Epidemiology and Prevention

Retrospective Analysis of Long-Term Outcomes After Combat Injury
A Hidden Cost of War

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Background—During the conflicts in Iraq and Afghanistan, 52,087 service members have been wounded in combat. The long-term sequelae of these injuries have not been carefully examined. We sought to determine the relation between markers of injury severity and the subsequent development of hypertension, coronary artery disease, diabetes mellitus, and chronic kidney disease.

Methods and Results—Retrospective cohort study of critically injured US military personnel wounded in Iraq or Afghanistan from February 1, 2002 to February 1, 2011. Patients were then followed until January 18, 2013. Chronic disease outcomes were assessed by International Classification of Diseases, 9th edition codes and causes of death were confirmed by autopsy. From 6011 admissions, records were excluded because of missing data or if they were for an individual’s second admission. Patients with a disease diagnosis of interest before the injury date were also excluded, yielding a cohort of 3846 subjects for analysis. After adjustment for other factors, each 5-point increment in the injury severity score was associated with a 6%, 13%, 13%, and 15% increase in incidence rates of hypertension, coronary artery disease, diabetes mellitus, and chronic kidney disease, respectively. Acute kidney injury was associated with a 66% increase in rates of hypertension and nearly 5-fold increase in rates of chronic kidney disease.

Conclusions—In Iraq and Afghanistan veterans, the severity of combat injury was associated with the subsequent development of hypertension, coronary artery disease, diabetes mellitus, and chronic kidney disease.

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Key Words: coronary disease ■ diabetes mellitus ■ hypertension ■ kidney ■ mortality
operations in Iraq and Afghanistan from February 1, 2002 to February 1, 2011. Patients were identified from the Department of Defense Trauma Registry (DoDTR). The injury must have been severe enough to require admission to the intensive care unit. The surveillance period for data collection continued through January 18, 2013, or until the person died or was lost to follow-up (whichever came first). Only data for a service member’s first admission were analyzed. The US Army Medical Research and Materiel Command Institutional Review Board (IRB) reviewed and approved the study protocol. Given the minimal risk nature, informed consent was deferred by the IRB.

Variables and Data Sources
We acquired data from the DoDTR, the Armed Forces Medical Examiner System (AFMES), and other datasets maintained by the Defense Health Agency (DHA) as previously published.9 International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes were used to identify incident diagnoses for the outcomes of interest (see Supplemental Material). ICD-9 codes were obtained from administrative databases including outpatient encounters from both Department of Defense hospitals and from civilian facilities billed through TRICARE (the US military health benefit program). Patients with preexisting HTN, CAD, DM, and CKD (defined as one of the ICD-9 codes of interest documented before the date of combat injury) were excluded from analysis. Because diagnoses made shortly after injury might reflect an acute trauma-related complication, and not a chronic medical condition, among patients who had an ICD-9 code of interest first assigned within 90 days of injury, a second ICD-9 code for that condition, assigned after 90 days, was required to confirm the diagnosis. These patients were included as condition present (if the diagnosis, was subsequently confirmed) or condition absent (if the diagnosis was not confirmed). We abstracted available demographic variables that could plausibly be associated with outcomes (age, race, and sex) and variables that reflect severity of injury (serum creatinine, injury severity score [ISS],9 presence of burn injury, heart rate, and mean arterial blood pressure [MAP]). Age was defined as the age in years on the date of injury. We chose MAP cutoffs to reflect hypotension that might require intervention (MAP <65 mm Hg10) in the low group and hypertension (MAP >106 mm Hg11) in the high group. We used the Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria12 to classify acute kidney injury (AKI; see the online-only Data Supplement). Baseline serum creatinine concentrations were determined by back calculating the Modification of Diet in Renal Disease (MDRD) Study equation assuming an estimated glomerular filtration rate of 75 mL/min/1.73 m². ISS is a validated scoring system for trauma patients based on body regions and anatomic structures. The score can range from 1 to 75, increasing with the degree of injury (see supplemental material).9

Statistical Methods
To test our hypotheses regarding the long-term development of the 4 chronic disease outcomes after trauma, we used competing risk proportional hazards regression models.13–16 Mortality was the competing risk in our models. To test differences in the incidence probabilities of the regression models, we analyzed the cumulative sums of the regression models, we analyzed the cumulative sums of weighted log rank test17 was used to compare cumulative incidence function curves. Duration was calculated as days from injury to diagnosis; time was truncated by death or last recorded encounter. To fully evaluate the structures of relations among ISS and the outcomes we examined linear, quadratic, dose response and threshold effects. Because of small subgroup sizes by KDIGO stage, AKI was considered a dichotomous variable, AKI versus no AKI. We used Akaike information criterion values to compare models. To test the assumptions of the regression models, we analyzed the cumulative sums of martingale-based residuals.18 Finally, chronic disease incidence rates were calculated as the number of patients with a given disease per 1000 person-years. These rates were compared with previously published incidence rates for the total US military population.19–21 J.T.H., J.A.S., and I.J.S. performed the analysis using SAS version 9.2 (Cary, NC) and R version 3.11. Two-tailed $P$ values <0.05 were considered statistically significant. We did not adjust our analyses for multiple comparisons.

Results
A total of 6011 injured service members were identified. After exclusions for missing data and preexisting diseases, the final cohort for study was $n=3846$ (Figure 1). Table 1 contains descriptive statistics for demographic, physiological, and injury severity measures for the sample. Patients who developed the outcomes tended to be older, have higher average ISS, and had more AKI. Patients who either died or developed long-term morbidities generally had higher proportions of head/neck and chest injuries, and lower proportions of extremity injuries than patients who survived without morbidity. The median follow-up time (from injury until diagnosis, death, or loss to follow-up) ranged from 1.1 years to 2.8 years for the chronic disease cohorts and was 4.3 years for the group that did not develop disease. There were 45 deaths during the follow-up period.

Results of multivariable competing risk proportional hazards regression analysis demonstrated that ISS was associated with an increased incidence rate of developing each outcome independent of the risk of death, even after adjusting for age, race, MAP, heart rate, presence of burn injury, and AKI (Table 2). Each 5-point increment in the ISS was associated with a 6%, 13%, 13% and 15% relative increase in the incidence rates of HTN (hazard ratio [HR], 1.06; 95% confidence interval [CI], 1.02–1.09; $P=0.003$), CAD (HR, 1.13; 95% CI, 1.03–1.25; $P=0.01$), DM (HR, 1.13; 95% CI, 1.04–1.23; $P=0.003$), and CKD (HR, 1.15; 95% CI, 1.04–1.27; $P=0.007$), respectively. These associations are demonstrated graphically in the online-only Data Supplement (see Figure 1 in the online-only Data Supplement).

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Figure 1. Cohort derivation with inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Full cohort N = 6,011</th>
</tr>
</thead>
<tbody>
<tr>
<td>First admission only</td>
</tr>
<tr>
<td>Exclude: 7 second admissions</td>
</tr>
<tr>
<td>Censor &gt;90 days</td>
</tr>
<tr>
<td>Exclude: 208 &lt;90 days</td>
</tr>
<tr>
<td>Creatinine data available</td>
</tr>
<tr>
<td>Exclude: 1539 without creatinine data</td>
</tr>
<tr>
<td>Vital signs data available</td>
</tr>
<tr>
<td>Exclude: 317 without vital signs data</td>
</tr>
<tr>
<td>Exclude pre-existing outcomes</td>
</tr>
<tr>
<td>Final cohort N = 3,846</td>
</tr>
</tbody>
</table>
After adjusting for covariates and the competing risk of death, AKI was associated with the subsequent development of HTN and CKD. Specifically, AKI was associated with a 66% increase in the incidence rate of HTN (HR, 1.66; 95% CI, 1.28–2.14; \( P < 0.001 \)) and a nearly 5-fold increase in the incidence rate of CKD (HR, 4.79; 95% CI, 2.53–9.08; \( P < 0.001 \)).

Figure 2 and Figure 3 illustrate the AKI and ISS associations. These plots illustrate the differences in cumulative incidence function by severity of injury (ISS \( \geq 25 \) versus ISS < 25) and AKI. Gray’s weighted log rank test was significant for ISS with all 4 outcomes, as well as for AKI with HTN and CKD. The results suggest that the proportionality assumption may not hold, particularly by risk type. However, our models stratified by risk type, and analysis of the Martingale residuals\(^{18} \) for each model, suggested that the proportionality assumption was not violated except for the CKD analysis. In the case of CKD, the rate associated with AKI appears to be proportional until around 5 years after the injury, at which point the rate accelerates.

Several other variables were also significant in the models. Age was associated with HTN (HR, 1.05; 95% CI, 1.04–1.07; \( P < 0.001 \)), CAD (HR, 1.07; 95% CI, 1.03–1.11; \( P < 0.001 \)), and DM (HR, 1.08; 95% CI, 1.05–1.11; \( P < 0.001 \)), but not CKD. Black service members had a 69% higher rate of HTN compared with whites (HR, 1.69; 95% CI, 1.26–2.27; \( P < 0.001 \)).

High MAP was associated with HTN (HR, 1.61; 95% CI, 1.30–1.99; \( P < 0.001 \)), and DM (HR, 2.10; 95% CI, 1.27–3.49; \( P = 0.004 \)), but not with CAD or CKD. Heart rate was associated with an increased rate of CKD (HR, 1.01; 95% CI, 1.00–1.03; \( P = 0.01 \)).

Patients excluded because of missing data were less likely to have developed HTN (11.6% versus 14.1%) than included patients, but no differences were observed for CAD, DM, or CKD between excluded and included patients. Missing cases also tended to be white (67% versus 56% for not missing), less likely to have a burn injury (13% versus 19% for not missing), had a lower heart rate (median 86 versus 95 for not missing), and lower ISS (median 9 versus 17 for not missing). Additional sensitivity analyses that included missing cases, using either missing categories or regression-based imputed values\(^{22} \) did not significantly change the results (data not shown). We also examined models that included what body regions were injured. In these models, area of injury was not significant and inclusion of these variables did not materially change our results.

### Discussion

We found that the severity of injuries experienced in combat is consistently associated with the subsequent development

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Disease</th>
<th>Death</th>
<th>HTN</th>
<th>CAD</th>
<th>DM</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3,184</td>
<td>45</td>
<td>551</td>
<td>55</td>
<td>84</td>
<td>47</td>
</tr>
<tr>
<td>Age, Mean years (SD)</td>
<td>25.1 (5.7)</td>
<td>25.7 (6.8)</td>
<td>28.0 (7.2)</td>
<td>29.2 (8.8)</td>
<td>29.9 (7.6)</td>
<td>26.7 (6.3)</td>
</tr>
<tr>
<td>Male, %</td>
<td>98.1</td>
<td>100.0</td>
<td>99.1</td>
<td>100.0</td>
<td>97.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4.5</td>
<td>8.9</td>
<td>9.6</td>
<td>10.9</td>
<td>7.1</td>
<td>8.5</td>
</tr>
<tr>
<td>White</td>
<td>55.6</td>
<td>66.7</td>
<td>57.2</td>
<td>52.7</td>
<td>54.8</td>
<td>59.6</td>
</tr>
<tr>
<td>Other</td>
<td>8.3</td>
<td>4.4</td>
<td>9.3</td>
<td>9.1</td>
<td>10.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Missing</td>
<td>31.7</td>
<td>20.0</td>
<td>24.0</td>
<td>27.3</td>
<td>27.4</td>
<td>27.7</td>
</tr>
<tr>
<td>MAP, Mean (SD)</td>
<td>87.4 (18.3)</td>
<td>88.3 (20.1)</td>
<td>90.3 (19.5)</td>
<td>91.9 (17.6)</td>
<td>91.3 (19.2)</td>
<td>87.1 (17.8)</td>
</tr>
<tr>
<td>High, %</td>
<td>12.9</td>
<td>22.2</td>
<td>19.6</td>
<td>18.2</td>
<td>25.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Normal, %</td>
<td>76.3</td>
<td>71.1</td>
<td>71.3</td>
<td>76.4</td>
<td>67.9</td>
<td>74.5</td>
</tr>
<tr>
<td>Low, %</td>
<td>10.9</td>
<td>6.7</td>
<td>9.1</td>
<td>5.6</td>
<td>7.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Heart rate, Mean (SD)</td>
<td>98 (25)</td>
<td>104 (30)</td>
<td>99 (25)</td>
<td>100 (26)</td>
<td>99 (27)</td>
<td>110 (30)</td>
</tr>
<tr>
<td>ISS, Mean (SD)</td>
<td>18.0 (11.4)</td>
<td>25.7 (15.3)</td>
<td>19.8 (13.6)</td>
<td>22.6 (15.3)</td>
<td>22.3 (16.0)</td>
<td>25.5 (12.2)</td>
</tr>
<tr>
<td>Injury location*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head/Neck</td>
<td>43.0</td>
<td>51.1</td>
<td>47.7</td>
<td>47.3</td>
<td>45.2</td>
<td>44.7</td>
</tr>
<tr>
<td>Face</td>
<td>36.7</td>
<td>37.8</td>
<td>39.2</td>
<td>40.0</td>
<td>41.7</td>
<td>38.3</td>
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<tr>
<td>Chest</td>
<td>30.4</td>
<td>48.9</td>
<td>33.9</td>
<td>36.4</td>
<td>36.9</td>
<td>48.9</td>
</tr>
<tr>
<td>Abdomen</td>
<td>33.6</td>
<td>26.7</td>
<td>31.8</td>
<td>29.1</td>
<td>23.8</td>
<td>42.6</td>
</tr>
<tr>
<td>Extremities</td>
<td>68.9</td>
<td>51.1</td>
<td>64.1</td>
<td>65.5</td>
<td>66.7</td>
<td>66.0</td>
</tr>
<tr>
<td>External</td>
<td>89.9</td>
<td>88.9</td>
<td>90.4</td>
<td>90.0</td>
<td>90.5</td>
<td>97.9</td>
</tr>
<tr>
<td>AKI (%)</td>
<td>7.7</td>
<td>20.0</td>
<td>13.4</td>
<td>16.4</td>
<td>15.5</td>
<td>34.0</td>
</tr>
<tr>
<td>Follow up, years†</td>
<td>4.3 (4.2)</td>
<td>1.1 (2.3)</td>
<td>1.4 (3.1)</td>
<td>2.8 (4.5)</td>
<td>2.1 (3.4)</td>
<td>1.2 (3.8)</td>
</tr>
</tbody>
</table>

AKI indicates acute kidney injury; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; ISS, injury severity score; MAP, mean arterial pressure; and SD, standard deviation.

*Percentage of patients with injuries in the six body regions. Note that since patients can have multiple injuries, these do not sum to 100%.

†Follow-up for death and conditions of interest are truncated by death or the development of the diagnosis, respectively.
of HTN, CAD, DM, and CKD. After adjustment for other factors, every 5-point increase in ISS resulted in a 6%, 13%, 13%, and 15% relative increase in the rate of HTN, CAD, DM, and CKD, respectively. AKI also increased the rate of HTN and CKD by 66% and 479%, respectively. When compared with historical data, the rates of HTN, CAD, and DM are much higher than would be expected. For example, the incidence rates of HTN, CAD, and DM for the most severely injured patients were from 2-fold to 4-fold higher than published rates for the overall US military population.19–21 These findings could have profound implications for both those wounded in combat and for federal health systems.

### ISS and Outcomes

The association between ISS and long-term outcomes is biologically plausible by several mechanisms. First, a variety of proinflammatory cytokines have been associated with HTN,23 DM,24 CAD,25 and CKD.26 Furthermore, cytokine mediated chronic inflammation has been implicated as a “common disease of the vasculature, kidney, and central nervous system” and has downstream effects to include HTN, CKD, and heart disease.23 Although evidence for long-term inflammation after trauma is lacking, one hypothesis for our findings is that combat injury, which increases the inflammatory response,7 initiates a cascade that predisposes to a wide variety of chronic medical conditions. An alternate hypothesis is that PTSD,

### Table 2. Results of Multivariable, Competing Risk Proportional Hazards Regression for Morbidity and Mortality Outcomes

<table>
<thead>
<tr>
<th></th>
<th>HTN</th>
<th></th>
<th>CAD</th>
<th></th>
<th>DM</th>
<th></th>
<th>CKD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.04–1.07)</td>
<td>&lt;0.001</td>
<td>1.07 (1.03–1.11)</td>
<td>&lt;0.001</td>
<td>1.08 (1.05–1.11)</td>
<td>&lt;0.001</td>
<td>1.02 (0.98–1.06)</td>
<td>0.41</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>1.69 (1.26–2.27)</td>
<td>&lt;0.001</td>
<td>1.82 (0.75–4.42)</td>
<td>0.18</td>
<td>1.15 (0.49–2.71)</td>
<td>0.75</td>
<td>1.29 (0.45–3.72)</td>
<td>0.64</td>
</tr>
<tr>
<td>Other</td>
<td>1.35 (1.00–1.83)</td>
<td>0.05</td>
<td>1.50 (0.57–3.95)</td>
<td>0.42</td>
<td>1.72 (0.83–3.58)</td>
<td>0.15</td>
<td>0.40 (0.09–1.70)</td>
<td>0.40</td>
</tr>
<tr>
<td>Missing</td>
<td>0.86 (0.70–1.05)</td>
<td>0.14</td>
<td>1.27 (0.67–2.41)</td>
<td>0.46</td>
<td>1.10 (0.66–1.83)</td>
<td>0.73</td>
<td>0.88 (0.45–1.73)</td>
<td>0.71</td>
</tr>
<tr>
<td>White (Ref)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High</td>
<td>1.61 (1.30–1.99)</td>
<td>&lt;0.001</td>
<td>1.27 (0.63–2.56)</td>
<td>0.50</td>
<td>2.10 (1.27–3.49)</td>
<td>0.004</td>
<td>1.12 (0.51–2.44)</td>
<td>0.78</td>
</tr>
<tr>
<td>Low</td>
<td>0.83 (0.61–1.12)</td>
<td>0.22</td>
<td>0.39 (0.12–1.28)</td>
<td>0.12</td>
<td>0.60 (0.26–1.41)</td>
<td>0.24</td>
<td>0.44 (0.16–1.28)</td>
<td>0.13</td>
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<tr>
<td>Normal (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>1.06 (1.02–1.09)</td>
<td>0.003</td>
<td>1.13 (1.03–1.25)</td>
<td>0.01</td>
<td>1.13 (1.04–1.23)</td>
<td>0.003</td>
<td>1.15 (1.04–1.27)</td>
<td>0.007</td>
</tr>
<tr>
<td>AKI</td>
<td>1.66 (1.28–2.14)</td>
<td>&lt;0.001</td>
<td>1.65 (0.78–3.53)</td>
<td>0.19</td>
<td>1.54 (0.82–2.88)</td>
<td>0.18</td>
<td>4.79 (2.53–9.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No AKI (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.00 (0.99–1.01)</td>
<td>0.58</td>
<td>1.00 (0.99–1.01)</td>
<td>0.27</td>
<td>1.00 (0.99–1.01)</td>
<td>0.80</td>
<td>1.01 (1.00–1.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Burn Injury</td>
<td>1.15 (0.94–1.41)</td>
<td>0.17</td>
<td>1.43 (0.78–2.64)</td>
<td>0.25</td>
<td>1.04 (0.61–1.78)</td>
<td>0.89</td>
<td>0.87 (0.43–1.79)</td>
<td>0.71</td>
</tr>
<tr>
<td>No Burn (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Hazard ratios for age represent per one unit increase in years, and for ISS they represent a 5-U increase in ISS scores. AKI indicates acute kidney injury; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ISS, injury severity score; MAP, mean arterial pressure; and Ref, reference group.

Figure 2. Cumulative incidence plots for outcomes and acute kidney injury. A, Results for the outcome of hypertension (HTN). B, Results for the outcome of chronic kidney disease (CKD). P values represent the weighted log rank of the 2 cumulative incidence function curves. The numbers of patients at risk are displayed on the x axis. The inserted figures show the same results on a shortened y axis for ease of viewing.
which is common in combat casualties,\textsuperscript{5} modulates this effect either directly via an inflammatory response\textsuperscript{27} or indirectly via weight gain\textsuperscript{28} and substance abuse.\textsuperscript{6} However, work examining the correlation between ISS and PTSD is conflicting\textsuperscript{29,30}, which suggests that this alone cannot account for the differences observed. It is also possible that more severely injured patients have more severe functional limitations resulting in poor outcomes. It should be noted that these potential pathophysiologic mechanisms need not be mutually exclusive because both PTSD\textsuperscript{27} and obesity\textsuperscript{31} have been associated with inflammatory states. The increased rate of HTN, CAD, DM, and CKD may therefore reflect a complicated interplay of injury, hospital course, PTSD, and sustained functional limitations. Although a significant amount of work remains to disentangle these possible mechanisms, our study demonstrates an association between severity of combat injury and subsequent development of these chronic medical conditions.

**AKI and Subsequent HTN and CKD**

Our analysis demonstrated that the development of AKI was associated with HTN and CKD. Acute kidney injury modulates the systemic inflammatory response\textsuperscript{32} and thus may represent a similar end common pathway with the multitude of other immune modulatory reactions induced by ISS, PTSD, and obesity noted above. Although there is a large body of work that associates AKI with CKD,\textsuperscript{33} the observational nature of this evidence cannot prove causality. As noted by Rifkin and colleagues,\textsuperscript{34} the apparent association between AKI and CKD may be confounded by the effects of ascertainment bias, misclassification of exposure, and misclassification of outcome. Our study is also observational in nature and cannot prove causation. However, our findings are less subject to some of these caveats because we studied a homogeneous cohort of young patients with few preexisting comorbidities.

Another striking observation of this study is the strong relationship between AKI and subsequent HTN. Although HTN is a recognized risk factor for AKI and CKD,\textsuperscript{33} there is little evidence that AKI is a risk factor for subsequent HTN. However, animal models have demonstrated that renal ischemia/reperfusion injury induces salt sensitive HTN in rats.\textsuperscript{35} Although AKI was associated with CAD in the unadjusted model, it was not an independent predictor in the adjusted model. In light of

![Figure 3. Cumulative incidence plots for outcomes and injury severity score (ISS). A, Results for the outcome of hypertension (HTN). B, Results for the outcome of chronic kidney disease (CAD). C, Results for diabetes mellitus (DM). D, Results for chronic kidney disease (CKD). P values represent the weighted log rank of the 2 cumulative incidence function curves. The numbers of patients at risk are displayed on the x axis. The inserted figures show the same results on a shortened y axis for ease of viewing. Although a linear response best described the relationship in the multivariate analysis, on visual inspection of the curves the first 3 quartiles appeared to overlap. Therefore, for ease of viewing, the cumulative incidence plots compare the highest with the other 3 quartiles combined.](http://circ.ahajournals.org/)

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previous work demonstrating that myocardial infarction complicated by AKI predisposes to subsequent cardiac events, it is possible that we simply did not have enough CAD outcomes (n=59) to fully examine this hypothesis.

Implications for Veteran Care
This work has significant implications. Care for veterans is estimated to have a total cost of 970 billion dollars, 288 billion of which are expected to be attributable to direct VA medical expenditures. Our work demonstrates that these costs may increase as the veterans of the wars in Iraq and Afghanistan develop service connected chronic medical conditions that could be associated with the injuries they suffered. In the present study, we were limited to establishing an association between injury severity and outcomes in critically ill patients. However, if less severely injured service members are also at increased risk of developing chronic conditions, the costs could be even higher.

Comparisons With the Millennium Cohort Study
One limitation of the present study is the lack of a control group. We mitigated this limitation by comparing the incidence rates observed in our cohort, stratified by injury severity, with previous estimates in the military population of HTN, CAD, and DM from the Millennium Cohort Study (Table 3). The Millennium Cohort study is a large, observational study of randomly selected US military members who were on active service on October 1, 2000. To make comparisons as similar as possible, we selected subsets who deployed to Iraq or Afghanistan and saw combat where available. Sufficient data were available for HTN and CAD, but not for DM. In the study that examined HTN, the incidence rate for subjects that deployed to Iraq or Afghanistan and had combat exposure was 20.0 per 1000 person-years. This rate is lower than we observed in our cohort stratified by ISS quartile (50.3 and 31.1 per 1000 person-years for ISS Q4 and ISS Q1–Q3, respectively). Another study examined the impact of combat deployment on rates of CAD. Extrapolating from the reported percentage of patients with CAD that deployed and saw combat (0.6%) with an average follow-up time of 5.6 years, arrives at an estimate of 1.1 per 1000 person-years. This rate is lower than what we observed (4.5 and 2.5 per 1000 person-years for ISS Q4 and ISS Q1–Q3, respectively). In the study that examined DM, the incidence of DM was 2.8 per 1000 person-years. Although not enough data are presented to arrive at a specific estimate for those who saw combat, deployment to Iraq and Afghanistan with combat exposure was not associated with the development of DM (odds ratio, 0.99; 95% CI, 0.68–1.42). Although this estimate is roughly comparable with the rate of 3.7 per 1000 person-years seen in quartiles 1 to 3 of ISS, it appears lower than the rate of 7.4 per 1000 person-years seen in the most severely injured patients (quartile 4). A limitation of these comparisons is that the previous work cited above used self-reported questionnaires to determine outcomes. Taken together, this body of evidence suggests a correlation between combat injury and the subsequent development of HTN, CAD, and DM.

Limitations
Our study has several limitations. First, because prospective data collection in a war theater are very challenging, we were limited to using previously collected administrative data. Our use of a retrospective cohort study design in which we first identified a cohort of critically injured patients, and then tracked incident diagnoses of chronic conditions subsequent to the injury while adjusting for the competing risk of death, is therefore a relative strength of the study. The use of administrative data to identify patients with specific diagnoses can be problematic. However, ICD-9 codes are likely to be more specific than sensitive, leading to an underestimate of the incidence of these conditions. We did not have access to known baseline serum creatinine to determine AKI and had to use a surrogate. However, back calculation has been shown to be a reasonable method in cohorts with low prevalence of preexisting CKD, such as ours. We had a high proportion of missing data as shown in Figure 1, but the data were collected in an austere combat environment. Furthermore, this is the only dataset of its kind available, not only from the current conflicts but also from all previous wars. To account for missing data, we applied rigorous sensitivity analyses and the results did not change significantly. Second, our study was observational and thus provides only evidence of a dose response association between injury and chronic disease, and does not delineate a specific causal pathway. Additional research on our study population linked to biological specimens could provide some insights into pathophysiology. Third, our follow-up time was relatively short. Additional follow-up studies will be needed to understand the longer-term impact of

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate for ISS Q4*</th>
<th>Incidence Rate for ISS Q1 Through Q3*</th>
<th>Relative Risk†</th>
<th>Incidence Rate for US Military Population*</th>
<th>Relative Risk‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>50.3</td>
<td>31.1</td>
<td>1.6 (1.2–1.6)</td>
<td>20.0</td>
<td>2.5 (2.0–3.2)</td>
</tr>
<tr>
<td>CAD</td>
<td>4.5</td>
<td>2.5</td>
<td>1.8 (1.04–3.04)</td>
<td>1.1</td>
<td>4.0 (2.5–6.4)</td>
</tr>
<tr>
<td>DM</td>
<td>7.4</td>
<td>3.7</td>
<td>2.0 (1.2–3.0)</td>
<td>2.8</td>
<td>2.6 (1.9–3.7)</td>
</tr>
<tr>
<td>CKD</td>
<td>5.9</td>
<td>1.5</td>
<td>4.0 (2.1–6.5)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Injury severity score top quartile (ISS ≥ 25): ISS Q4. Injury severity score bottom three quartile (ISS < 25): ISS Q1–Q3. CAD indicates coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; and HTN, hypertension.

*Incidence rates represents per 1000 person-years.
†Comparing injury severity score top quartile to bottom 3 quartiles.
‡Comparing injury severity score top quartile to the general US military population.
combat injury on development of these conditions. Fourth, we studied a unique military population and thus our findings may not be generalizable to those not severely injured in combat. However, because military service members deployed to a combat zone are exceptionally healthy, this might also be considered a strength because this allows it to better separate out the pure effect of acute illness on subsequent chronic disease. Patients injured in combat may also be different from the military population in general. For example, patients with combat exposure had higher rates of smoking compared with those who deployed but did not see combat (18.1% versus 15.6%, respectively), which raises the prospect of reverse causation. We did not have data on smoking to include in our models. However, although smoking has been associated with the development of CAD, it is not a demonstrated risk factor for DM or HTN in similar cohorts. Finally, it is also possible that patients with higher ISS scores had more frequent physician encounters, thus allowing more opportunities to be diagnosed with a chronic disease. However, given the limitations of our data we were unable to test this hypothesis.

Conclusion

In summary, ISS was associated with the development of incident HTN, CAD, DM, and CKD in our cohort of critically wounded service members. AKI after combat injury was associated with HTN and CKD. For the most severely injured subgroup, the rates of HTN, CAD, and DM were notably higher compared with previously published rates for the overall US military population. Our study and the establishment of this group, the rates of HTN, CAD, and DM were notably higher for the military population in general. For example, patients with combat injury on development of these conditions.

Acknowledgments

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Disclosures

None.

References

Veterans have high rates of hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), and coronary artery disease (CAD). This study examined the possible role of combat injury severity as a risk factor for HTN, DM, CKD, and CAD in a cohort of 3846 critically wounded US service members. Disease outcomes were defined using International Classification of Diseases, 9th edition codes from administrative databases that captured outpatient encounters from both Department of Defense (DoD) and civilian facilities that were billed to the military health insurance system. We found that injury severity score was independently associated with the development of incident HTN, CAD, DM, and CKD. We also found that acute kidney injury after combat injury was independently associated with HTN and CKD. The incidence rates of HTN, CAD, and DM for the most severely injured patients were from 2-fold to 4-fold higher than published rates for the overall US military population. This work has significant implications for the long term care of patients in the Veterans Affairs and DoD Health Systems because it establishes combat injury as a risk factor for a wide range of chronic medical conditions. Our study and the establishment of this cohort of severely injured patients lays important ground work for additional research to better understand the causal pathways and the longer-term effects of combat-related injury on the risk of chronic disease.
Retrospective Analysis of Long-Term Outcomes After Combat Injury: A Hidden Cost of War

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Supplemental Methods

Derivation of acute kidney injury
We used the KDIGO definition to determine AKI (12). Of note, we did not have access to urine output, therefore only creatinine was used to determine AKI stage. We also did not have access to known baseline creatinine values. Therefore, baseline creatinine was estimated by back calculating the Modification of Diet in Renal Disease (MDRD) Study equation assuming an estimated glomerular filtration rate of 75 ml/min/1.73 m². For the purposes of this back calculation, if race was unknown non-African American race was assumed. Lastly, we had creatinine available at both Role III and Role IV locations which were used to determine AKI staging (truncated at 14 days). A brief discussion of the combat casualty evacuation chain is warranted to put this into context. Immediately after injury, patients are taken to small combat support hospitals where they are stabilized (Roles I and II). They are then transferred to one of the larger hospitals in Iraq or Afghanistan (Role III) where more definitive procedures and further stabilization occurs. From there, they are evacuated to a US Military hospital in Germany (Role IV) and subsequently back to Military hospitals in the United States (Role V). Again, for the purposes of this study we used creatinine data from Roles III and IV.

Injury Severity Score
The injury severity score (ISS) is an anatomic based scoring system to quantify the severity of traumatic injury. ISS ranges from 1 to 75 and increases with severity. It is based on abbreviated injury scale (AIS) scores for 6 different body regions: head and neck, face, chest, abdomen, extremities and external. The severity in the AIS body region ranges from 1 (minor) to 6 (likely unsurvivable). To calculate an ISS, the most severe code from the three most severely injured body regions are squared and then summed. If any AIS code has a severity of 6, the ISS is by definition set at 75. AIS and subsequent ISS codes are determined using a proprietary technique from the Association for the Advancement of Automotive Medicine licensed by the US Military.

Example 1
Injuries:
- Major, likely unsurvivable injury to skull (body region head, severity 6)
- Minor injury to left leg (body region extremities, severity 1)

ISS: 75
The head injury is maximal severity (6), therefore the ISS is automatically 75.

Example 2
Injuries:
- Moderate injury to the left leg (body region extremities, severity 2)
- Serious injury to the chest (body region chest, severity 3)
- Critical injury to the abdomen (body region abdomen, severity 5)
- Mild burn (body region external, severity 1)

ISS: 38
Sum of the top three injured body regions ($5^2+3^2+2^2=38$).
Example 3
Injuries:
- Moderate injury to the left leg (body region extremities, severity 2)
- Mild injury to the right leg (body region extremities, severity 1)
- Serious injury to the chest (body region chest, severity 3)

ISS: 13
Only the most severe injury from the extremity body region is included ($3^2 + 2^2 = 13$)

Derivation of ICD-9 codes used for outcomes
Procedures for determining codes reviewed with an epidemiologist (JAO), using the “2013 ICD-9-CM for hospitals” Vol 1,2,3, Professional edition by two physicians (IJS and JAS). Double codes include both outcomes of interest. Therefore, if a patient had one of these codes it counted as an endpoint for both outcomes. The sources of data were administrative databases from the Defense Health Agency. There were several used for this study including the Comprehensive Ambulatory/Provider Encounter Record (CAPER), the Standard Ambulatory Data Record (SADR) and the TRICARE Encounter Data Non-Institutional (TED-NI) database. CAPER, SADR and TED-NI collect all ICD-9 codes used for outpatient billing purposes in both civilian and military facilities that are paid for by TRICARE (the military health insurance system).

Included CKD codes
V420  Kidney Transplant Status
V568  Dialysis
V560  Hemodialysis
585.6  ESRD
585.1  CKD stage 1
585.2  CKD stage 2
585.3  CKD stage 3
585.4  CKD stage 4
585.5  CKD stage 5
586  Renal failure, unspecified
585.9  CKD, unspecified

CKD codes not included
587 Includes FSGS and the focus of the study was not glomerular disorders
588 Complications of Renal disease. This was not felt to be accurate if CKD was also not coded.
589 Small kidneys, may not reflect renal damage

Included CAD codes
410.00  Acute MI, anterolateral
410.01  Acute MI, anterolateral, acute care
410.02  Acute MI, anterolateral, subsequent care
410.10  Acute MI, Anterol wall
410.11  Acute MI, Anterol wall, acute care
410.12  Acute MI, Anterol wall, subsequent care
410.20  Inferolateral MI
410.21  Inferolateral MI, acute care
410.22  Inferolateral MI, subsequent care
410.30 Inferoposterior wall MI
410.31 Inferoposterior wall MI, initial care
410.32 Inferoposterior wall MI, subsequent care
410.40 Inferior wall MI
410.41 Inferior wall MI, initial care
410.42 Inferior wall, MI, subsequent care
410.50 Lateral wall MI
410.51 Lateral wall MI, acute care
410.52 Lateral wall MI, subsequent care
410.60 Inferior apical MI
410.61 Inferior apical MI, acute care
410.62 Inferior apical MI, subsequent care
410.70 Subendocardial MI
410.71 Subendocardial MI, acute care
410.72 Subendocardial MI, subsequent care
410.80 Right Ventricle MI
410.81 Right Ventricle MI, acute care
410.82 Right Ventricle MI, subsequent care
410.90 Acute MI
410.91 Initial care, new MI
410.92 Subsequent care, recent MI
411.0 Postmyocardial infarction syndrome
411.1 Intermediate coronary syndrome
411.81 Acute occlusion without MI
411.89 Acute coronary insufficiency
412 Old myocardial infarction
413.9 Angina pectoris
413.0 Angina decubitus
413.1 Prinzmetal angina
414.00 Coronary Atherosclerosis
414.01 Coronary atherosclerosis
414.02 CAD with various bypass graft
414.03 CAD with various bypass graft
414.04 CAD with various bypass graft
414.05 CAD with various bypass graft
414.06 CAD with various bypass graft
414.07 CAD with various bypass graft
414.4 Coronary atherosclerosis, due to calcified coronary lesion
414.3 Coronary atherosclerosis, due to lipid rich plaque
414.10 Aneurysm of heart (wall)
414.11 Aneurysm of coronary vessels
414.12 Dissection of coronary artery
414.19 Other aneurism of heart
414.8 Ischemic heart disease, chronic, other
414.9 Ischemic heart disease, chronic, unspecified
414.2 Chronic total occlusion of coronary artery
429.2 Cardiovascular disease of the heart, unspecified
429.71 Acquired cardiac septal defect after MI
Complications of MI

**CAD codes not included**
We did not include codes that could not be plausibly related to atherosclerosis and codes that were not necessarily ischemic in etiology. This included:

- 415 primary lung
- 420 Pericarditis
- 421 Endocarditis
- 422 Myocarditis
- 424 Valvular dz
- 425 Cardiomyopathy
- 426 Conduction disorders
- 427 Dysrythmias
- 428 Heart failure

**Included DM Codes**
- 250.00 Diabetes mellitus
- 250.01 DM type 1
- 250.02 DM type 2
- 250.03 DM type 1, uncontrolled
- 250.10 Diabetes with ketoacidosis
- 250.11 Diabetes with ketoacidosis, type 1
- 250.12 Diabetes with ketoacidosis, type 2
- 250.13 Diabetes with ketoacidosis, type 1 uncontrolled
- 250.20 Diabetes with hyperosmolarity, type 2
- 250.21 Diabetes with hyperosmolarity, type 1
- 250.22 Diabetes with hyperosmolarity, type 2
- 250.23 DM type 1, uncontrolled, with hyperosmolality
- 250.30 Diabetes with other coma, type 1
- 250.32 Diabetes with other coma, type 2
- 250.33 Diabetes with other coma, type 1, uncontrolled
- 250.50 Diabetes with ophthalmic manifestations
- 250.51 Diabetes with ophthalmic manifestations, type 1
- 250.52 Diabetes with ophthalmic manifestations, type 2, uncontrolled
- 250.53 Diabetes with ophthalmic manifestations, type 1, uncontrolled
- 250.60 Diabetes with neurological manifestations, type 2
- 250.62 Diabetes with neurological manifestations, type 2, uncontrolled
- 250.61 Diabetes with neurological manifestations, type 1
- 250.63 Diabetes with neurological manifestations, type 1, uncontrolled
- 250.70 Diabetes with peripheral circulatory disorders
- 250.71 Diabetes with peripheral circulatory disorders, type 1
- 250.72 Diabetes with peripheral circulatory disorders, type 2, uncontrolled
- 250.73 Diabetes with peripheral circulatory disorders, type 1, uncontrolled
- 250.80 Diabetes with other specified manifestations
- 250.81 DM type 1, with manifestations
- 250.82 DM type 2 with manifestations, uncontrolled
250.83  DM type 1, with manifestations, uncontrolled
250.90  DM with complication
250.91  DM with complication, type 1
250.93  DM with complication, type 1 uncontrolled
250.92  Diabetes type 2 with unspecified complication, uncontrolled

DM codes not included
The only DM code not included was 249, because this is secondary DM.

Included HTN Codes
401.0  Hypertension, malignant
401.1  Hypertension, benign
401.9  Hypertension, Unspecified
402.00  Hypertensive heart disease. Malignant
402.01  Malignant HTN heart dz with heart failure
402.90  Hypertensive heart disease
402.10  Hypertensive heart disease, benign
402.11  Hypertensive heart disease, benign, with heart failure
402.91  Hypertensive heart disease, with heart failure
403.00  Malignant hypertensive renal disease
403.01  Malignant hypertensive renal failure
403.10  Benign hypertensive renal disease
403.11  Nephrosclerosis with HTN and renal failure
403.90  Nephrosclerosis with HTN
403.91  Nephrosclerosis with HTN, stage 5
404.01  HTN with CKD and CHF malignant
404.02  HTN with CKD and renal failure
404.03  HTN with CKD with CHF and renal failure
404.90  HTN with CKD
404.10  HTN with CKD, benign
404.11  HTN with CKD and CHF
404.12  HTN with CKD and renal failure
404.13  HTN with CKD, renal failure and CHF
404.00  HTN with CKD, malignant
404.91  HTN with CKD, with CHF
404.92  HTN with CKD, with renal failure
404.93  HTN with CKD, with CHF and renal failure

HTN codes not included
Congestive heart failure sub-codes not double coded with CAD (as heart failure might not be due to ischemic etiology), but was double coding with CKD. 405 codes (secondary HTN) were not included.

Double code CKD and HTN
403.01  Malignant hypertensive renal failure
403.10  Benign hypertensive renal disease
403.11  Nephrosclerosis with HTN and renal failure
403.90  Nephrosclerosis with HTN
403.91  Nephrosclerosis with HTN, stage 5
404.01  HTN with CKD and CHF malignant
404.02  HTN with CKD and renal failure
404.03  HTN with CKD with CHF and renal failure
404.90  HTN with CKD
404.10  HTN with CKD, benign
404.11  HTN with CKD and CHF
404.12  HTN with CKD and renal failure
404.13  HTN with CKD, renal failure and CHF
404.00  HTN with CKD, malignant
404.91  HTN with CKD, with CHF
404.92  HTN with CKD, with renal failure
404.93  HTN with CKD, with CHF and renal failure

Double code CKD and DM
250.40  Diabetes with renal manifestations
250.43  Diabetes with renal manifestations, type 1, uncontrolled
250.42  Diabetes with renal manifestations, type 2 uncontrolled
Estimated total cumulative incidence of HTN, CAD, DM, CKD and death, after adjustment, stratified by 5 point increments in injury severity score (ISS).