%). The majority of patients (57.6%) had AKI identified at admission to our institution, whereas 24.8%, 10%, and 7.6% had AKI

Table 1. Characteristics of patient cohort

Characteristic	Value
Age (yr)	25.5±5.9
Men (%)	97.5
African Americans (%)	7.9
Median ISS (IQR)	9 (1 24)
Median TBSA (IQR) (%)	9 (4 24)
Median FT TBSA (IQR) (%)	1 (0 13.75)
Median ventilator days (IQR)	0 (0 4)
Median ICU days (IQR)	0 (0 10.5)
Median hospital days (IQR)	12 (6-35.5)
Inhalation injury (%)	16.6
Renal replacement therapy (%)	5.9
Mortality rate (%)	5.9
Admission creatinine in patients with AKI ^a (mg/dl)	1.24±0.82
Admission creatinine in patients without AKI ^a (mg/dl)	0.89±0.15
Admission eGFR in patients with AKI ^a by CKD-EPI (ml/min per 1.73 m ²)	97±31
Admission eGFR in patients without AKI ^a by CKD-EPI (ml/min per 1.73 m ²)	116±16
Admission eGFR in patients with AKI ^a by MDRD (ml/min per 1.73 m ²)	89±32
Admission eGFR in patients without AKI ^a by MDRD (ml/min per 1.73 m ²)	109±24
Creatinine at AKI ^a (mg/dl)	1.39±0.81
Peak creatinine in patients without AKI ^a (mg/dl)	0.94±0.16
AKIN-1 peak creatinine (mg/dl)	1.20±0.31
AKIN-2 peak creatinine (mg/dl)	1.98±0.57
AKIN-3 peak creatinine (mg/dl)	3.70±2.11
Median day of AKI diagnosis ^a (IQR)	1 (1 4)

Data expressed with a plus/minus sign are the mean ± SD. ISS, Injury Severity Score; IQR, interquartile range; TBSA, percentage of total body surface area burned; FT TBSA, percentage of TBSA that is full thickness; eGFR, estimated GFR; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

^aAs defined by the Acute Kidney Injury Network criteria.

Table 2. Characteristics of subgroup with ≥20% burn injury

Characteristic	Value
Age (yr)	25.8±6.5
Men (%)	98.5
African Americans (%)	8.8
Median ISS (IQR)	27.5 (24 35)
Median TBSA (IQR) (%)	37.25 (28 56.75)
Median FT TBSA (IQR) (%)	29.5 (16.75 47.75)
Median ventilator days (IQR)	6 (3 15.5)
Median ICU days (IQR)	15 (8 41)
Median hospital days (IQR)	47 (21 85)
Inhalation injury (%)	40.2
Sepsis (%)	57.8
PRBCs	27.5±35.1
ARDS or ALI (%)	10.3
TBI (%)	8.8
Renal replacement therapy (%)	11.8
Mortality (%)	18.1

Data expressed with a plus/minus sign are the mean ± SD. IQR, interquartile range; ISS, Injury Severity Score; TBSA, percentage of total body surface area burned; FT TBSA, percentage of TBSA that is full thickness; PRBCs, number of units of packed red blood cells per patient; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; TBI, traumatic brain injury.

identified at hospital days 2 7, days 8 14, and day 15 or later, respectively (Figure 4).

After logistic regression, age, TBSA, ISS, and AKIN were associated with an increased risk for death. Sex, inhalation injury, and FT TBSA were removed from the final model via backward elimination because they were not significantly associated with mortality (defined as $P>0.1$). In the model that included AKIN, odds ratios (ORs) were 1.10 (95% confidence interval [CI], 1.03 1.18; $P=0.004$) for age (per year increase), 1.03 (95% CI, 1.01 1.06; $P=0.02$) for TBSA (per 1% increase), and 1.04 (95% CI, 1.00 1.09; $P=0.08$) for ISS (per 1-point increase). The ORs for AKIN-2 and -3 were 23.70 (95% CI, 2.32 242; $P=0.008$) and 130 (95% CI, 13.38 >999; $P<0.001$), respectively (Table 3). In the subgroup of patients with TBSA ≥20% ($n=204$), only age (OR, 1.13; 95% CI, 1.04 1.22; $P=0.003$), TBSA (OR, 1.07; 95% CI, 1.03 1.11; $P<0.001$), acute respiratory distress syndrome or acute lung injury (OR, 6.02; 95% CI, 1.57 23.13; $P=0.009$), and AKIN-3 (OR, 32.59; 95% CI, 3.13 339; $P=0.004$) were associated with mortality after adjustment (Table 4). ISS, sepsis, TBI, PRBCs, AKIN-1, and AKIN-2 did not achieve significance. Similar results were seen in the regression model for the RIFLE criteria. After adjustment, the RIFLE categories of risk (OR, 15.34; 95% CI, 1.75 134; $P=0.01$), injury (OR, 46.28; 95% CI, 5.02 427; $P<0.001$) and failure (OR, 126; CI, 13.39 >999; $P<0.001$) were associated with an increased risk for death (Table 5). In patients with TBSA ≥20%, the RIFLE categories of injury (OR, 14.26; 95% CI, 1.46 139; $P=0.02$) and failure (OR,

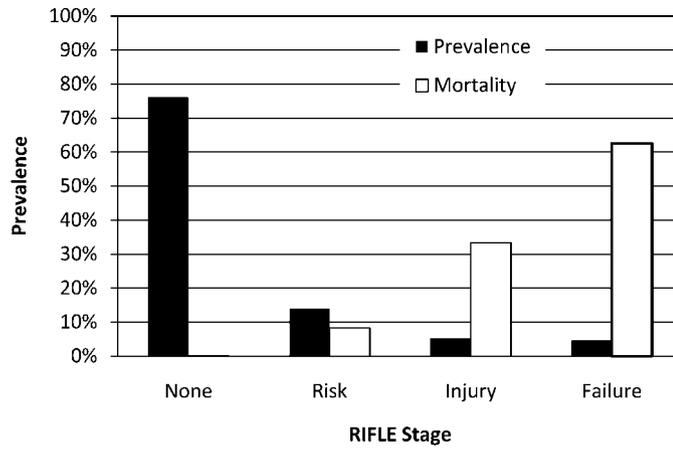


Figure 2. | Prevalence of AKI by Risk-Injury-Failure-Loss-End Stage (RIFLE) stage with corresponding mortality.

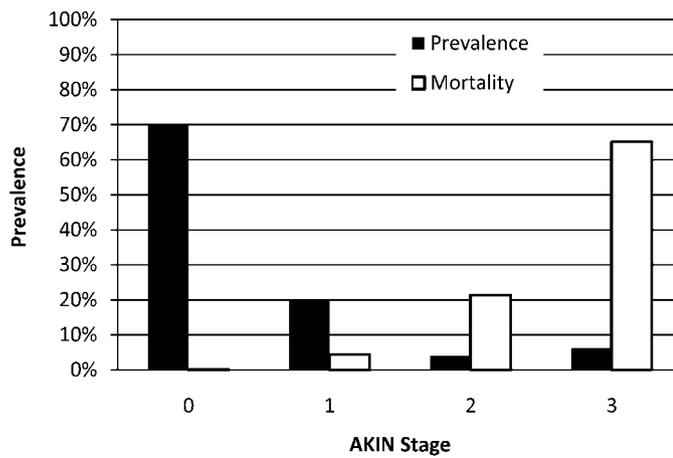


Figure 3. | Prevalence of AKI by Acute Kidney Injury Network (AKIN) stage with corresponding mortality.

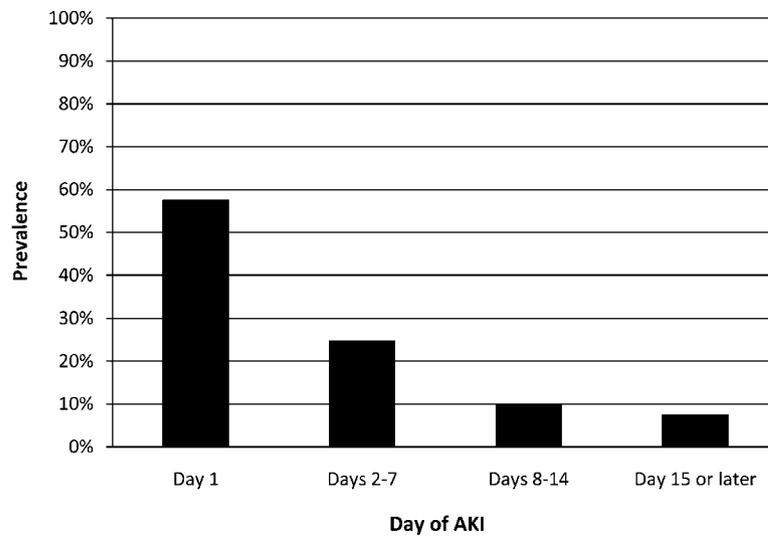


Figure 4. | Hospital day of the diagnosis of AKI injury (by the Acute Kidney Injury Network criteria).

Table 3. Multivariate logistic regression analysis for mortality with Acute Kidney Injury Network stage as the AKI variable

Variable	Odds Ratio for Hospital Mortality (95% CI) ^a	P Value
Age (yr)	1.10 (1.03 1.18)	0.004
ISS	1.04 (1.00 1.09)	0.08
Percentage TBSA	1.03 (1.01 1.06)	0.02
AKIN-1 ^b	6.75 (0.73 62.48)	0.09
AKIN-2 ^b	23.70 (2.32 242)	0.008
AKIN-3 ^b	130 (13.38 >999)	<0.001

CI, confidence interval; ISS, Injury Severity Score; TBSA = total body surface area burned; AKIN, Acute Kidney Injury Network.

^aOdds ratios for age, ISS, and percentage TBSA reflect per year increase in age, per 1 point increase in score, and per 1% increase in percentage TBSA, respectively.

^bCompared with no AKI by Acute Kidney Injury Network criteria.

Table 5. Multivariate logistic regression analysis for mortality with RIFLE as the AKI variable

Variable	Odds Ratio for Hospital Mortality (95% CI) ^a	P Value
Age (yr)	1.09 (1.02 1.16)	0.009
ISS	1.04 (1.00 1.08)	0.08
Percentage TBSA	1.03 (1.01 1.06)	0.007
Risk ^b	15.34 (1.75 134)	0.01
Injury ^b	46.28 (5.02 427)	<0.001
Failure ^b	126 (13.39 >999)	<0.001

CI, confidence interval; ISS, Injury Severity Score; TBSA, total body surface area burned.

^aOdds ratios for age, ISS, and percentage TBSA reflect per year increase in age, per 1 point increase in score, and per 1% increase in percentage TBSA, respectively.

^bCompared with no AKI by RIFLE (Risk Injury Failure Loss End Stage) criteria.

Table 4. Multivariate logistic regression analysis for mortality with Acute Kidney Injury Network stage as the AKI variable in the subgroup with ≥20% burn injury

Variable	Odds Ratio for Hospital Mortality (95% CI) ^a	P Value
Age (yr)	1.13 (1.04 1.22)	0.003
ARDS or ALI	6.02 (1.57 23.13)	0.009
Percentage TBSA	1.07 (1.03 1.11)	<0.001
AKIN-1 ^b	2.52 (0.25 25.93)	0.44
AKIN-2 ^b	6.15 (0.55 68.82)	0.14
AKIN-3 ^b	32.59 (3.13 339)	0.004

CI, confidence interval; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; TBSA, total body surface area burned; AKIN, Acute Kidney Injury Network.

^aOdds ratios for age and percentage TBSA reflect per year increase in age and per 1% increase in percentage TBSA, respectively.

^bCompared with no AKI by Acute Kidney Injury Network criteria.

Table 6. Multivariate logistic regression analysis for mortality with RIFLE as the AKI variable in the subgroup with ≥20% burn injury

Variable	Odds Ratio for Hospital Mortality (95% CI) ^a	P Value
Age (yr)	1.11 (1.03 1.20)	0.006
ARDS or ALI	5.45 (1.45 20.49)	0.01
Percentage TBSA	1.07 (1.04 1.11)	<0.001
Risk ^b	4.47 (0.45 43.94)	0.20
Injury ^b	14.26 (1.46 139)	0.02
Failure ^b	38.91 (3.99 380)	0.002

CI, confidence interval; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; TBSA, total body surface area burned.

^aOdds ratios for age and percentage TBSA reflect per year increase in age and per 1% increase in percentage TBSA, respectively.

^bCompared with no AKI by RIFLE (Risk Injury Failure Loss End Stage) criteria.

38.91; 95% CI, 3.99 380; *P*=0.002) remained significant after adjustment (Table 6).

Receiver-operating characteristic curves for the full model (which included age, ISS, TBSA, and AKIN) demonstrated excellent prediction for mortality, with an area under the curve (AUC) of 0.98 (95% CI, 0.96–0.99). Removing AKIN from the model resulted in an AUC of 0.95 (95% CI, 0.92–0.97), a difference that was significant (*P*=0.02). Notably, AKIN alone had an AUC of 0.95 (95% CI, 0.91–0.98). Similar results were seen for RIFLE (data not shown).

In our analysis for morbidity, we examined ventilator, ICU, and hospital days. In the models for these variables, only TBSA and AKI were significantly correlated with increases in these outcomes. There was a strong interaction between TBSA and RIFLE stage, with all stages increasing

the number of days on mechanical ventilation as TBSA increased compared with patients without AKI. Risk and failure, but not injury, were associated with an increase in ICU days. Conversely, only injury was significant for longer hospital stays. Notably, however, one highly influential observation increased the intercept, which resulted in a significant difference for the outcome of hospital days, despite a lower slope, compared with no AKI. These results are summarized in Table 7. A similar interaction was observed for AKIN (data not shown).

Discussion

Our retrospective review is, to our knowledge, the first assessment of AKI, defined by AKIN and RIFLE, in combat

Table 7. Interaction between percentage of total body surface area burned and RIFLE stage

Variable	RIFLE Stage	Slope (d/percentage TBSA) (95% CI)	P Value
Mechanical ventilation days	No AKI	0.15 (0.06 0.24)	0.004
	Risk	0.37 (0.22 0.53)	
	Injury	0.42 (0.24 0.61)	
	Failure	0.51 (0.31 0.72)	
ICU days	No AKI	0.49 (0.32 0.66)	0.005
	Risk	0.88 (0.61 1.15)	
	Injury	0.57 (0.24 0.90)	
	Failure	1.36 (1.00 1.72)	
Hospital days	No AKI	1.15 (0.89 1.41)	0.60
	Risk	1.26 (0.85 1.68)	
	Injury	0.56 (0.05 1.07)	
	Failure	1.46 (0.90 2.01)	

Slope and 95% confidence of the analysis of covariance model comparing the outcome (in days) versus RIFLE stage with percentage TBSA as the covariate. P values reflect the comparison between the specified RIFLE stage versus no AKI. RIFLE, Risk Injury Failure Loss End Stage; TBSA, total body surface area burned; CI, confidence interval; ICU, intensive care unit.

casualties. We found that AKI was significantly correlated with mortality. Furthermore, AKI modulated the effect of TBSA on morbidity. The logistic regression model (which included age, ISS, TBSA, and AKIN) had a very high AUC (0.98), which implies that few other factors can explain mortality in this population. These results raise the possibility that AKI is a major contributor to both morbidity and mortality after combat injury. Furthermore, because increasing evidence suggests that an episode of AKI increases the risk for long-term mortality and CKD (18 23), these results raise that possibility that future complications may be seen in patients who survive their initial hospitalization.

Although AKI has been associated with increased mortality in large ICU cohorts (5,6), these patients differ from our study population: They were older, had more comorbid conditions, and had medical causes for their AKI. Recent work in the trauma, burn, and TBI populations is more relevant to our cohort. Although not universally demonstrated (24), AKI has been associated with increased mortality in trauma patients. Bihorac and colleagues (15) examined a cohort of 982 adults (average age, 41 years) with severe blunt trauma (82% had an ISS of >25) and found a 26% incidence of AKI by the RIFLE classification. The OR for death with RIFLE stages of injury and failure in that study were 2.67 and 4.55, respectively, seemingly much lower than the ORs of 46.28 and 126 seen in our study. This is despite the lower ISS scores in our population (only 18.4% of our patients had an ISS of >25). Concordant with our results, the study of Bihorac and colleagues found that AKI was associated with longer ICU stays (15).

Studies of patients with burn injuries using the RIFLE classification have revealed an AKI incidence of approximately 25% (9 11). These studies demonstrated high mortality rates in patients with AKI, especially in the failure category. Patients in this category had mortality rates of 60%–83%, compared with 6%–8% in persons without AKI. On the basis of the RIFLE criteria, our study found a similar incidence of AKI (23.8%), a similar mortality rate in the failure category (62.5%), and a lower rate of death in the

non-AKI category (0.2%). In the one study that reported a full multivariate model (9), the ORs for death with risk, injury, and failure were 1.1, 1.8, and 18.17, respectively (only the failure category was significant), compared with 15.34, 46.28, and 126, respectively, in our study (with all achieving significance). AKI, therefore, seems to have a similar incidence and is more closely associated with death in combat casualties than in the civilian burn population.

It is unclear why this study demonstrated a higher association of mortality with AKI than that seen in similar cohorts. One possible explanation is that TBI, which is common in combat casualties, is modulating the effect. In a recent study, the incidence of AKI in the setting of TBI was 9.2% and was associated with a mortality rate of 42.1% compared with 18.1% in patients without AKI (25). Although TBI was not associated with mortality in our population, the low incidence (8.8% in the cohort with $\geq 20\%$ TBSA) makes a significant difference difficult to detect. Another possible explanation is that the high levels of health and physical fitness in military personnel necessitate a larger insult (and thus higher risk for death) to develop AKI. However, the ISS scores seen in the study by Bihorac and colleagues were higher than those in our study (15).

We looked at additional factors in the subgroup of our population with TBSA $\geq 20\%$, including PRBCs, the presence of sepsis, acute respiratory distress syndrome or acute lung injury, and TBI. After adjustment, only acute respiratory distress syndrome or acute lung injury was found to increase the risk for death. Notably, AKI (AKIN-3 and the RIFLE categories of injury and failure) remained significant in these models. To our knowledge, with the exception of sepsis (9), this is the first examination of these variables in a multivariate regression with AKI in the burn population.

Our study provides insight into the causes of AKI in patients burned in support of combat operations in Iraq and Afghanistan. The majority of our patients (57.6%) had AKI diagnosed at admission, implying that factors related to the immediate postinjury period (e.g., hypotension,

blood loss, and exposure to contrast material) are the most likely etiologic factors. Conversely, patients who developed AKI after the first week (17.6%) most likely had complications from their hospitalization (e.g., further contrast material exposure, nephrotoxins, and sepsis) as the cause of their AKI. Patients in the intermediate range, hospital days 2–7 (24.8%), probably had some combination of the preceding factors. Prospective trials will be required to elucidate specific causes more effectively.

This study has a variety of limitations. First, it is a retrospective review and, as such, cannot establish a cause-and-effect relationship between the development of AKI and subsequent mortality. Data were collected at a single center and therefore might not be generalizable. The use of the ISS, which was validated in a heterogeneous civilian population, may not be entirely applicable to our population. This study also highlights some of the pitfalls of creatinine as a biomarker of AKI. We were limited to laboratory data obtained at our institution, necessitating the use of the 7-day low as the patient's baseline creatinine. Although this method has been demonstrated to be superior to back-calculating creatinine using the MDRD equation (a method we also used for some patients), it still overestimates AKIN-1 and underestimates AKIN-2 and -3 (26). The peak creatinine values seen in our population (1.20, 1.98, and 3.70 mg/dl for AKIN-1, -2, and -3, respectively), as well as the average creatinine at AKI diagnosis (1.39 mg/dl), suggest that our method may have been overly sensitive. Irrespective, our creatinine data demonstrate that we selected subgroups with substantial elevations. Notably, more patients in the non-AKI group had their baseline creatinine values derived by back-calculation than did those in the AKI group (31.6% versus 4.8%), which could introduce bias. The major reason for this discrepancy, however, was that many non-AKI patients were less ill and had only one creatinine measured. It is therefore less likely that significant AKI was missed. The ORs for AKI should be interpreted with caution given the broad confidence intervals. This is partly a result of the low overall number of patients who died ($n=41$), but is mostly attributable to the fact that only one patient in the non-AKI group died. A few more deaths in the non-AKI group would have narrowed our confidence intervals significantly. Finally, our analysis of morbidity is limited because death is a competing endpoint. One would expect, however, that this would make it more difficult to demonstrate significance.

In summary, after adjustment, AKI was associated with increased morbidity and mortality in military burn casualties. The only other factors significantly associated with mortality were age, ISS, and TBSA. As such, AKI represents the only potentially modifiable risk factor. Although a cause-and-effect relationship is not yet established, the profound effect seen in this cohort supports further allocation of Department of Defense research resources to AKI in combat casualties.

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Disclosures

None.

References

- Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: Acute Dialysis Quality Initiative workgroup: Acute renal failure: Definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 8: R204–R212, 2004
- Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A: Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11: R31, 2007
- Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 16: 3365–3370, 2005
- Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR: The prognostic importance of a small acute decrement in kidney function in hospitalized patients: A systematic review and meta-analysis. *Am J Kidney Dis* 50: 712–720, 2007
- Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 35: 1837–1843, quiz 1852, 2007
- Bagshaw SM, George C, Dinu I, Bellomo R: A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 23: 1203–1210, 2008
- Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C: An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 34: 1913–1917, 2006
- Kuitunen A, Vento A, Suojaranta Y, Iininen R, Pettilä V: Acute renal failure after cardiac surgery: Evaluation of the RIFLE classification. *Ann Thorac Surg* 81: 542–546, 2006
- Coca SG, Bauling P, Schiffner T, Howard CS, Teitelbaum I, Parikh CR: Contribution of acute kidney injury toward morbidity and mortality in burns: A contemporary analysis. *Am J Kidney Dis* 49: 517–523, 2007
- Lopes JA, Jorge S, Neves FC, Caneira M, da Costa AG, Ferreira AC, Prata MM: An assessment of the RIFLE criteria for acute renal failure in severely burned patients. *Nephrol Dial Transplant* 22: 285, 2007
- Steinvaill I, Bak Z, Sjöberg F: Acute kidney injury is common, parallels organ dysfunction or failure, and carries appreciable mortality in patients with major burns: A prospective exploratory cohort study. *Crit Care* 12: R124, 2008
- Lameire N: The pathophysiology of acute renal failure. *Crit Care Clin* 21: 197–210, 2005
- Bentley ML, Corwin HL, Dasta J: Drug-induced acute kidney injury in the critically ill adult: Recognition and prevention strategies. *Crit Care Med* 38[Suppl]: S169–S174, 2010
- De Waele JJ, De Laet I, Kirkpatrick AW, Hoste E: Intra-abdominal hypertension and abdominal compartment syndrome. *Am J Kidney Dis* 57: 159–169, 2011
- Bihorac A, Delano MJ, Schold JD, Lopez MC, Nathens AB, Maier RV, Layon AJ, Baker HV, Moldawer LL: Incidence, clinical predictors, genomics, and outcome of acute kidney injury among trauma patients. *Ann Surg* 252: 158–165, 2010
- Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality. A cohort analysis. *JAMA* 275: 1489–1494, 1996
- Baker SP, O'Neill B, Haddon W Jr, Long WB: The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 14: 187–196, 1974
- van Kuijk JP, Flu WJ, Chonchol M, Hoeks SE, Winkel TA, Verhagen HJ, Bax JJ, Poldermans D: Temporary perioperative decline of renal function is an independent predictor for chronic kidney disease. *Clin J Am Soc Nephrol* 5: 1198–1204, 2010
- Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ: Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 20: 223–228, 2009
- Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, Allison JJ: Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med* 168: 609–616, 2008
- Lafrance JP, Miller DR: Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol* 21: 345–352, 2010

22. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, Bihorac A: Acute kidney injury is associated with increased long term mortality after cardiothoracic surgery. *Circulation* 119: 2444-2453, 2009
23. Lopes JA, Fernandes P, Jorge S, Resina C, Santos C, Pereira A, Neves J, Antunes F, Gomes da Costa A: Long term risk of mortality after acute kidney injury in patients with sepsis: A contemporary analysis. *BMC Nephrol* 11: 9, 2010
24. Gomes E, Antunes R, Dias C, Araújo R, Costa Pereira A: Acute kidney injury in severe trauma assessed by RIFLE criteria: A common feature without implications on mortality? *Scand J Trauma Resusc Emerg Med* 8: 1, 2010
25. Moore EM, Bellomo R, Nichol A, Harley N, Macisaac C, Cooper DJ: The incidence of acute kidney injury in patients with traumatic brain injury. *Ren Fail* 32: 1060-1065, 2010
26. Pickering JW, Endre ZH: Back calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. *Clin J Am Soc Nephrol* 5: 1165-1173, 2010

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