

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eAppendix. Supplemental Methods and Results

### METHODS

#### Inverse Selection Probability Weighting

Selection bias is a common problem in nonrandomized, observational studies. Inverse probability weighting was used to correct for this bias, and to obtain population level estimates of associations between key explanatory factors and mortality outcomes. Since aggregate total population counts of casualties and deaths are available via Department of Defense (DoD) administrative databases, and because all deaths are available at the individual level, the weighting procedure affects only individual survivors who were entered into the DoD Trauma Registry (DoDTR), as this is the only gap in individual level data coverage (**Table S1**).

Population weights for survivors were calculated as the inverse probability of selection into the DoDTR database by month, as follows

$$W_{survivor_{month}} = \frac{\text{Total Number of Wounded Survivors from DCAS in each month}}{\text{Number of Wounded Survivors in DoDTR in each month}}$$

and

$$W_{deaths_{month}} = 1$$

where each individual survivor is weighted to the total number of wounded survivors in the population within each month. Decedents are assigned a weight of 1 because all deaths are accounted for at the individual level. Summation of the weights then produces the correct total population counts of survivors and decedents by month throughout the entire period from October 1, 2001 through December 31, 2017. Having the correct population counts then enables the use of simulation analysis to estimate effects of counterfactual scenarios on population metrics, such as the case fatality rate.

#### Assessments of Model Fit, Collinearity and Sensitivity Analyses

The potential for collinearity between the three intervention variables (tourniquet use, blood transfusion, and prehospital transport within 60 minutes) was examined by first assessing the correlation matrix (**Table S3**). The Akaike Information Criterion (AIC) statistic was used to evaluate the fit of each multinomial logistic regression model, where the lower the value the better the fit. Sensitivity analysis was then performed, in which individual variables were removed from the model one-at-a-time and the parameter estimates and AIC values of the constrained models were compared with the full model (**Table S4**).

#### Simulation Methodology

The predicted probabilities of being KIA and DOW are calculated by the following equation:  $P = \frac{1}{1+e^{-(\beta_0+\beta_i x_i)}}$ , where  $e$  is the natural log, approximately 2.718, and  $\beta_i x_i$  is the linear combination of covariates in the model.  $P_{KIA}$  and  $P_{DOW}$  are both calculated in this manner with their corresponding regression coefficients. The probability of being in Alive status is calculated by subtracting  $P_{KIA}$  and  $P_{DOW}$  from 1. For purposes of simulating the counterfactual scenario, the pre-simulation mean values for use of tourniquets, blood transfusion and prehospital transport times were used in these probability calculations during the simulation period. Using the resulting predicted probabilities for KIA, DOW and Alive status, the following classification rules were used to assign simulated KIA, DOW and Alive status. For Afghanistan, if  $P_{KIA} > P_{DOW}$  and  $P_{KIA} \geq 82^{\text{nd}}$  percentile (0.3323) then Status = KIA, else if  $P_{DOW} > P_{KIA}$  and  $P_{DOW} > P_{\text{Alive}}$  or  $P_{DOW} \geq 75^{\text{th}}$  percentile (0.035877) then Status = DOW, else Status = Alive. For Iraq, if  $P_{KIA} > P_{DOW}$  and  $P_{KIA} \geq 78^{\text{th}}$  percentile (0.335335) then Status = KIA, else if  $P_{DOW} > P_{KIA}$  and  $P_{DOW} > P_{\text{Alive}}$  or  $P_{DOW} \geq 70^{\text{th}}$  percentile (0.0375) then Status = DOW, else Status = Alive. Sankey transition plots were then derived from the cross-tabulation of simulated versus actual status.

In order to estimate the relative contribution of each intervention and other factors, including demographics and injury characteristics, to the difference between the simulated and actual deaths, rate-difference decomposition techniques for binary outcomes were used based on Fairlie's extension<sup>27</sup> of the Oaxaca-Blinder decomposition

method. This approach estimates the percent contribution of a set of factors to an observed difference in rates based on the relationship between each factor and the outcome, from logistic regression coefficients, and the difference in the distribution of each factor between the two groups, or time periods, being compared.

## RESULTS

Results of multivariable, multinomial logistic regression models (**Table S2**) suggest that the percentage of casualties transported to surgical capability within 60 minutes was associated with lower odds of KIA mortality in Afghanistan (OR=0.98; 95%CI=0.98-0.99;  $p<0.001$ ), but a slight increase in odds of KIA mortality in Iraq (OR=1.00; 95%CI=1.00,1.01;  $p<0.001$ ). The percentage of casualties who received a blood transfusion was associated with lower odds of DOW mortality (OR=0.97; 95%CI=0.95-0.99;  $p=0.01$ ) in Afghanistan. The percentage of casualties with extremity injuries who had tourniquets placed was associated with lower odds of KIA (OR=0.98; 95%CI=0.97-1.00;  $p=0.02$ ) and DOW (OR=0.99; 95%CI=0.99-1.00;  $p=0.06$ ) mortality in Iraq. Explosive MOI was associated with higher odds of KIA mortality in Afghanistan and Iraq, and higher odds of DOW mortality in Iraq. ISS was associated with higher odds of KIA and DOW mortality in Afghanistan and Iraq.

Results of the correlation matrix (**Table S3**) between the three intervention variables indicate that there were moderate to strong correlations between these variables. For Afghanistan, the tourniquet use variable had a correlation coefficient of 0.54 with both the blood transfusion and the prehospital transport variables. The blood transfusion and prehospital transport correlation was 0.43. For Iraq, the correlation between tourniquet use and blood transfusion was 0.70, but the correlations between blood transfusion and prehospital transport (0.02) and tourniquet use and prehospital transport (0.28) were negligible.

Results of sensitivity analyses (**Table S4**) for Afghanistan indicate that removal of the prehospital transport time variable adversely impacts the overall fit of the model because the AIC value increased from 4969 to 4989, while at the same time the p-values associated with the tourniquet use and blood transfusion variables in the KIA portion of the model decreased from 0.80 to 0.02 and 0.19 to 0.05, respectively. This suggests that the prehospital transport time variable is exerting a collinear influence on the other two variables, which is biasing their estimated effects toward the null. The blood transfusion variable exhibits a similar effect on the tourniquet use variable in the DOW portion of the model as well.

Results of sensitivity analyses for Iraq indicate that removal of the blood transfusion variable did not adversely impact the overall fit of the model, and at the same time reduced the p-value associated with the tourniquet use variable from 0.02 to  $<0.001$  in the KIA portion and from 0.06 to  $<0.001$  in the DOW portion of the model. This suggests that the blood transfusion variable is collinear with the tourniquet use variable to a great enough extent that it is biasing the estimated effects of tourniquet use toward the null. However, removing this variable from the model would mean that an important intervention variable was being ignored. We decided that ignoring this variable was worse than accepting some collinearity and imprecision in individual variable parameter estimates.

These results suggest that the overall estimates and net effects for each of the three intervention variables may be underestimated in the full models. However, since the primary objective of the models was to use them for prediction purposes, in order to simulate counterfactual scenarios, the precision of the individual parameter estimates for each variable were less important than the estimated net effect of all three in combination. Therefore, we determined it was reasonable to use the full models for simulation purposes.

### Future Research

Future research would benefit from more robust measurement of specific in-hospital interventions. More data and analysis regarding critical interventions, such as advanced imaging technology (CT, MRI); ventilator management strategies; progress in identification and management of invasive fungal or other infections; Role 2 versus Role 3 admission from point of injury; availability of certain specialties on outcomes (CT surgery, vascular, pulmonologists). Efforts should be made to collect such data in a more comprehensive and systematic manner in the future.

**eTable 1. Overall Combat Casualty Care Statistics**

<b>Afghanistan</b>										
Year	Counts				Annual			Cumulative		
	WIA	DOW	KIA	RTD	CFR	%DOW	%KIA	CFR	%DOW	%KIA
2001	33	3	0	0	9.1	9.1	0.0	9.1	9.1	0.0
2002	74	2	16	0	20.0	2.7	17.8	17.1	4.7	13.0
2003	99	8	9	5	15.7	8.5	8.7	16.5	6.5	11.1
2004	217	11	14	46	10.8	6.4	7.6	13.6	6.5	9.5
2005	270	7	59	134	20.1	5.1	30.3	16.3	6.1	16.2
2006	402	9	56	165	14.2	3.8	19.1	15.5	5.4	17.1
2007	751	9	74	286	10.1	1.9	13.7	13.4	4.0	15.9
2008	798	20	111	206	14.4	3.4	15.8	13.7	3.8	15.8
2009	2,155	63	208	1,061	11.5	5.8	16.0	12.7	4.6	15.9
2010	5,264	130	307	3,048	7.8	5.9	12.2	10.2	5.1	14.3
2011	5,223	99	260	3,018	6.5	4.5	10.5	9.0	4.9	13.2
2012	2,971	63	174	878	7.5	3.0	7.7	8.8	4.5	12.0
2013	1,368	34	57	298	6.4	3.2	5.1	8.6	4.4	11.4
2014	454	14	24	123	7.9	4.2	6.8	8.6	4.4	11.2
2015	76	2	8	16	11.9	3.3	11.8	8.6	4.4	11.2
2016	71	5	4	14	12.0	8.8	6.6	8.6	4.4	11.2
2017	102	4	7	19	10.1	4.8	7.8	8.6	4.4	11.2
Total	20,328	483	1,388	9,317	8.6	4.4	11.2			

<b>Iraq</b>										
Year	Counts				Annual			Cumulative		
	WIA	DOW	KIA	RTD	CFR	%DOW	%KIA	CFR	%DOW	%KIA
2001	-	-	-	-	-	-	-	-	-	-
2002	-	-	-	-	-	-	-	-	-	-
2003	2,423	53	260	246	11.7	2.4	10.7	11.7	2.4	10.7
2004	8,004	176	536	4,062	8.3	4.5	12.0	9.1	3.7	11.5
2005	5,944	171	502	3,912	10.4	8.4	19.8	9.6	4.9	13.7
2006	6,414	160	544	4,331	10.1	7.7	20.7	9.8	5.5	15.3
2007	6,121	143	621	3,926	11.3	6.5	22.1	10.1	5.7	16.5
2008	2,052	70	148	1,382	9.9	10.4	18.1	10.1	5.9	16.6
2009	680	19	55	422	10.1	7.4	17.6	10.1	5.9	16.6
2010	392	10	9	261	4.7	7.6	6.4	10.0	5.9	16.6
2011	221	12	22	120	14.0	11.9	17.9	10.0	6.0	16.6
2012	-	1	-	-	-	-	-	10.0	6.0	16.6
2013	-	-	-	-	-	-	-	10.0	6.0	16.6
2014	-	-	-	-	-	-	-	10.0	6.0	16.6
2015	5	-	1	1	16.7	0.0	20.0	10.1	6.0	16.6
2016	24	3	4	3	25.0	14.3	16.0	10.1	6.0	16.6
2017	32	4	1	2	15.2	13.3	3.2	10.1	6.0	16.5
Total	32,312	822	2,703	18,668	10.1	6.0	16.5			

**eTable 2. Results of Multivariable, Multinomial Logistic Regression Analysis**

<b>Model Variables</b>	<b>Afghanistan OR (95% CI); p value</b>	<b>Iraq OR (95% CI); p value</b>
<b><u>KIA Model</u></b>		
Age	1.02 (1.00,1.04); 0.01	1.02 (1.01,1.04); <0.001
Sex (Female vs. Male)	0.96 (0.36,2.52); 0.93	1.41 (0.80,2.49); 0.23
Service Branch		
Army (ref)		
Air Force	2.07 (0.94,4.04); 0.07	2.36 (1.13,4.92); 0.02
Marine	0.82 (0.62,1.07); 0.14	1.28 (1.06,1.53); 0.01
Navy	1.84 (0.97,3.51); 0.06	0.70 (0.39,1.25); 0.22
Body Region Indicators (not mutually exclusive)		
Head	0.67 (0.51,1.14); 0.31	0.88 (0.73,1.05); 0.16
Face	0.79 (0.60,1.03); 0.09	0.79 (0.65,0.95); 0.01
Chest	0.96 (0.71,1.25); 0.93	0.89 (0.74,1.07); 0.23
Abdomen	0.59 (0.44,0.80); <0.001	0.47 (0.38,0.57); <0.001
Extremity	1.15 (0.87,1.50); 0.20	0.90 (0.76,1.06); 0.21
External	0.01 (0.01,0.02); <0.001	0.02 (0.01,0.02); <0.001
Mechanism of Injury		
Gunshot (ref)		
Explosive	1.34 (1.02,1.77); 0.04	2.14 (1.76,2.60); <0.001
Other	2.05 (1.11,3.80); 0.02	3.21 (2.23,4.62); <0.001
ISS	1.22 (1.21,1.23); <0.001	1.20 (1.19,1.21); <0.001
Interventions (per 10 percent unit change)		
% of Extremity Injuries with Tourniquet	0.98 (0.87,1.11); 0.80	0.85 (0.74,0.97); 0.02
% Received Blood Product Transfusion	0.87 (0.71,1.08); 0.19	0.89 (0.73,1.07); 0.22
% Transported within 60 Minutes	0.89 (0.84,0.94); <0.001	1.05 (1.02,1.08); <0.001
<b><u>DOW Model</u></b>		
Age	1.02 (1.00,1.04); 0.04	1.01 (1.00,1.03); 0.04
Sex (Female vs. Male)	1.54 (0.59,4.04); 0.49	2.32 (1.31,4.10); 0.004
Service Branch		
Army (ref)		
Air Force	0.63 (0.20,2.01); 0.08	0.00 (0.00,999); 0.94
Marine	1.18 (0.90,1.54); 0.26	1.05 (0.85,1.29); 0.66
Navy	0.54 (0.21,1.38); 0.14	0.04 (0.01,0.31); 0.002
Body Region Indicators (not mutually exclusive)		
Head	0.67 (0.51,0.88); 0.004	0.71 (0.58,0.87); 0.001
Face	0.66 (0.48,0.89); 0.006	0.58 (0.46,0.73); <0.001
Chest	0.95 (0.71,1.25); 0.70	1.02 (0.83,1.25); 0.86
Abdomen	0.59 (0.44,0.80); <0.001	0.57 (0.46,0.71); <0.001
Extremity	1.15 (0.87,1.50); 0.33	0.67 (0.55,0.80); <0.001
External	0.01 (0.01,0.02); <0.001	0.02 (0.01,0.02); <0.001
Mechanism of Injury		
Gunshot (ref)		
Explosive	1.08 (0.81,1.44); 0.59	1.72 (1.40,2.13); <0.001
Other	1.05 (0.52,2.15); 0.89	1.13 (0.72,1.80); 0.59
ISS	1.18 (1.16,1.19); <0.001	1.17 (1.16,1.18); <0.001
Interventions (per 10 percent unit change)		
% of Extremity Injuries with Tourniquet	0.91 (0.79,1.05); 0.17	0.87 (0.74,1.01); 0.06
% Received Blood Product Transfusion	0.75 (0.60,0.94); 0.01	0.84 (0.68,1.05); 0.11
% Transported within 60 Minutes	1.03 (0.96,1.10); 0.40	1.02 (0.99,1.05); 0.23

**eTable 3. Correlation Matrix for Intervention Variables**

<b>Afghanistan</b>			
	% of Extremity Injuries with Tourniquet	% Received Blood Product Transfusion	% Transported within 60 Minutes
% of Extremity Injuries with Tourniquet	1.00	--	--
% Received Blood Product Transfusion	0.54	1.00	--
% Transported within 60 Minutes	0.54	0.43	1.00
<b>Iraq</b>			
% of Extremity Injuries with Tourniquet	1.00	--	--
% Received Blood Product Transfusion	0.70	1.00	--
% Transported within 60 Minutes	0.28	0.02	1.00

**eTable 4. Results of Sensitivity Analysis of Multivariable, Multinomial Logistic Regression Analysis**

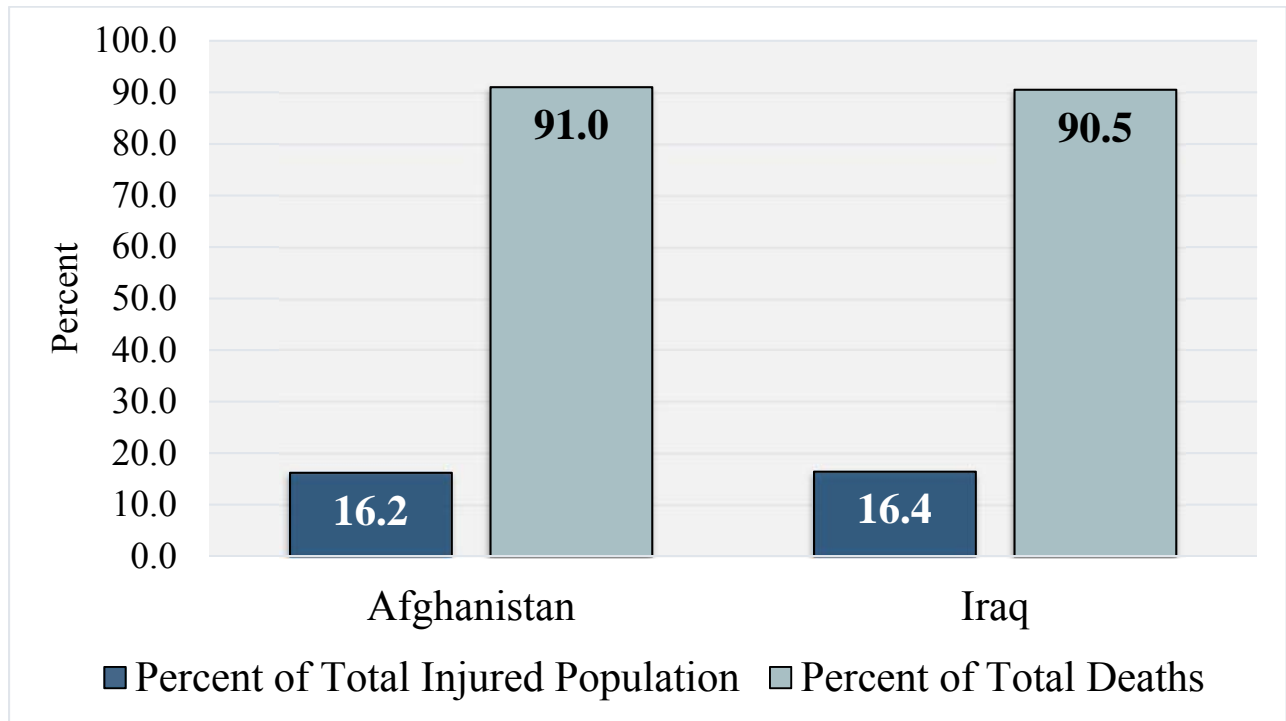
	<b>Afghanistan</b> <b>OR (95% CI); p value</b>	<b>Iraq</b> <b>OR (95% CI); p value</b>
<b><u>KIA Models</u></b>		
<b>Full Model:</b>		
% of Extremity Injuries with Tourniquet	0.99 (0.98,1.01); 0.80	0.98 (0.97,0.99); 0.02
% Received Blood Product Transfusion	0.98 (0.97,1.01); 0.19	0.99 (0.97,1.01); 0.22
% Transported within 60 Minutes	0.98 (0.98,0.99); <0.001	1.00 (1.00,1.01); <0.001
Model AIC	4969.085	9347.928
<b>Model excluding Transport Time variable:</b>		
% of Extremity Injuries with Tourniquet	0.98 (0.98,0.99); 0.02	0.99 (0.9,1.00); 0.27
% Received Blood Product Transfusion	0.98 (0.96,1.00); 0.05	0.98 (0.96,0.99); 0.03
% Transported within 60 Minutes	--	--
Model AIC	4989.641	9355.997
<b>Model excluding Blood Transfusion variable:</b>		
% of Extremity Injuries with Tourniquet	0.99 (0.98,1.00); 0.41	0.98 (0.97,0.99); <0.001
% Received Blood Product Transfusion	--	--
% Transported within 60 Minutes	0.99 (0.98,0.99); <0.001	1.00 (1.00,1.01); <0.001
Model AIC	4971.104	9346.676
<b><u>DOW Models</u></b>		
<b>Full Model:</b>		
% of Extremity Injuries with Tourniquet	0.99 (0.98,1.00); 0.17	0.99 (0.97,1.00); 0.06
% Received Blood Product Transfusion	0.97 (0.95,0.99); 0.01	0.98 (0.96,1.00); 0.11
% Transported within 60 Minutes	1.00 (1.00,1.01); 0.40	1.00 (1.00,1.00); 0.23
Model AIC	4969.085	9347.928
<b>Model excluding Transport Time variable:</b>		
% of Extremity Injuries with Tourniquet	0.99 (0.98,1.00); 0.29	0.98 (0.96,1.00); 0.13
% Received Blood Product Transfusion	0.97 (0.95,0.99); 0.02	0.98 (0.96,1.00); 0.06
% Transported within 60 Minutes	--	--
Model AIC	4989.641	9355.997
<b>Model excluding Blood Transfusion variable:</b>		
% of Extremity Injuries with Tourniquet	0.98 (0.97,0.99); 0.009	0.98 (0.97,0.99); <0.001
% Received Blood Product Transfusion	--	--
% Transported within 60 Minutes	1.00 (0.99,1.01); 0.61	1.00 (1.00,1.01); 0.11
Model AIC	4971.104	9346.676

**eTable 5. Injury Characteristics of Patients Who Transitioned From KIA to DOW and From KIA and DOW to Alive**

Variables	Afghanistan				Iraq			
	KIA to DOW	KIA to Alive	DOW to Alive	No Forward Transition	KIA to DOW	KIA to Alive	DOW to Alive	No Forward Transition
N	300	278	1,312	18,873	536	450	1,867	29,479
Body Region, Percent								
Head	63.3	57.7	43.0	59.6	64.0	73.4	40.4	35.3
Face	29.2	39.4	16.2	26.5	26.6	34.4	14.1	26.4
Chest	60.0	73.5	30.5	17.6	54.3	61.1	35.5	14.8
Abdominal	55.1	73.9	28.2	22.7	44.2	41.9	25.4	18.5
Extremity	63.9	67.8	84.5	46.3	52.6	50.7	59.4	49.6
Traumatic Amputation	21.0	34.2	14.4	10.3	11.5	12.5	8.5	7.6
Severe (AIS 3-6)	51.8	59.8	58.5	24.9	43.2	35.2	47.6	24.9
External	6.2	61.9	30.3	78.0	10.0	42.6	20.2	81.0
Polytrauma (ISS 16 or more)	82.6	95.2	34.0	22.9	78.1	88.1	34.2	21.4
Mechanism of Injury, Percent								
Explosive	59.7	68.4	60.0	79.6	69.4	65.9	69.4	79.8
Gunshot Wound	37.4	30.8	37.4	19.0	25.9	31.2	28.4	16.9
Other	2.9	0.8	2.6	1.4	4.7	2.9	2.2	3.3
Severity, Percent								
ISS 1-9 (Mild)	0.0	0.0	48.9	61.0	0.0	0.0	46.4	59.0
ISS 10-15 (Moderate)	0.0	0.0	13.6	14.8	0.0	0.0	12.7	17.5
ISS 16-24 (Severe)	3.9	5.0	6.5	11.7	1.7	4.9	15.7	10.5
ISS 25-75 (Critical)	95.7	95.0	31.0	12.5	98.3	95.1	25.2	13.1
ISS, Mean (STD)	42.8 (17.3)	46.6 (25.0)	18.8 (24.3)	11.9 (23.1)	44.9 (18.4)	43.5 (30.1)	17.2 (22.0)	12.3 (26.1)

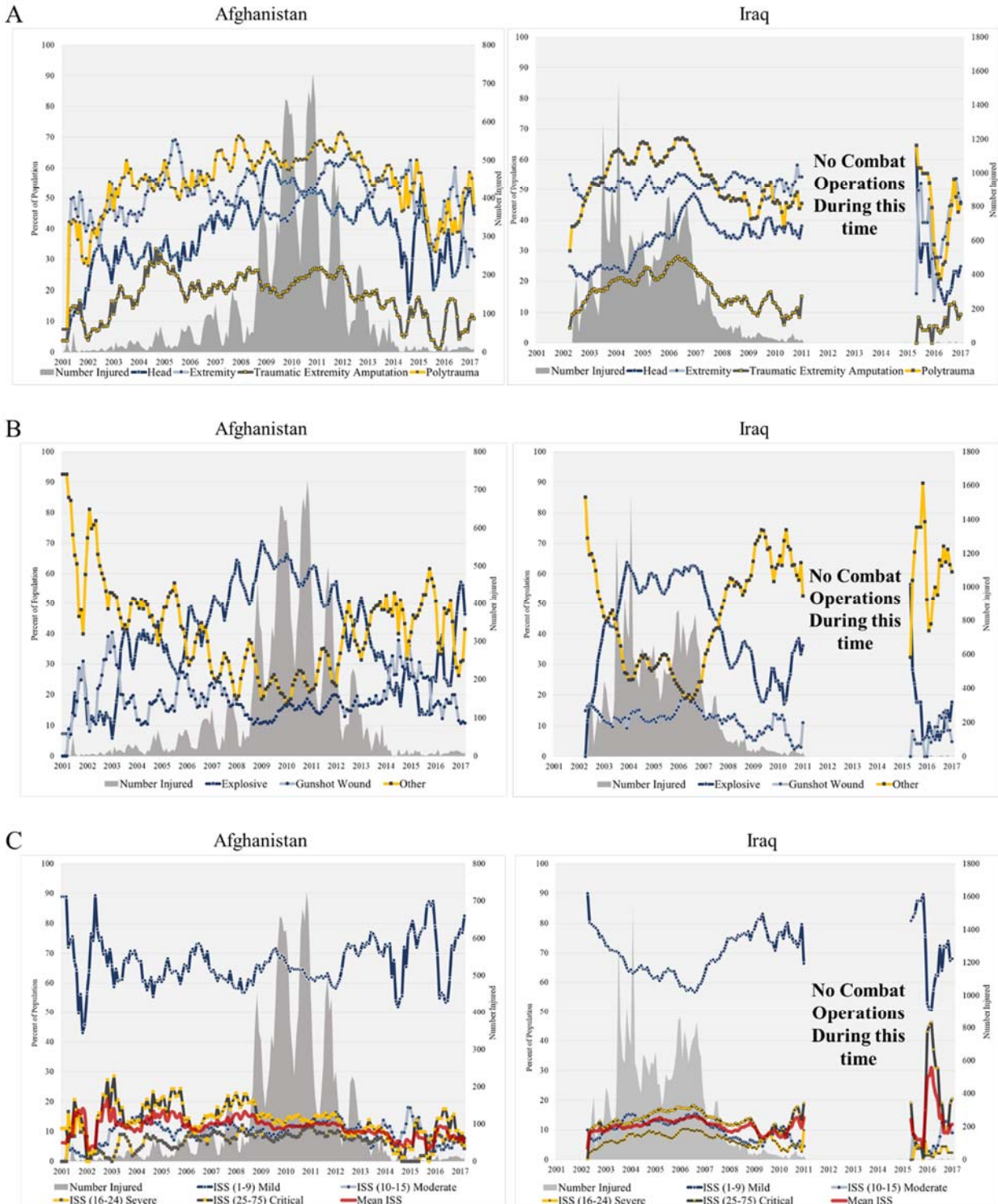


**eFigure 1. Mortality for Critically Injured Patients With Injury Severity Score (ISS) of 25 or Higher**



## eFigure 2. Key Injury Descriptions

Percent of Patients with Injuries by Selected Body Region (Panel A), Mechanism of Injury (Panel B), Injury Severity Score (ISS) with Mean ISS (Panel C) for Afghanistan and Iraq, 6-month Moving Average from October 2001 through December 2017.



### eFigure 3. Major Interventions and Policy Directives

Percent of Patients with Extremity Injuries who had Tourniquet Use Documented (Panel A), Percent of Total Patients who Received Blood Transfusion (Panel B), and Percent of Total Patients Transported from Point of Injury to Surgical Care within 60 Minutes (Panel C) for Afghanistan and Iraq, 6-month Moving Average from October 2001 through December 2017.

