2018-05-09

Follow Your Heart: Evaluating Cardiac Function to Predict Outcomes Among ICU Patients with Traumatic Brain Injury

Patric Gibbons
University of Massachusetts Medical School

Follow Your Heart: Evaluating Cardiac Function to Predict Outcomes Among ICU Patients with Traumatic Brain Injury

Patric Gibbons, MS4

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in the United States and is an important contributory factor in approximately 30% of all injury related deaths.[1] In 2013, there were 2.5 million emergency department (ED) visits in the U.S. for TBI resulting in 282,000 hospitalizations and approximately 50,000 deaths.[1]

Persons who initially survive a severe TBI are often admitted to a Neurological Intensive Care Unit (Neuro ICU) where they require complex medical and surgical care. These patients are prone to a number of clinical complications during their ICU hospitalization. A "Cardio-Cerebral Syndrome" has been previously described in a small number of recent studies, which found cardiac dysfunction to be related to the development of intracranial pathologies, particularly ischemic stroke and subarachnoid hemorrhage.[2,3,4] The published literature describing brain-heart interactions in the setting of TBI, however, is even more limited, with a few case reports and one prospective study showing transient reduced systolic function in a small number of patients with moderate-to-severe TBI (msTBI).[5]

What remains largely unknown is how often cardiac complications occur, if they affect various patient outcomes, and whether cardiac biomarker and imaging studies can be utilized to predict prognosis in patients with a msTBI. To date, no studies have examined the frequency of cardiovascular complications among patients hospitalized with a TBI, the impact of these clinical complications on patient's short-term survival, or the relationship between the severity of brain injury with the degree of cardiac dysfunction.

Using data from a large cohort study (Muehlschlegel et al. 2013), we determined the frequency of cardiovascular complications in patients with msTBI and examined the relationship between the severity of brain injury and degree of cardiac dysfunction. A secondary study goal was to examine the influence of cardiovascular dysfunction on 30-day hospital survival.

METHODS

Study Population

The data for this observational study were derived from a longitudinal study of patients enrolled in the *Outcome Prognostication in Traumatic Brain Injury* (OPTIMISM) investigation.[6] We collected data on a cohort of patients enrolled in the OPTIMISM study between November 2009 and January 2017 with msTBI (Glasgow Coma Scale (GCS)≤12) admitted to the Neurological-Trauma-Intensive Care Unit (NTICU) at the University of Massachusetts Medical Center, a level-I trauma center in Worcester, MA. The diagnosis of TBI was based on patient's

history and mechanism of injury. This diagnosis was confirmed with non-contrast computed tomography (CT), which was reviewed by a neuroradiologist and corroborated by three board-certified neurointensivists.

Study Data

A number of sociodemographic and clinical variables were collected in the OPTIMISM study at the time of admission to the ICU. These factors included patients' demographic characteristics, medical history, GCS findings, physiologic data, injury severity score (ISS), Marshall CT classification, and mechanism of trauma. Pre-ICU variables including hypoxia in the field or emergency department (ED), hypotension in the field or ED, and pupillary response were also collected. The GCS ranges from 3-15, with 3 being the worst possible score, commonly seen in patients who are comatose, while patients who are fully awake and oriented would be scored as a 15. The ISS ranges from 0 to 75 and measures the overall severity of the patient's trauma, with higher numbers indicating more severe overall injuries. Information about cardiovascular disease (CVD), which included whether patients had been previously diagnosed with either coronary artery disease, myocardial infarction (MI), hypertension, hypercholesterolemia, arrhythmias, heart failure, or hyperlipidemia was also collected. Patients were followed throughout the course of their ICU hospitalization. Pre-specified medical and neurological complications were prospectively recorded and confirmed by three neurointensivists during a weekly review process.[6]

We collected data on several additional cardiac parameters in the present study including the results of patient's baseline EKGs, echocardiography reports, and peak serum troponin levels during the NTICU hospitalization. EKG reports included computer-generated estimates of the ventricular rate, PR interval, QTc interval, R wave axis, T wave axis, and bundle branch block patterns. Echocardiography reports were generated by a board-certified cardiologist and included ejection fraction (%), fractional shortening (FS), and qualitative assessments such as diastolic function and wall motion abnormalities. EKGs, Echocardiograms, and serum troponin levels were ordered at the discretion of the attending ICU physician.

For purposes of this study, we examined several CVD complications including the development of hypotension requiring pharmacologic management, and occurrence of a new atrial or ventricular arrhythmia, MI, deep venous thrombosis (DVT), or pulmonary embolism (PE).

We created a Cardiac Dysfunction Index (CDI) which consisted of three equally-weighted components: 1) elevated serum troponin findings (>0.04 ng/mL); 2) development of an EKG abnormality which included either a prolonged corrected QTc interval, widened QRS, presence of T-wave inversions, or irregularity of the R-R interval; and 3) Transthoracic Echocardiography (TTE) abnormalities including reduced ejection fraction (EF <60%), wall motion abnormalities (e.g., global hypokinesis), and fractional shortening (FS). Patients received 1 point for each component of the CDI for a minimum score of 0 and a maximum of 3.

Statistical Analysis

We initially compared differences in the baseline demographic and clinical characteristics of patients with and without cardiovascular dysfunction using ANOVA and Pearson's chi-square tests. Since the severity of brain injury is scored on an ordinal scale in ascending order of GCS (3 to 12) or motor GCS (1 to 6), an ordinal logistic regression model was utilized to examine the association between increasing levels of brain injury and degree of cardiac impairment as measured by the CDI. Our logistic regression model adjusted for patient's age, sex, and history of CVD. We performed a survival analysis using the Kaplan-Meier estimate, and compared 30-day hospital survival rates for those with and without CVD-related complications with the logrank test to examine the significance of differences in estimated survival curves. Multivariable Cox regression analysis comparing CDI scores adjusted for age, sex, history of CVD, and GCS was performed and hazard ratios (HRs) were calculated with accompanying 95% confidence intervals. Model assumptions were tested with Schoenfield residuals and goodness of fit tests. A graphical representation of the CDI-score Cox regression was also constructed. Statistical analysis was performed using STATA version 14.0 (Stata Corporation, Bryan, TX).

RESULTS

A total of 497 patients were enrolled in the OPTIMISM study between November 2009 and January 2017. The mean age of the study population was 52 years and approximately 30% of patients were women. The most common cause of TBI in this population was a fall (48%) followed by a motor vehicle accident (19%). We excluded patients with chest trauma (n= 154), because we were interested in isolating cardiac injury from TBI without influence from blunt cardiac injury. We also excluded 19 patients with a GCS greater than 12, which resulted in a total of 326 patients who were included in the present analyses. In examining differences in selected baseline demographic and clinical characteristics between those with and without cardiac dysfunction, patients with cardiac dysfunction were, on average, 6 years older, were more likely to have a history of CVD, and were more likely to experience hypotension in the field or ED prior to their initial presentation (Table 1).

Frequency of Cardiovascular Complications

The frequency of major CVD complications and abnormal echocardiography and EKG findings are shown in Table 2. We found that approximately 1 in every 7 patients with msTBI experienced a new cardiac arrhythmia during their NTICU hospitalization. Approximately two thirds of patients had an EKG abnormality, one third had an echocardiographic abnormality, and 52% had increases in their serum troponin levels (Table 2).

Relationship Between CDI and GCS

We were able to calculate CDI scores for a subset of 68 patients based on availability of echocardiography findings and troponin testing (Table 2). After adjusting for several potentially confounding demographic and clinical factors, patients with more severe brain injury, as measured by lower motor GCS scores, were significantly more likely to have indicators of cardiac injury as reflected by higher CDI scores (OR 0.76; 95%CI 0.58-0.99).

In-hospital Survival

In examining in-hospital survival rates (Figure 1), patients who developed any of the examined EKG abnormalities, echocardiography abnormalities, or developed hypotension requiring pharmacologic intervention were at greater risk for dying in comparison with those who did not experience these complications. Patients who developed a new atrial or ventricular arrhythmia in the ICU had a similar survival experience compared with those who did not experience a new cardiac arrhythmia (Figure 1).

Each individual component of the CDI was shown to relatively similarly predict patient's short-term mortality (figure 1). In our mutlivariable adjusted regression analyses, we found a HR of 1.97 (95% CI 0.90-4.34) for any EKG abnormality, a HR of 4.00 (95% CI 1.67-9.59) for any Echo abnormality, and a HR of 1.74 (95% CI 0.84-3.62) for patients who had elevated serum troponin findings. Based on these results, our CDI model was built with equal weighting to each of the three components for our final regression analyses.

Univariate Cox regression showed CDI, GCS, mGCS to be independently associated with patient's survival, with hazard ratios of 2.26 (95% CI 1.39-3.70), 0.81 (95% CI 0.73-0.89), and 0.73 (95% CI 0.64-0.84), respectively. In the multivariable adjusted regression analysis, which simultaneously controlled for patient's age, sex, history of CVD, Marshall CT score, pupillary response, hypoxia in the field, hypotension in the field, and GCS or motor GCS scores, ICU mortality was significantly higher for those with elevated CDI scores (HR 2.41; 95% CI 1.29-4.53; Figure 2). The effect estimates for total GCS and motor GCS were attenuated when CDI was included in the full regression model with a HR of 1.05 (95% CI 0.88-1.27) and 1.14 (95% CI 0.83-1.56), respectively.

Since a number of drugs used in the ICU potentially lengthen the QTc interval (e.g., Propofol, proton pump inhibitors), we performed a separate subgroup analysis excluding this covariate from the EKG abnormality parameter and CDI score. This analysis continued to show a statistically significant increase in the risk of death with increasing CDI scores (HR 2.68; 95%CI 1.54-4.67).

DISCUSSION

The objectives of this longitudinal study were to describe the frequency of cardiovascular abnormalities in patients with msTBI and determine their potential impact on hospital survival. Our results suggest that cardiac dysfunction in the setting of TBI is common and is associated with worse in-hospital survival. We also showed an association between increasing severity of TBI and greater cardiovascular injury. Taken together, these findings provide evidence for a post-TBI "cardio-cerebral syndrome" and show that such a syndrome has important implications for patient outcomes.

Frequency of Cardiovascular Complications

We found that approximately two thirds of study patients had an EKG abnormality and 52% had elevated serum troponin levels. These findings are similar to a 2016 study of 50 Egyptian patients with severe TBI, which found that 62% of patients had abnormal EKG findings and 54%

had elevated troponin levels.[10] In addition, we found that echocardiographic abnormalities (e.g., low EF, hypokinesis, fractional shortening) were found in approximately one third of study patients. These results suggest that cardiac injury is a common sequela of msTBI affecting more than one half of these seriously ill patients.

Relationship Between CDI and GCS

It is unclear in describing brain-heart interactions whether cardiac injury is related to the brain injury, or if it is simply a marker of severe physiologic stress secondary to the traumatic cerebral insult. Previous studies have examined cardiac dysfunction in the setting of severe sepsis and septic shock.[7,8] This "sepsis-induced cardiomyopathy" has been associated with a lower EF, reduced cardiac index, and elevated serum troponin levels.[8] A small number of case reports and a retrospective study have also highlighted the potential for an increased frequency of stress cardiomyopathy in patients admitted to the ICU.[9,10] These data suggest that there may be a greater frequency of cardiac dysfunction among critically ill patients across a variety of acute illnesses.

In the present study, we showed a significant association between the severity of brain injury and the degree of cardiovascular dysfunction. Those with more severe brain injuries at the time of hospital admission were shown to have an increased likelihood of developing cardiac injury as reflected by higher CDI scores. Furthermore, the hazard ratios for GCS and motor GCS became non-significant when CDI was included in the Cox regression model, indicating that a significant portion of the relationship between GCS and short-term mortality is mediated by cardiac injury. These results suggest a plausible pathway between the brain and heart in the setting of TBI and give further credence to a "Cardio-Cerebral Syndrome."

In Hospital Survival

A question that remains among patients with the "Cardio-cerebral syndrome" is whether cardiac injury affects survival in patients with msTBI. Our results showed a significantly greater risk of dying among patients with increased makers of cardiac dysfunction and higher levels of cardiac injury compared to those without evidence of reduced cardiac function. This is similar to the results of a previous study that found derangements in troponin, echocardiography, and systolic blood pressure to be associated with increased mortality in a cohort of 50 patients with severe TBI (GCS <8).[11] There is some evidence to suggest that protecting the heart during the course of illness with beta blockers in patients with TBI can improve patients' short-term survival. This is presumably due to their cardio-protective effects against the adrenergic surge commonly noted after a severe brain injury; however, the level of quality evidence is limited.[12,13] Although approximately one in every seven patients developed a new cardiac arrhythmia in our study, their presence did not appear to impact in-hospital survival.

Study Strengths and Limitations

To date, this is the largest study that has examined the relationship between the brain and heart in the setting of msTBI. Our CDI score also provides a simple and clinically useful set of parameters to objectively measure cardiac dysfunction in this patient population. We decided to equally weight the three components of this CDI for the purposes of this exploratory analysis

based on the results of a small prior study as well as our life table survival curves. Future studies will be needed to determine more exact prognostication scores with different weighting assigned to each of the individual components included in any such score.

Our study has the limitations of an observational study design. Although many patients received an EKG within 24 hours of the initial trauma, a significant number lacked an EKG prior to this event. There is also the potential for bias with regards to the echocardiography and troponin findings, since these tests were ordered at the discretion of the attending ICU physician. Additionally, there was a considerable amount of missing data with many patients having EKGs but lacking data on either echocardiography or troponin findings.

CONCLUSIONS

Our study shows an association between TBI severity and development of subsequent cardiac injury in ICU patients with msTBI. These CVD complications were associated with a poorer in-hospital survival. Further prospective studies are needed to serially and more systematically examine various cardiac findings among patients who develop an msTBI and provide insights to the development of prognostic tools and indices for intervention in this population.

TABLES AND FIGURES

Table 1: Patient demographic and clinical characteristics at the time of ICU admission.

	Cardiac Dysfunction n=142	No Cardiac Dysfunction n=184	p-value
Age, mean (SD)	59.6 (20.9)	53.7 (21.4)	0.014
Male	71.8%	68.5%	0.51
Race			0.21
White	87.3%	91.8%	
Black	4.2%	4.9%	
Asian	2.8%	1.6%	
American Indian or Alaskan Native	0.0%	0.5%	
Unknown/Not Documented	5.6%	1.1%	
Cause of TBI			0.15
Motor Vehicle Accident (MVA)	9.9%	9.2%	
Vehicle vs. Pedestrian	2.1%	8.7%	
Fall	64.1%	56.5%	
Assault	4.2%	8.7%	
Gunshot	11.3%	6.5%	
Motorcycle/Scooter Accident	3.5%	3.3%	
Other	4.9%	6.9%	
Total GCS, mean (SD)	5.8 (2.9)	6.2 (2.6)	0.26
Motor GCS, mean (SD)	3.1 (1.9)	3.5 (1.9)	0.032
Initial Marshall CT Classification			0.85
Diffuse Injury Type II	54.2%	57.6%	
Diffuse Injury Type III	9.9%	10.9%	
Diffuse Injury Type IV	7.0%	5.4%	
Type 6 (Non-Evacuated Mass Lesion)	28.9%	26.1%	
ISS, mean (SD)	27.8 (11.3)	25.7 (9.1)	0.069
Cardiovascular History			0.005
No Reported History	42.3%	56.5%	
Arrhythmia	2.8%	0.5%	
CHF	0.7%	0.5%	
Hypertension	33.1%	34.8%	
Myocardial Infarction	2.8%	1.1%	
Coronary Artery Disease	18.3%	6.5%	
Current Smoker			0.15
No	40.8%	37.5%	
Yes	35.9%	45.7%	
Unknown	23.2%	16.8%	
Pupil Reactivity			0.90
None	25.4%	23.9%	
1 Pupil	8.5%	7.6%	
Both Pupils	66.2%	68.5%	
Hypotensive in Field/ED	12.7%	5.4%	0.021
Hypoxic in Field/ED	7.0%	4.9%	0.41

Table 2: Frequency of cardiac complications and measures of cardiac dysfunction.

Clinical Characteristic/Complication N	Value 326
New Arrhythmia During ICU Course	(48) 14.7%
AFib with RVR	11 (3.4%)
Atrial Flutter	7 (2.1%)
Sinus Tachycardia	14 (4.3%)
Symptomatic Bradycardia	11 (3.4%)
Ventricular Fibrillation	2 (0.6%)
Ventricular Tachycardia	8 (2.5%)
Prolonged PR Interval	5 (3.8%)
*Any EKG Abnormality	93 (62.8%)
Widened QRS	11 (7.7%)
Prolonged QTc Interval	63 (42.9%)
T Wave Inversion	49 (34.0%)
Hypotension (requiring pressors)	139 (42.6%)
Myocardial Infarction	4 (1.2%)
Pulmonary Embolism	2 (0.6%)
Deep Venous Thrombosis	8 (2.5%)
ICU Cardiac Arrest	25 (7.7%)
‡Any Echo Abnormality	23 (32%)
Troponin Elevation	60 (52.6%)
Cardio-Cerebral Score	
0	10 (15%)
1	16 (24%)
2	25 (37%)
3	17 (25%)

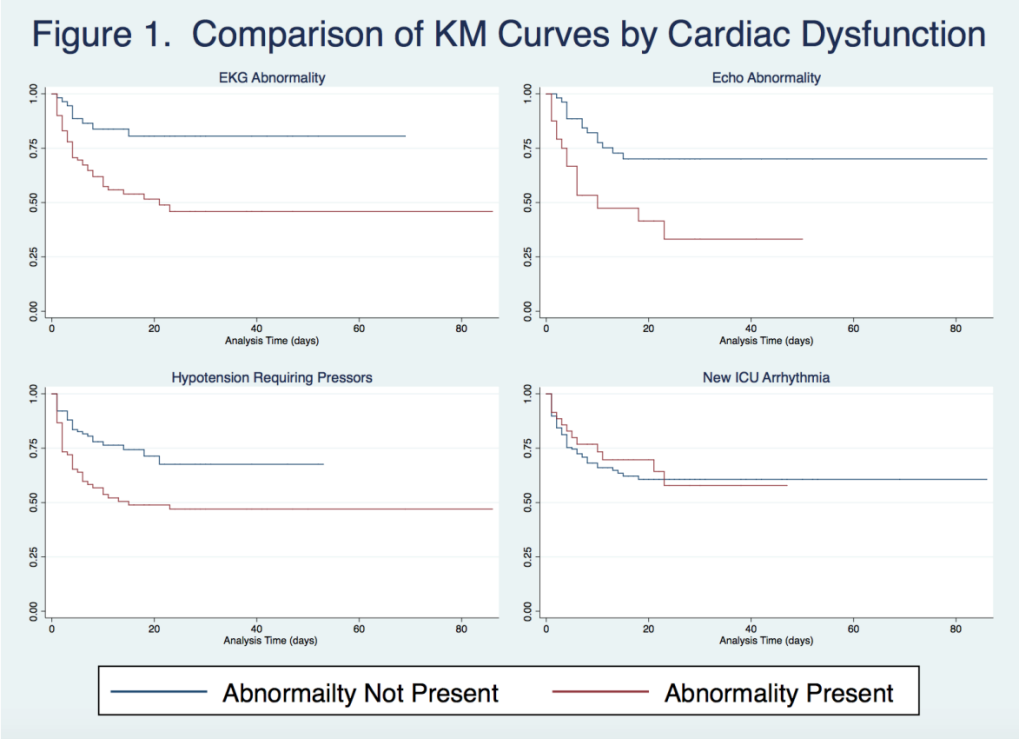

Figure 1: Kaplan-Meier survival curve analysis based on the occurrence of EKG abnormalities, Echocardiography abnormalities, hypotension requiring pharmacologic intervention, and new arrhythmias.

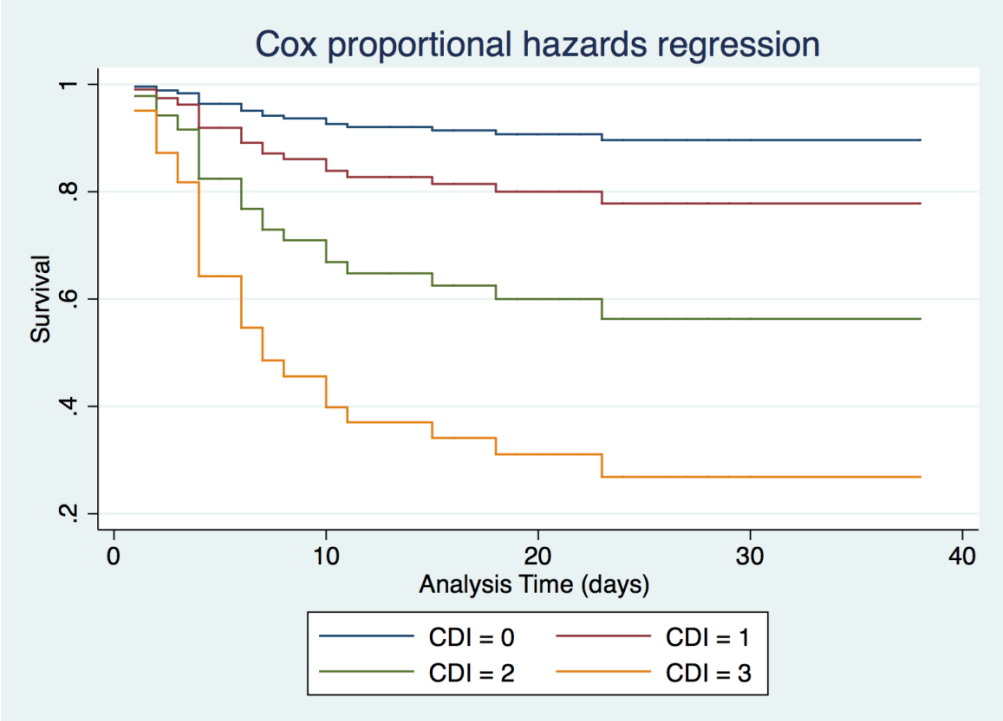

Figure 2: Survival function of Cox proportional hazards regression across 4 levels of cardiac injury. Cardiac dysfunction index = 0 indicates there were no EKG, Echocardiography, or Troponin abnormalities. Cardiac dysfunction index of 3 indicates all three abnormalities present.

References:

[1] Taylor, Christopher A. "Traumatic brain injury–related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013." *MMWR. Surveillance Summaries* 66 (2017).

[2] Gao, Lei, et al. "Early asymmetric cardio-cerebral causality and outcome after severe traumatic brain injury." *Journal of neurotrauma* 34. (2017): 2743-2752.

[3] Cheung, Raymond TF, and Vladimir Hachinski. "Cardiac effects of stroke." *Current treatment options in cardiovascular medicine* 6. (2004): 199-207.

[4] Bulsara, Ketan R., et al. "Use of the peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage." *Journal of neurosurgery* 98. (2003): 524-528.

[5] Krishnamoorthy, Vijay, et al. "Early systolic dysfunction following traumatic brain injury: A cohort study." *Critical care medicine* 45. (2017): 1028-1036.

[6] Muehlschlegel, Susanne, et al. "Frequency and impact of intensive care unit complications on moderate-severe traumatic brain injury: early results of the Outcome Prognostication in Traumatic Brain Injury (OPTIMISM) Study." *Neurocritical care* 18. (2013): 318-331.

[7] Antonucci, Elio, et al. "Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment." *Journal of critical care* 29.4 (2014): 500-511.

[8] Sato, Ryota, and Michitaka Nasu. "A review of sepsis-induced cardiomyopathy." *Journal of intensive care* 3.1 (2015): 48.

[9] Oras, J., et al. "Takotsubo syndrome in hemodynamically unstable patients admitted to the intensive care unit–a retrospective study." *Acta Anaesthesiologica Scandinavica*61.8 (2017): 914-924.

[10] Taniguchi, Kohei, et al. "Takotsubo cardiomyopathy caused by acute respiratory stress from extubation: A case report." *Medicine* 96.48 (2017).

[11] Hasanin, Ahmed, et al. "Incidence and outcome of cardiac injury in patients with severe head trauma." *Scandinavian journal of trauma, resuscitation and emergency medicine* 24. (2016): 58.

[12] Zangbar, Bardiya, et al. "Metoprolol improves survival in severe traumatic brain injury independent of heart rate control." *Journal of Surgical Research* 200. (2016): 586-592.

[13] Alali, Aziz S., et al. "Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and eastern association for the surgery of trauma guideline." *Annals of Surgery* 266.6. (2017): 952-961.