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Original Investigation

Acute Kidney Injury in Critically Injured Combat Veterans: A Retrospective Cohort Study

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Background: Acute kidney injury (AKI) has been associated with mortality after traumatic injury. However, there is a paucity of data for military service members with injuries received in combat. We sought to identify risk factors for AKI after combat trauma and evaluate whether AKI is a predictor of mortality.

Study Design: Retrospective observational study.

Settings & Participants: US service members who were critically wounded in Iraq or Afghanistan from February 1, 2002, to February 1, 2011, and survived until evacuation to Landstuhl Regional Medical Center, Germany.

Predictors: Demographic variables, vital signs, injury severity score, presence of burn injury, and mechanism of injury as defined at the time of initial injury, as well as the presence of AKI ascertained within the first 7 days using KDIGO (Kidney Disease: Improving Global Outcomes) serum creatinine criteria.

Outcomes: Logistic regression models were used to identify risk factors for both AKI and death.

Results: Of 6,011 records, 3,807 were included for analysis after excluding patients with missing data. AKI occurred in 474 (12.5%) patients and 112 (2.9%) died. More patients with versus without AKI died (n = 62 [13.1%] vs n = 50 [1.5%]; $P < 0.001$). After adjustment, AKI was a predictor of mortality (OR, 5.14; 95% CI, 3.33-7.93; $P < 0.001$). Predictors of AKI were age, African American race, injury severity score, amputations, burns, and presenting vital signs.

Limitations: AKI diagnoses limited to creatinine-based definitions.

Conclusions: AKI predicted mortality in combat veterans injured in the wars in Iraq and Afghanistan.

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INDEX WORDS: Acute kidney injury (AKI); trauma; combat veteran; mortality; death; risk factors; combat; military service; war casualty; military personnel; serum creatinine; KDIGO AKI criteria; burn injury.

Acute kidney injury (AKI) has been studied in a wide range of settings and patient populations, including those with severe trauma.[1-6] However, to our knowledge, the overall rate of AKI among those severely injured during the course of combat operations in Iraq and Afghanistan has not been systematically examined in a large cohort.

Although data for the combat-injured population are limited to those with burn injury,[7] a small cohort of critically injured combat casualties,[8] and those who required renal replacement therapy (RRT),[9] there is a body of evidence from the civilian trauma population. The rate of AKI reported in civilian trauma ranges from 6%[4] to 36.8%[5] and is associated with a 14.9%[5] to 57%[6] mortality rate. This wide range in estimates represents different patient populations, different definitions of AKI, and different time courses examined.

Three of these studies have used the RIFLE (risk, injury, failure, loss, end-stage renal disease)[10] criteria to classify AKI. The first was a large cohort of critically injured trauma patients (N = 9,449). After admission, AKI was assessed for the first 24 hours and occurred in 18.1%.[1] It was associated with a 16.7% mortality rate compared with 7.8% for those without AKI. The second study found that AKI occurred in 26% of 982 patients with severe blunt trauma over the first 28 days after injury.[2] Patients without AKI had a mortality rate of 5% compared to 32% for those with AKI. The third study examined 666 patients admitted to a trauma intensive care unit (ICU). AKI occurred in 15% and was associated with a mortality rate of 57%[6]; the high mortality rate in this study is an outlier, possibly because more than half the AKI in this study was RIFLE class failure.

Two studies have used the AKI Network (AKIN) criteria[11] to define AKI in ICU trauma cohorts. In the first (N = 400), AKI occurred in 36.8% of patients

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within 5 days of injury.[5] It was associated with a mortality rate of 14.9% compared to 3.8% for those without AKI. In the second study of 901 patients, early AKI (defined as within 72 hours of admission) occurred in 6% of patients.[4] Patients with AKI were more likely to die (29.6%) compared with patients without AKI (7.9%).

One recent study used the KDIGO (Kidney Disease: Improving Global Outcomes)[12] criteria to define AKI in 412 patients with trauma admitted to an ICU.[3] These authors found that AKI occurred in 24.9% of patients within the first 7 days after injury and was associated with higher risk for death at both 30 days (17.5% vs 5.8%) and 1 year (26.2% vs 7.1%) after injury.

Given the strong association between AKI and mortality for the civilian trauma population and the paucity of data for combat veterans, we sought to describe the epidemiology, outcomes, and predictors for AKI in a large cohort of critically injured combat casualties.

METHODS

This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol (log number M-10223). The institutional review board waived the need for informed consent.

Data were collected from a variety of Department of Defense databases, including the Department of Defense Trauma Registry, the Armed Forces Medical Examiner System, and data systems of the Defense Health Agency. Patient selection and data sources have been previously described.[13] Briefly, US military personnel who were injured in combat from February 1, 2002, to February 1, 2011; required ICU level care; and survived to be evacuated out of Iraq or Afghanistan were included in the cohort. Data collected for this study included demographic variables (age, sex, and race), mechanism of injury, presenting vital signs (heart rate, temperature, and mean arterial blood pressure [MAP]), injury severity score (ISS)[14] using the 2005 abbreviated injury scale update,[15] creatinine level, and 90-day mortality (obtained from the Armed Forces Medical Examiner System).

To be included for analysis, a patient must have had at least one creatinine value measured in the first 7 days after injury. Individuals were excluded if data were missing for one of the prespecified covariates (with the exception of race). Excluded individuals were examined and compared to the full-case sample to determine differences across demographic and injury data when available. Sensitivity analyses were performed to determine the extent to which estimates based on the full-case sample may differ from the total sample. For individuals missing demographic or injury data, we performed sensitivity analyses by imputing the mean value and using multiple regression techniques to impute missing values based on the combination of other covariates. For individuals missing creatinine data, we estimated models assuming all missing cases had AKI (following the observed distribution by KDIGO stage) and assuming all missing cases did not have AKI. This established upper and lower bounds for our estimates based on variability attributable to missing data.

KDIGO criteria[12] served as the basis for determining AKI. We did not have data for urine output; therefore, only changes in creatinine levels were used to determine AKI stage. When available, a known creatinine value (drawn 7-365 days prior to the date of injury) was used as the baseline. If the patient did not have a known preinjury creatinine value, we back-calculated one using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation,[16] assuming an estimated glomerular filtration rate of 100 mL/min/1.73 m^2. If a back-calculated creatinine value was used and race was unknown, it was assumed to be non–African American. Assessment for AKI was determined for 7 days after injury. Those treated with RRT were identified by *International Classification of Diseases, Ninth Revision* codes V568 and V560.

The ISS is a validated anatomic-based scoring system used to quantify the severity of injury. The score ranges from 1 to 75, increasing with severity.[14] This method has been used to quantify severity of injury in multiple studies that use data from the Department of Defense Trauma Registry[17,18] and studies that have examined AKI in the setting of trauma.[2-6] We modeled a variety of functional forms for ISS, including continuous, quadratic, log, exponential, and categorical, and compared them using the Akaike information criterion. None of the other methods was superior to considering ISS as a continuous variable. Given our observation that outcomes appear to be worse for patients at extremes of MAP, this variable was divided into 3 categories. We chose cutoffs reflecting a level that might require intervention in the low group (<65 mm Hg[19]) and a value representing hypertension (>106 mm Hg[20]) in the high group.

Standard descriptive statistics were used to compare the group of patients who developed AKI with those who did not. Although race was assumed to be non–African American for the purposes of back-calculation, race missing was considered as a separate category in subsequent analyses. Two different univariate and multivariable analyses were performed. The first was a logistic regression model examining the effect of baseline injury characteristics on the subsequent development of AKI. The second analysis examined 90-day mortality, with baseline injury characteristics and AKI as independent variables. All variables were included in multivariable analyses. Statistics were performed using SAS, version 9.2 (SAS Institute Inc).

RESULTS

Of 6,011 records identified, 3,807 patients were included for analysis. Reasons for exclusion were no recorded creatinine value within 7 days after injury (n = 1,159), no recorded heart rate (n = 301), no recorded MAP (n = 89), and no recorded temperature (n = 655). Only 7.2% (n = 276) of patients had a known baseline for the purposes of AKI staging. Baseline characteristics are presented in Table 1. There were 474 (12.5%) patients in whom AKI occurred. More patients with AKI died compared with patients without AKI (13.1% vs 1.5%, respectively; $P < 0.001$). Patients with AKI were more likely to have burn injury compared with patients without AKI (28.1% vs 17.6%, respectively; $P < 0.001$). The median ISS for patients with AKI was 26 (interquartile range [IQR], 17-36), which was higher than that for patients without AKI (14; IQR, 9-22; $P < 0.001$). Patients with AKI were slightly, but significantly, older than patients without AKI (mean age, 27 ± 7 [standard deviation] vs 25 ± 6 years; $P = 0.002$). Amputations were more common in patients with AKI (28.3% vs 17.7%; $P < 0.001$). Differences in both heart rate and MAP category were also observed.