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Outcomes in patients with gunshot wounds to the brain

Leigh Anna Robinson,[1] Lauren M Turco ,[2] Bryce Robinson,[3] Joshua G Corsa,[3] Michael Mount,[4] Amy V Hamrick,[4] John Berne,[5] Dalier R Mederos,[5] Allison G McNickle ,[6] Paul J Chestovich,[6] Jason Weinberger,[7] Areg Grigorian ,[8] Jeffry Nahmias,[8] Jane K Lee,[9] Kevin L Chow,[9] Erik J Olson,[10] Jose L Pascual,[10] Rachele Solomon,[11] Danielle A Pigneri,[11] Husayn A Ladhani,[12] Joanne Fraifogl,[12] Jeffrey Claridge,[12] Terry Curry,[13] Todd W Costantini,[13] Manasnun Kongwibulwut,[14] Haytham Kaafarani,[14] Janika San Roman,[15] Craig Schreiber,[15] Anna Goldenberg-Sandau,[15] Parker Hu ,[16] Patrick Bosarge,[16] Rindi Uhlich,[16] Nicole Lunardi,[17] Farooq Usmani,[17] Joseph Victor Sakran,[17] Jessica M Babcock,[18] Juan Carlos Quispe,[18] Lawrence Lottenberg,[19] Donna Cabral,[19] Grace Chang,[20] Jhoanna Gulmatico,[20] Jonathan J Parks,[21] Rishi Rattan,[21] Jennifer Massetti,[22] Onaona Gurney,[22] Brandon Bruns,[22] Alison A Smith,[23] Chrissy Guidry,[23] Matthew E Kutcher,[24] Melissa S Logan,[24] Michelle Y Kincaid,[25] Chance Spalding,[25] Matthew Noorbaksh,[26] Frances H Philp ,[26] Benjamin Cragun,[26] Robert D Winfield[1]

For numbered affiliations see end of article.

Correspondence to
Dr Lauren M Turco, Emergency Medicine, Spectrum Health Butterworth Hospital, Grand Rapids, MI 49503, USA; turco.lauren@gmail.com

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ABSTRACT

Introduction Gunshot wounds to the brain (GSWB) confer high lethality and uncertain recovery. It is unclear which patients benefit from aggressive resuscitation, and furthermore whether patients with GSWB undergoing cardiopulmonary resuscitation (CPR) have potential for survival or organ donation. Therefore, we sought to determine the rates of survival and organ donation, as well as identify factors associated with both outcomes in patients with GSWB undergoing CPR.

Methods We performed a retrospective, multicenter study at 25 US trauma centers including dates between June 1, 2011 and December 31, 2017. Patients were included if they suffered isolated GSWB and required CPR at a referring hospital, in the field, or in the trauma resuscitation room. Patients were excluded for significant torso or extremity injuries, or if pregnant. Binomial regression models were used to determine predictors of survival/organ donation.

Results 825 patients met study criteria; the majority were male (87.6%) with a mean age of 36.5 years. Most (67%) underwent CPR in the field and 2.1% (n=17) survived to discharge. Of the non-survivors, 17.5% (n=141) were considered eligible donors, with a donation rate of 58.9% (n=83) in this group. Regression models found several predictors of survival. Hormone replacement was predictive of both survival and organ donation.

Conclusion We found that GSWB requiring CPR during trauma resuscitation was associated with a 2.1% survival rate and overall organ donation rate of 10.3%. Several factors appear to be favorably associated with survival, although predictions are uncertain due to the low number of survivors in this patient population. Hormone replacement was predictive of both survival and organ donation. These results are a starting point for determining appropriate treatment algorithms for this devastating clinical condition.

Level of evidence Level II.

BACKGROUND

In the USA, there are approximately 70 000 victims of gunshot wounds resulting in an estimated 30 000 deaths per year.[1] Gunshot wounds to the brain (GSWB) are a subset of these injuries that carry high lethality and uncertain recovery; however, aggressive resuscitation has been associated with increased survival and organ donation.[2] During the last several years, GSWB have gained national and international interest after US Congresswoman Gabrielle Gifford sustained a gunshot wound to her brain in an attempted assassination in 2011. She received aggressive management and ultimately recovered well. Cases such as hers reinforce the need for evidence-based algorithms for the management of these injuries.[3]

Multiple studies have analyzed different predictive factors for prognosis of patients with GSWB. Until recently, patients with a Glasgow Coma Scale (GCS) score of 3–5 or bihemispheric head injuries did not always receive aggressive resuscitation due to the high mortality rate of the injury.[4–6] More recently, though, Joseph and colleagues conducted a retrospective analysis which showed that aggressive resuscitation—specifically hemostatic resuscitation with blood components and hyperosmolar therapy—was associated with increased survival and organ donation regardless of GCS at presentation.[2]

Determining which patients would benefit from aggressive resuscitation is necessary to refine management and improve resource utilization. An immediate question is whether patients with GSWB undergoing cardiopulmonary resuscitation (CPR) during trauma resuscitation either recover or become donors, as this has not been specifically addressed in prior investigations on this topic. To inform future work in this area, we sought to determine the rates of survival and organ donation, as well as identify factors associated with both outcomes in patients with GSWB undergoing CPR.

METHODS

Study population

We identified patients through a retrospective, multicenter study at 25 US level I and level II trauma centers between June 1, 2011 and December 31, 2017. Patients who suffered GSWB and required CPR at the referring hospital, in the field, or at the trauma center were included. Exclusion criteria were significant torso or extremity injuries (Abbreviated Injury Scale (AIS) score greater than 2 for thorax, abdomen, spine, upper or lower extremities, or unspecified) or current pregnancy. Data were collected for a total of 825 patients meeting these criteria. All data were collected from the participating level I and level II trauma centers. Data from referring facilities and prehospital were not collected.

Outcomes

The primary outcome was survival rate, defined as the number of patients surviving hospitalization among the total number of patients meeting study criteria. Secondary outcomes included rate of successful donation of any organ, predictors of organ donation, predictors of survival, overall cost of treatment, cost of survival, and cost of organ donation.

Statistical analysis

Depending on distribution of the data, continuous variables are presented as mean±SD or median with IQR. Categorical variables are presented as frequencies and percent. A binomial logistic regression was considered to determine predictors of survival. Due to the very low frequency of survival (17 survivors vs. 808 non-survivors), a multiple logistic regression model was not possible. Thus, an exploratory complete case analysis was undertaken to examine bivariate relationships between survival and several predictors. Predictors were selected on the basis of significant correlation with survival using χ^2 contingency tables (for categorical predictors) or Kruskal-Wallis one-way analysis of variance test (for continuous predictors). Each predictor was individually fitted to a binomial regression model using maximum likelihood estimators.

For the subset of 808 non-survivors, binomial logistic regression was again considered to determine predictors of organ donation. Model selection was performed with the 'regsubset' function in R using an exhaustive search approach. Using selection criteria (adjusted R^2, Mallow's C_p, and Bayesian information criterion), a three-predictor model was fitted for 627 subjects with complete data. Results are reported in terms of ORs. Statistical significance for all analyses was predetermined at $p \leq 0.05$, which is reported alongside 95% CIs. All analyses were conducted with R V.3.5.1 (2018-07-02).

RESULTS

A total of 825 patients from 25 trauma centers with isolated GSWB met study criteria (table 1). The majority were male (87.6%) with a mean age of 36.5 years. Most (67%) underwent CPR in the field. There was no significant difference in mortality by location of CPR (98.7% in the field vs. 98.2% in-hospital).

Table 1 Patients contributed by participating institutions

Trauma center	Eligible patients
University of Maryland	100
University Medical Center Las Vegas	76
University of Alabama	72
Johns Hopkins University	60
Tulane Medical Center	60
Harborview Medical Center	52
University of California-Irvine	50
St Mary's Medical Center	35
MetroHealth	35
Cooper Health	32
University of Illinois-Chicago	32
Allegheny Health	26
Mount Sinai Hospital-Chicago	24
Jackson Memorial Hospital-Miami	22
University of Mississippi	19
Grant Medical Center	18
Christiana Healthcare System	17
Memorial Regional Hospital	16
Broward Health	14
University of Kansas	14
University of Pennsylvania	13
Loma Linda University	11
Mass General Hospital	10
University of California-San Diego	10
Spartanburg Medical Center	7

Only 2.1% (n=17) survived to discharge; 47% went to rehabilitation, 27% home, 20% skilled nursing facilities, and 13% long-term acute care. Of the patients who did not survive, 17.5% (n=141) were considered eligible donors by the local organ procurement organization, with a donation rate of 58.9% (n=83) in this group and an overall donation rate of 10.3% among non-survivors. Survivors had lower Injury Severity Score (ISS) (international normalized ratio (INR) 22.2 vs. 37.4, p=0.003) (table 2). Data on resuscitative interventions, neurosurgical interventions, and base deficit were collected; however, due to a large amount of missing data, these measures were not found to significantly impact results.

Several individual binomial regression models identified factors associated with survival (table 3). Fifty-five patients required transfer to a level I or level II trauma center but did not have significantly different characteristics in terms of age, ISS, and AIS head. However, transfer patients were more likely to survive (p=0.0001). Non-surviving transfer patients were more likely to become organ donors than those who were not transferred (25% vs. 9.8%). Survivors also received more units of packed red blood cells (RBC; mean 4.8 units vs. 1.6 units, p=0.0007), plasma (2.3 units vs. 0.8 units, p=0.009), platelets (0.87 units vs. 0.16 units, p=0.01), and larger volumes of crystalloid (6.7 L vs. 2.4 L, p=0.002).

Overall, the frequency of organ donation was low (83 donors vs. 693 non-donors). The mean age for donors was significantly less than non-donors (32.5 years vs. 37.1 years, p=0.007). As expected, donors presented with higher systolic blood pressure (86.7 mm Hg vs. 41.8 mm Hg, p<0.001) and heart rate (85.7 bpm vs. 42.9 bpm, p<0.001). Donors also received

Table 2 Patient demographics

	Total	Survivors	Non-survivors
Age	31 (23–46)	32 (23–44)	31 (23–46)
Male gender	723 (88)	14/17 (82)	709/808 (88)
Race			
Black	362 (44)	9 (56)	353 (47)
White	340 (41)	5 (31)	335 (45)
Other	123 (15)	2 (13)	57 (8)
Injury Severity Score	26 (25–41)	25 (17–26)	26 (25–75)
Abbreviated Injury Scale-Head	5 (5–6)	5 (4–5)	5 (5–6)
Injury intent			
Assault	355 (50)	11 (65)	344 (50)
Suicide	294 (41)	6 (35)	288 (42)
Accident	54 (8)	0	54 (8)
Legal intervention	6 (1)	0	6 (1)

significantly more units of packed RBCs (4.2 units vs. 1.3 units, p<0.0001), platelets (0.63 units vs. 0.11 units, p<0.0001), and larger volumes of crystalloid (4.9 L vs. 2.2 L, p<0.0001). ISS and AIS head were not statistically different between donors and non-donors. Independent predictors of organ donation were crystalloid volume and replacement of one or more hormones (methylprednisolone, vasopressin, insulin, or levothyroxine/triiodothyronine) (table 4).

Specifically, each additional 1 L of crystalloid resulted in 15.4% increased odds of organ donation (95% CI 5.98 to 26.5, p=0). However, it is important to note that this association is likely, in part, due to fluid imbalance secondary to brain death and subsequent homeostatic derangements. Replacement of at least one hormone was associated with over 10-fold increased odds of organ donation (OR 10.03, 95% CI 5.19 to 20.13, p=0).

Due to positively skewed data, costs (in US$) are reported in geometric averages to mitigate the effect of exceptionally large values.[7] The total cost for all patients with reported data (n=488) was $22.7 million dollars. The geometric average cost of treatment per patient was $24 176. Cost of survival was reported for 8 of the 17 survivors and totaled $1.7 million. The geometric average cost of treatment per survivor was $188 480. In contrast, treatment of non-survivors totaled $21 million with a geometric average of $23 363 per non-survivor (for n=480 non-survivors). Cost of organ donation was $5.6 million overall with a geometric average of $56 870 per organ donor (for n=56 donors). The organ procurement organization—not the trauma center—assumes all costs related to donation.

Table 3 Predictors of survival to hospital discharge

Predictor	Sample size	OR	95% CI	P value
Signs of life at trauma center	824	8.30	2.32 to 52.91	0.001
Receipt of tranexamic acid (TXA)	793	7.90	1.71 to 27.15	0.0001
Transfer to level I/II trauma center	793	6.61	2.02 to 18.94	0.000
Replacement of ≥1 hormone(s)	819	3.82	1.32 to 10.79	0.01
Units of platelets	801	1.66	1.16 to 2.21	0.001
Units of packed red blood cells	803	1.14	1.05 to 1.22	0.000
Systolic blood pressure	745	1.02	1.01 to 1.03	0.000
Injury Severity Score	769	0.55	0.23 to 0.76	0.01
Abbreviated Injury Scale	609	0.48	0.28 to 0.87	0.01

Table 4 Predictors of successful organ donation

Predictor	Sample size	OR	95% CI	P value
Volume (L) of crystalloid	453	1.15	1.06 to 1.26	0.001
Replacement of ≥1 hormone(s)	453	10.03	5.19 to 20.13	0.000

DISCUSSION

GSWB have high rates of mortality and morbidity. Our current understanding of these lethal injuries is primarily extrapolated from lessons learnt through military experiences, which tend to report improved outcomes with more aggressive management.[8] Prospective civilian studies are sparse and often contain lower levels of evidence. Thus, there is no standard approach to treating these injuries in the published literature. In effort to address this deficit, our current effort was to identify specific factors associated with patient outcome—namely survival or organ donation. In this study, we report several resuscitative practices that are associated with survival to hospital discharge or organ donation in patients with GSWB who subsequently underwent CPR (tables 3 and 4).

An interesting parallel between our study and others with similar patient populations is the effect—or lack thereof—of age, race, and intent on outcome. Our study population had large disparities between these groups; assault was more common among black patients (235 black vs. 64 white) whereas suicides were more frequent in white patients (212 white vs. 42 black). Additionally, black patients in our study were significantly younger (mean 29.8 years vs. 45.0 years in white patients). Despite these differences, neither age, race, nor intent was predictive of survival. Similarly, Crutcher *et al*[9] reported disparities in injury intent between races, but intent and race were not predictive of survival in this study either.

With regard to specific factors associated with survival, various items have been previously identified. In a 2016 study, Jesin *et al*[10] concluded that mortality was related to increasing ISS and age. Lee *et al*[11] found GCS, AIS head, and age to be associated with survival in isolated head trauma but did not focus on penetrating injuries. In contrast, the strongest factors associated with outcome in our study were signs of life (SOL) on arrival, receipt of tranexamic acid (TXA), and transfer to a higher level trauma center. Patients who arrived at a trauma center with SOL were 8.3 times more likely to survive. We could not find any other published literature that documented SOL as a statistically significant predictor of outcome for this specific injury.

We found that receipt of TXA had a significant effect on survival (OR 7.90, p=0.0001). A meta-analysis[12] of the two largest randomized controlled trials[13,14] on TXA in traumatic brain injury (TBI) found a significant reduction in intracranial hemorrhage expansion (relative risk (RR)=0.72) and mortality (RR=0.63) when TXA had been given. Yet unpublished, the results of the Clinical Randomization of an Antifibrinolytic in Significant Head Injury-3 trial, an international multicenter randomized trial studying the effects of TXA in TBI, are expected to provide novel and clinically significant information. Our third strongest predictor of survival, transfer to a trauma center, has been associated with lower risk of death in prior studies.[15,16] In this study, patients transferred to trauma centers were 6.6 times more likely to survive. Similarly, Sugerman *et al*[17] reported an improved survival rate when patients with severe TBI were transferred to a trauma center.

As discussed above, a wide range of survival-associated factors have been identified—both in our study and previous reports. Without significant overlap of results, the interpretation of data and application of specific management is challenging. Muehlschlegel *et al*[18] have attempted to combine several predictors into the Surviving Penetrating Injury to the Brain (SPIN) score, a logistic regression-based clinical risk stratification scale estimating survival after penetrating TBI. Components of the SPIN score include motor GCS, pupillary examination, whether the injury was self-inflicted, transfer status, gender, ISS, and INR. Although the SPIN score does not address CPR, it does include transfer and ISS, which were both significant predictors in our study. Further identification of similar threads across studies may reveal that certain predictors are more consistent and significant than others.

A particularly noteworthy area is hormone replacement therapy. In our study, patients who received at least one hormone (methylprednisolone, insulin, vasopressin, and/or thyroid hormone) during the initial resuscitation had significantly improved survival or greater rates of successful organ donation. However, the overall donation rate was very low at 10.3% of non-survivors. This is lower than other reported rates in the literature, which range from 26.1% to 34.7% in patients with GSWB.[19 20] This is likely because our study focused on patients in extremis at the time of presentation, and thus, the least likely to be salvageable. The findings of this study and numerous other retrospective reports[2 21–24] on the benefits of hormone replacement therapy have provided the basis for a future prospective, randomized trial.

LIMITATIONS

The primary limitation of our study is its retrospective design and reliance on a registry for data collection. This registry is subject to errors, incompleteness, and interhospital differences in reporting practices. This multi-institutional study included several level 1 trauma centers that tend to see a disproportionate number of high-acuity injuries. As such, the patient sample is not necessarily representative of all US trauma centers.

Additionally, institutional differences and physician-specific biases may have contributed to different approaches to resuscitation. A particularly important example is the differences in hormone replacement usage. Although we did not specify the timing of administration, some institutions/physicians have begun using hormones as part of the initial resuscitation in the trauma bay whereas others use these therapies only in patients who have either impending or declared brain death. Thus, the use and timing of hormone replacement is a critical area for future study in these patients.

Another limitation of this study—and others like it—is the uncertainty in making statistically significant associations. As evidenced above, there is a wide range of reported factors associated with outcome that differs between studies. One reason for this observation is the low frequency of survival in GSWB, which renders the inferences drawn from these populations extremely uncertain. With mortality of GSWB approaching 98.0%, survival is considered a 'rare event'. Statistically speaking, '[t]he cost of numerically calculating probabilities of rare events rapidly becomes prohibitive as the event of interest becomes rare.'[25] In this study, the low survival rate precluded us from controlling for covariates when identifying factors associated with survival. Additionally, it is also important to note that these factors are subject to survival bias (eg, survivors may have received more fluid and blood product resuscitation because they lived (longer)).

CONCLUSION

Survival after GSWB involving cardiopulmonary arrest is rare; however, this multi-institutional study of patients with GSWB who received CPR identified several factors associated with outcome. These data represent a starting point to determine appropriate treatment algorithms that maximize survival and organ donation and minimize wastage of scarce and expensive resources. Our findings suggest that patients with GSWB and subsequent CPR should be transferred to a trauma center when clinically feasible. Outcomes (both survival and organ donation) may be favorably impacted when trauma resuscitation includes hormone replacement, TXA, and blood transfusions. Although the survival rate for this injury is dismal, 10% of patients became organ donors with the potential of saving numerous lives. Many gaps in our understanding of this complex clinical problem remain and further prospective studies are necessary to develop standard practice for the management of patients with GSWB.

Author affiliations
[1]Department of Surgery, University of Kansas Medical Center, Kansas City, Kansas, USA
[2]Emergency Medicine, Spectrum Health Butterworth Hospital, Grand Rapids, Michigan, USA
[3]Department of Surgery, Harborview Medical Center, Seattle, Washington, USA
[4]Division of Surgery, Spartanburg Regional Healthcare System, Spartanburg, South Carolina, USA
[5]Division of Trauma and Critical Care, Broward Health, Fort Lauderdale, Florida, USA
[6]Department of Surgery, UNLV School of Medicine, Las Vegas, Nevada, USA
[7]Christiana Care Health System, Wilmington, Delaware, USA
[8]Department of Surgery, University of California Irvine School of Medicine, Irvine, California, USA
[9]Department of Surgery, University of Illinois at Chicago, Chicago, Illinois, USA
[10]Department of Surgery, University of Pennsylvania Health System, Philadelphia, Pennsylvania, USA
[11]Memorial Regional Hospital, Hollywood, Florida, USA
[12]Department of Surgery, Case Western Reserve University Hospital, Cleveland, Ohio, USA
[13]Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery, UC San Diego Health, San Diego, California, USA
[14]Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA
[15]Division of Trauma, Surgical Critical Care & Acute Care Surgery, Cooper University Hospital, Camden, New Jersey, USA
[16]Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA
[17]Department of Surgery, The Johns Hopkins University, Baltimore, Maryland, USA
[18]Department of Surgery, Loma Linda University, Loma Linda, California, USA
[19]St. Mary's Medical Center, Boca Raton, Florida, USA
[20]Department of Surgery, Mount Sinai Hospital, Chicago, Illinois, USA
[21]Department of Surgery, University of Miami School of Medicine, Miami, Florida, USA
[22]Department of Surgery, University of Maryland Medical System, Baltimore, Maryland, USA
[23]Department of Surgery, Tulane Medical Center, New Orleans, Louisiana, USA
[24]Department of Surgery, University of Mississippi, University Park, Mississippi, USA
[25]Trauma and Acute Care Surgery, Grant Medical Center, Columbus, Ohio, USA
[26]Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

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ORCID iDs
Lauren M Turco http://orcid.org/0000-0002-8897-8630
Allison G McNickle http://orcid.org/0000-0002-2400-8440
Areg Grigorian http://orcid.org/0000-0002-0998-796X
Parker Hu http://orcid.org/0000-0002-2491-6107
Frances H Philp http://orcid.org/0000-0002-2511-4667

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