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ORIGINAL SCIENTIFIC REPORT

Mild and Moderate Traumatic Brain Injury and Gender-Based Critical Care Outcomes

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Abstract

Background Traumatic brain injury (TBI) is a major contributor to death and complications. Previous studies have identified gender disparities among trauma patients. This study aims to examine the association between gender and outcomes in TBI patients.

Study design and methods Review of our trauma registry: Patients were classified into groups according to their gender. Demographics extracted from the registry included age, injury severity score (ISS), Glasgow Coma Score (GCS), head abbreviated injury score (AIS), and the presence of an epidural hematoma (EDH). The primary outcome was mortality; secondary outcomes included ICU length of stay (ICU-LOS), craniotomy rate, ventilator-associated pneumonia (VAP), and readmission rates. Significance was defined as $p < 0.05$.

Results Nine hundred and thirty-five patients with TBI were studied: 62.1% ($n = 581$) were male and 37.9% ($n = 354$) were female. There were no differences in GCS, ISS, and head AIS. Males were younger [53 (IQR 30–77) vs. 76 (IQR 49.25–84), $p < 0.05$] and were more likely to have an EDH (9.6% vs. 4.8%, $p = 0.007$). Males also had a longer median ICU-LOS [4 days (IQR 2–8) vs. 3 days (IQR 0–5), $p < 0.05$] and were significantly more likely to require a craniotomy (44.6% vs. 19.2%, $p < 0.001$). In addition, males were more likely to develop VAP (4.1% vs. 0.8%, $p = 0.004$). Predicted survival (79.2% vs. 72.9%) and actual mortality rates (4.5% vs. 4.5%) were similar in both genders ($p > 0.05$).

Conclusion In the context of our study, male patients with TBI were significantly younger, were more likely to sustain an EDH, and were also more likely to require a craniotomy, but mortality rates between both genders were similar. The male gender was also associated with a significantly increased ICU-LOS and VAP.

Background

Traumatic brain injury (TBI) is a significant cause of disability and death. The Centers for Disease Control and Prevention (CDC) analysis of the Healthcare Cost and Utilization Project (HCUP) and National Vital Statistics System (NVSS) databases revealed that TBI led to 2.5 million emergency department visits in the USA for 2013 with roughly 56,000 resulting in death. TBI contributed to approximately 30% of all injury-related deaths [1]. Additionally, mild TBI (GCS 13–15) is the most common form of TBI [2, 3] and the highest incidence of TBI occurs in elderly adults, particularly those 75 years of age or older [4].

Variables that influence trauma outcomes are of great interest in the literature. One demographic characteristic known to affect trauma care is patient gender. George et al. examined gender-based outcome differences as a result of

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blunt and penetrating trauma for all injury types, not only TBI, and determined that men less than the age of 50 who experienced blunt trauma were at a significantly higher risk of fatality than matched female counterparts. Interestingly, for patients over 50 years of age, the mortality difference between men and women was not statistically significant. With respect to penetrating trauma, they observed that men over the age of 50 actually had a survival advantage compared to women and also that no significant gender difference was observed in terms of mortality when compared to that of their younger penetrating cohort [5].

Focusing on gender-dependent outcomes for neurologic trauma, Berry et al. [6] examined the morbidity and mortality of patients with moderate to severe TBI. Their assessment of the National Trauma Data Bank version 6.2 covering the years 2000–2005 determined that overall women had lower mortality rates and fewer complications than men following TBI. In a subset analysis, younger women (age 14–45) did not have a survival advantage compared to similar age men, while perimenopausal women (age 46–55) and postmenopausal women (age > 55) had significantly lower mortality than their male counterparts. The study's findings suggest the female gender to be a protective variable for TBI patients, while these differences among age within the female gender indicate that neuroprotection in females is independent of estrogen, since the advantage occurs in perimenopausal and postmenopausal women [6].

Further, there is much debate regarding the severity and classification of TBI. For the purposes of our study, we used the GCS classification as outlined in the advanced trauma life support manual, tenth edition [2]. Additionally, although there are no agreed upon ranges for head AIS score and severity of TBI, consistent with values reported in the literature, we interpreted a head AIS score of 1–2 as mild TBI, 3–4 as moderate TBI, and ≥ 5 as severe TBI [7].

The purpose of this epidemiologic study was to examine the association between gender and TBI, with mortality rate as the primary outcome measure. Secondary outcomes were ICU length of stay (ICU-LOS), craniotomy rate, ventilator-associated pneumonia (VAP), and readmission. Significance was defined as $p < 0.05$.

Study design and methods

Our institutional review board granted exempt approval to conduct this study in compliance with ethical standards. We performed a retrospective review using the trauma registry at our American College of Surgeons Level 1 institution. All patients of any age who experienced a TBI from the years 2014–2017 were included in the study. Patients were not excluded on the basis of their age, ethnicity, or socioeconomic status. The study population was first divided into two groups—male and female—based on their documented gender. Demographic characteristics such as age, injury severity score (ISS), Glasgow Coma Scale (GCS), body mass index (BMI), mechanism of injury (MOI), abbreviated injury score (AIS) for the head based on the non-contrast CT brain, and probability of survival with trauma-related injury severity score (TRISS) were collected and compared between groups. The presence of an epidural hematoma (EDH) was also collected. Additional outcome measures including ICU length of stay (ICU-LOS), ventilator-associated pneumonia (VAP), deep venous thrombosis (DVT), surgical site infection (SSI), craniotomy rate, readmission rate, and mortality rate were collected and analyzed between groups. Our institution follows the Trauma Brian Foundation guidelines to determine the need for surgical intervention [8]. Hypothesis testing with Chi-squared and t tests was used with significance defined as $p < 0.05$.

Results

Our trauma registry review identified 935 patients who sustained a TBI from 2014–2017. Our study population included patients up to 100 years of age with a median of 61.5 years (IQR 34–81); 581 (62.1%) were male and 354 (37.9%) were female. The median age in the male group was younger than that of the female group [53 (IQR 30–77) vs. 76 (IQR 49.25–84), $p = 0.002$]. Other measures of baseline characteristics between males and females, respectively, included median ISS [17 (IQR 10–25) vs. 16 (IQR 10–22), $p > 0.05$], median GCS [15 (IQR 12–15) vs. 15 (IQR 14–15), $p > 0.05$], mean BMI (27.9 vs. 26.4, $p > 0.05$), percentage of blunt mechanism of injury (95.2% vs. 98.3%, $p > 0.05$), median head AIS [4 (IQR 3–4) vs. 3 (IQR 3–4), $p > 0.05$], and mean predicted probability of survival based on TRISS (79.2% vs. 72.8%, $p > 0.05$) (Table 1).

Looking at the primary outcome variables, there were no significant differences in the predicted survival based on TRISS methodology. Males had a mean predicted probability of survival of 79.2% versus 72.8% for females ($p > 0.05$). The actual mortality rates were also similar with 4.5% (26/555) of males and 4.5% (16/354) of females. Furthermore, the male cohort in our study had significantly higher rates of EDHs compared to females. The males had an EDH 9.6% (56/581) of the time, while females had an EDH 4.8% (17/354) of the time ($p = 0.007$). Concordant with EDH rates, males were significantly more likely to require craniotomy than females. Males required craniotomy 44.6% (259/581), while 19.2% (68/354) of females underwent craniotomy ($p < 0.001$). Among other

Table 1 Demographic characteristics and outcome measures comparing male to female patients with TBI from 2014 to 2017

	Male (n = 581)	Female (n = 354)	p-value
Age in years, median (IQR)	53 (30–77)	76 (49.25–84)	0.002
ISS, median (IQR)	17 (10–25)	16 (10–22)	> 0.05
GCS, median (IQR)	15 (12–15)	15 (14–15)	> 0.05
BMI, mean	27.9	26.4	> 0.05
Blunt mechanism of injury (MOI)	95.2% (553/581)	98.3% (348/354)	> 0.05
Head AIS, median (IQR)	4 (3–4)	3 (3–4)	> 0.05
% Predicted probability of survival (TRISS)	79.2%	72.8%	> 0.05
ICU-LOS (days), median (IQR)	4 (2–8)	3 (0–5)	< 0.05
VAP	4.1% (24/581)	0.8% (3/354)	0.004
DVT	2.6% (15/581)	2.3% (8/354)	> 0.05
SSI	0.5% (3/581)	0% (0/354)	> 0.05
Readmission rate %	4.3% (25/581)	2.5% (9/354)	> 0.05
Craniotomy	44.6% (259/581)	19.2% (68/354)	< 0.001
EDH	9.6% (56/581)	4.8% (17/354)	0.007
Mortality rate %	4.5% (26/555)	4.5% (16/354)	> 0.05

IQR interquartile range, *VAP* ventilator-associated pneumonia, *DVT* deep vein thrombosis, *SSI* surgical site infection, *EDH* epidural hematoma

secondary outcome measures, males in our study experienced a longer median ICU-LOS than females [4 days (IQR 2–8) vs. 3 days (IQR 0–5), $p < 0.05$]. Additionally, males were more likely to develop VAP than females (4.1% vs. 0.8%, $p = 0.004$). There were no significant differences between genders in their risk of developing DVT, SSI, or readmission at 30 days ($p > 0.05$).

According to GCS, the majority of our sample population fell into the mild TBI category (78%; 729/935), while only 5% of the patients had moderate TBI (50/935) and 17% of our study population could be classified as having severe TBI (156/935). According to head AIS, however, 6.6% of our population was comprised of mild TBI patients (i.e., head AIS 1–2) and the majority or 72% of our population consisted of moderate TBI patients (i.e., head AIS 3–4). Approximately 20% of the patients in our study were classified as severe TBI using head AIS scores to classify the degree of TBI. Lastly, the predicted mortality was over 20% in both genders [probability of survival (Ps) was 73–79%] which is another indicator of the severity of TBI.

We stratified our results based on ISS, displaying the range of injured patients included in our study (Tables 2, 3). Our results showed that patients with an ISS $\geq$ 25 were more likely to have EDHs, craniotomies, VAP, as well as longer hospital and ICU stays—regardless of gender. Congruent with our overall results, more males in our study cohort sustained EDHs and required craniotomies. Additionally, a higher ISS was correlated with a lower GCS. For example, males and females with ISS 1–14 had an average GCS of 13.7 and 14.2, while males and females with ISS $\geq$ 25 had GCS's of 10.3 and 10.7, respectively.

Discussion

When comparing baseline characteristics between our male and female groups, only age demonstrated a significant difference between genders, where males had a median age of 53 years and females had a median age of 76 years ($p = 0.002$). While we did include pediatric patients in our study, the overall age of our study population consisted of older adults, as evidenced by the demographic data provided. Our younger male group is consistent with widespread findings that young men are disproportionately affected by physical trauma [9] in association with risk-taking behavior that some studies have correlated with testosterone and cortisol [10, 11]. The remaining baseline characteristics for the median ISS, arrival GCS, BMI, percentage of blunt injury, head AIS, and MOI were similar between the two groups, making it more likely that the outcome differences observed were influenced by gender.

A number of studies on gender disparities in trauma were incorporated into a 2015 meta-analysis of all injuries by Liu et al., showing that women have improved outcomes with respect to mortality and length of hospitalization, albeit a higher incidence of complications [12, 13]. High-level-of-evidence literature specific to neurotrauma is still being accumulated, and the existing studies have yielded mixed results in some areas. Oppelt et al. evaluated

Table 2 Outcome measures for ICU length of stay, ventilator days, and total hospital days stratified by injury severity score (ISS)

	ICU length of stay (d)			Ventilator days (d)			Total hospital days (d)		
	Male	Female	*p*	Male	Female	*p*	Male	Female	*p*
ISS < 15	2.5	2.8	0.11	1.3	0.5	0.03	4.3	4.6	0.076
ISS 15–24	6.5	3.3	0.00009	3.0	0.8	0.001	15.7	7.1	0.19
ISS ≥ 25	12.8	9.97	0.06	8.3	6.1	0.11	20.3	12.4	0.014
All[a]	7.34	4.58	< 0.001	4	1.83	< 0.001	13.32	7.15	< 0.001

[a]Reported as mean values

Table 3 Outcome measures for epidural hematomas, craniotomy, and ventilator-associated pneumonia stratified by injury severity score (ISS)

	Epidural hematoma			Craniotomy			Ventilator pneumonia		
	Male	Female	*p*	Male	Female	*p*	Male	Female	*p*
ISS < 15	13/223	5/160	0.22	0/223	0/160	–	6/223	0/160	–
ISS 15–24	20/179	4/117	0.02	5/179	0/117	–	6/179	0/117	–
ISS ≥ 25	23/179	8/77	0.58	9/179	6/77	0.39	12/179	3/77	0.38
All	56/581	17/354	0.01	14/581	6/354	0.46	24/581	3/354	0.004

the psychological, neurologic, and vegetative outcomes and health status of 43 patients who survived a TBI. They used Glasgow Outcome Scale (GOS) and Disability Rating Scale (DRS) to assess recovery outcomes and did not identify a significant correlation between GOS or DRS and gender [14]. This differs from the findings of Berry et al. who examined patients with moderate to severe TBI and found that perimenopausal and postmenopausal females have lower mortality rates than when compared to males, but this did not hold for premenopausal women. Davis et al. [15] conducted a similar study and also found that postmenopausal females had improved outcomes compared to men of the same age and no differences in mortality rates for premenopausal women. From these results, it can be inferred that mortality rates in TBI might not be related to estrogen, but possibly age-related factors with females having more favorable mortality rates at higher ages. Mortality rates between males and females in our study were identical at 4.5% for each group. Our finding does not match with the mortality rate findings of Berry et al. and Davis et al., and we observed no difference much like the recent study by Oppelt et al. in 2018.

Differences in trauma outcomes between post-menopausal women compared to premenopausal women led some to believe there may be a relationship between estrogen and the body's ability to withstand injury. Estrogens and estrogen receptor agonists have been studied for their known protective effects following trauma and potential utility in augmenting multiorgan function [16]. Neurobiologists also empirically understand estrogens as neuroprotective against brain injury during experiments, but observing these effects in clinical trials is far more nuanced [17]. Estrogen's effect on coagulation following trauma has been studied with marked outcome differences between genders. Women exhibit an exaggerated hypercoagulable state post-trauma that protects from hemorrhage when compared to physiologic responses exhibited by men. Coleman et al. [18] examined coagulation parameters by gender in trauma activations seen at two level 1 trauma centers. They used thromboelastography (TEG) and found that females have a higher angle of clot propagation and maximum amplitude of clot strength. This suggests that severely injured females have a higher level of inherent protection from coagulopathy and hemorrhage than men. They also observed that men had higher rates of abnormal thrombolysis and hyperfibrinolysis. The authors clinically correlated this with the fatality of 20 men in their study with hyperfibrinolysis compared to only one female who died with hyperfibrinolysis. Despite this hypercoagulable post-trauma state in females, Berndston et al. [19] found there to be no significant difference between genders in regard to developing venous thromboembolism following trauma. Their findings were in accordance with our study where 2.6% of males and 2.3% of females experienced a deep vein thrombosis ($p > 0.05$). Men in our study also had higher rates of intracranial hemorrhage requiring craniotomy than women, which could be related to previously

studied coagulation differences between men and women following trauma.

Our observation that men were at increased risk of developing VAP compared to women is consistent with the existing literature. Studies by Sharpe et al. and Napolitano et al. evaluated gender disparities in VAP and ultimately found that while men develop VAP more often than women, mortality rates with VAP are actually higher among women [20, 21]. Croce et al. [22] had similar findings in which they determined that females had a higher mortality from post-trauma pneumonias despite having no significant difference in overall mortality compared to male trauma patients. The VAP trends among TBI patients in our study (4.1% vs. 0.8%, $p = 0.004$) are consistent with previous studies on other trauma patients. Nonetheless, the small volume of VAP cases we observed did not yield data on gender differences in mortality from this outcome measure.

To assess the prognosis of individuals with a moderate TBI, Einarsen et al. assessed the 12-month outcome for patients in Europe using the Glasgow Outcome Scale Extended (GOSE). At 12 months, they determined that 56% of patients had a successful recovery (GOSE of 7 or 8), while 31% were left moderately disabled (GOSE of 5 or 6), 8% were severely disabled (GOSE of 2, 3, or 4), and 6% were deceased (GOSE of 1) before the 12-month evaluation period. The study identified older age ($p < 0.001$), lower GCS ($p = 0.001$), presence of a subdural hematoma ($p = 0.004$), no preinjury alcohol intoxication ($p = 0.001$), the occurrence of a secondary event, such as hypoxia or hypotension ($p = 0.037$), and preinjury disability ($p = 0.043$) to be significant predictors of having a GOSE of 6 or less [23]. While long-term effects were not examined in our study, these long-term sequelae examined by Einarsen et al. are factors that can be examined in appropriate follow-up studies.

Limitations of this study include: a single-institution study, retrospective design, and relatively small sample size. Additionally, the older female population implies marked differences that make gender discrimination difficult. The older female population can also be an indication that underlying health status and other age-based changes potentially played a confounder role. Moreover, the TRISS methodology has been validated, but its limitations are well known and have been well documented in the literature. Also, preexisting co-morbidities were not assessed between groups. Further, information on size of bleed, midline shift, and prognostic scoring systems such as the Marshall score or Rotterdam score are not captured in our database.

At this time, we recommend future studies be performed and implement regression analysis to determine potential multivariate influences on TBI outcomes, including injury severity, injury type, ethnicity, insurance status, specific preexisting co-morbidities, and long-term functional outcomes of TBI. Similar studies should be performed that stratify gender cohorts by age to account for age-related morbidities. Additional studies can be performed across multiple trauma institutions, including the effect an institution's trauma-level setting has on patient morbidity and mortality. In consideration of the hypercoagulable state in women and their improved outcomes in the setting of TBI, further studies regarding the hematologic makeup of gender in trauma patients should be considered for the most efficacious treatment option for each gender. A large portion of our study population was comprised of elderly patients. Future research should further investigate the impact of certain prognostic factors such as the Marshall score or Rotterdam score, size of bleed, and the presence/absence of midline shift on outcomes. Future studies should also stratify results based on age as well paying special attention to patients' age 50 or higher.

Conclusion

In the context of our study, male patients with TBI were more likely to be younger, have an epidural hematoma, and required a craniotomy. Predicted and actual mortality rates between males and females were similar. Male gender was associated with a significantly increased ICU length of stay and incidence of ventilator-associated pneumonia. Other outcome variables including DVT and surgical site infections were similar between genders.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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