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Association between alcohol intoxication and mortality in severe traumatic brain injury in the emergency department: a retrospective cohort

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Background Acute alcohol intoxication is very common in patients with severe traumatic brain injury (TBI). Whether there is an independent association between alcohol intoxication and mortality is debated. This study hypothesized that alcohol intoxication is independently associated with less mortality after severe TBI (sTBI).

Methods This retrospective observational cohort study included all patients with sTBI [head-Abbreviated Injury Score (AIS) ≥ 3 , corresponding to serious head injury or worse] admitted from 1 January 2011 to 31 December 2016 in an academic level I trauma center. Patients were classified as with alcohol intoxication or without intoxication based on blood alcohol concentration or description of alcohol intoxication on admission. The primary endpoint was in-hospital mortality. Multivariable logistic regression analysis, including patient and injury characteristics, was used to assess independent association with alcohol intoxication.

Results Of the 2865 TBI patients, 715 (25%) suffered from alcohol intoxication. They were younger (mean age 46 vs. 68 years), more often male (80 vs. 57%) and had a lower median Glasgow Coma Scale upon arrival (14 vs. 15) compared to the no-intoxication group. There was no difference in injury severity by head AIS or Rotterdam

CT. Alcohol intoxication had an unadjusted association with in-hospital mortality [unadjusted odds ratio (OR) 0.51; 95% confidence interval (CI), 0.38–0.68]; however, there was no independent association after adjusting for potentially confounding patient and injury characteristics (adjusted OR 0.72; 95% CI, 0.48–1.09).

Conclusion In this retrospective study, there was no independent association between alcohol intoxication and higher in-hospital mortality in emergency patients with sTBI. *European Journal of Emergency Medicine* 28: 97–103 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Keywords: alcohol, cohort study, intoxication, neurotrauma, traumatic brain injury

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Introduction

Of the estimated 2.5 million people that annually sustain a traumatic brain injury (TBI) in the USA [1], 35–50% of the TBI patients suffer from alcohol intoxication at the time of injury [2]. Alcohol has been demonstrated to have a favorable effect on the secondary pathophysiological changes after severe TBI (sTBI) in various animal studies. The suggested underlying mechanism for neuroprotection is that alcohol exposure interferes with

post-traumatic cerebral and systemic responses. Alcohol exposure was associated with decrease of post-injury cerebral glucose metabolism and decreased rate of apoptosis, and less toxicity by sudden release of excitatory neurotransmitters via the *N*-methyl-D-aspartate receptor which is blunted by the presence of alcohol. Also, alcohol seemed to attenuate harmful changes in cerebral perfusion, and lessen the permeability of the blood–brain barrier [3–5].

In several clinical studies, acute alcohol intoxication is reported to be associated with better outcomes [6–9]. Many studies include the entire spectrum of brain injury and do not account for differences in injury- and trauma characteristics. The effect of alcohol intoxication may be diffused by large numbers of minor head injuries, which are mostly associated with good outcomes anyway [10].

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Table 1 Head Abbreviated Injury Score

Score	Severity	Example
1	Minor	Scalp laceration
2	Moderate	Concussion
3	Serious	Subdural hematoma <0.6 cm thick
4	Severe	Subdural hematoma 0.6–1 cm thick
5	Critical	Subdural hematoma with mass effect
6	Unsurvivable	Intracranial hemorrhage with severe mass effect with herniation

Therefore, the aim of this study was to evaluate the independent association between alcohol intoxication and patient outcomes after severe TBI by excluding minor TBI [head Abbreviated Injury Score (AIS) = 1 and 2]. The hypothesis is that after adjustment for differences in patient, trauma, and injury characteristics, alcohol intoxication on arrival to the Trauma Center is primarily associated with lower in-hospital mortality and secondarily with shorter hospital length of stay, ICU length of stay, and better neurological outcome after 1 year.

Material and methods

This retrospective cohort study was conducted at a large urban, academic, Level 1 Trauma Center in the USA. All patients aged 18 years or older who presented to the emergency department (ED) and had been admitted with sTBI (AIS \geq 3) between 1 January 2011 and 31 December 2016 were included. Patients who were admitted more than 72 h after the time of injury were excluded, as well as patients who died before arrival in the ED. Patients with head AIS equal to or higher than 3 were defined as sTBI. The AIS is globally used, anatomically based and consensus derived for indexing injury severity on a scale from 1 (least severe) to 6 (most severe) [11]. Head AIS for identification of sTBI patients was used despite the more common Glasgow Coma Score (GCS) since the use of GCS can be limited in the multitrauma and in the intoxicated population [12,13]. More details about head AIS are provided in Table 1.

Patients were identified through the institutional trauma registry, which also contributes to the American College of Surgeons National Trauma Data Bank. The trauma registry includes data points about demographics, the injury, pre-hospital status, ED information and in hospital events and outcomes. These data were supplemented with information acquired from the electronic medical records by the first five authors. Patients with head AIS 3 or higher were excluded if upon review of the electronic medical records no sTBI was present, since head AIS also codes for head injuries other than TBI, such as facial fractures.

The primary endpoint was in-hospital mortality. Secondary endpoints included length of hospital stay (HOS-LOS) and the ICU (ICU-LOS), and discharge disposition. These endpoints were assessed using the trauma registry and electronic medical records. The functional outcome determined by the Glasgow Outcome

Scale-Extended (GOS-E) 1 year after discharge was available for a subgroup of patients who were enrolled in the TBI Model System Database in an affiliated rehabilitation hospital. The data collection methods for this database are described in detail by Pretz *et al.* [14].

Variables

Demographic data, comorbidities, time and mechanism of injury, time interval between time of injury and ED admission, type of sTBI classified according to the International Classification of Diseases (ICD-9 in 2011–2014, ICD-10 in 2015–2016), severity of brain injury classified according to the AIS system, Injury Severity Score (ISS), Glasgow Coma Score (GCS) upon ED arrival, and vital signs including body temperature on admission were obtained from the trauma registry. The data about in-hospital mortality, the primary endpoint, were also obtained from the trauma registry and validated by the reports in the electronic medical records. Length of hospital stay and in the ICU was obtained as described above. Data about alcohol levels measured in the ED, history of alcohol use, coagulation status per the International Normalized Ratio (INR), and discharge disposition were collected from the EMR. To describe the pre-trauma condition of the patients, the Charlson Comorbidity Index (CCI) was calculated [15,16]. To summarize the severity of the brain imaging results, the Rotterdam CT score [17] was subtracted from the radiology reports of brain imaging. When parameters were missing or unclear in the report, the imaging itself was reviewed.

Alcohol intoxication was defined by either elevated blood alcohol concentration (BAC) or by a clear description of clinical intoxication on the medical record when BAC was not measured, versus no intoxication according to the BAC. Patients without a BAC measurement were included in the no intoxication group unless there was a clear description of clinical alcohol intoxication on the medical record. In that scenario, they were also included in the intoxicated group. In an additional analysis, BACs were subdivided into ‘none’ (<10 mg/dL), ‘low’ (10–99 mg/dL), ‘moderate’ (100–230 mg/dL) and ‘high’ (>230 mg/dL), as previously described by Taylor *et al.* [4]. In this analysis, the patients who were described as intoxicated but nevertheless had measured BAC = 0 were excluded.

Continuous variables, except age, were grouped across clinically relevant cutoff points. Heart rate was dichotomized at 100 beats per minute; SBP at 100 mmHg; INR at 1.5; body temperature at 36°C. The GCS was grouped in <8, 8–12 and >12. Isolated sTBI was defined as a head AIS \geq 3 and no major injuries to other anatomical regions, defined by a maximum AIS of 2 per region other than the head.

Statistical analysis

Normally distributed continuous variables were summarized as mean and SD and compared between patients with and without alcohol intoxication using unpaired

t-tests. Skewed continuous data and ordinal data were summarized as median and interquartile range (IQR) and compared using the Mann–Whitney *U* test. Effect size was demonstrated for continuous outcomes by mean difference and its 95% confidence intervals (95% CI). Categorical data were reported as number and proportion, and compared using the Chi-square test, and the odds ratios (ORs) with their 95% CI were included to demonstrate effect size.

The independent association between alcohol intoxication and in-hospital mortality was evaluated first by a bivariate logistic regression for clinically relevant variables, including age, CCI, mechanism of injury, head AIS, ISS, Rotterdam CT score, heart rate, SBP, body temperature and INR. Then, multivariable logistic regression was conducted, including variables that were associated with outcome ($P < 0.05$) in the bivariate analysis, after they were tested for multicollinearity using the variance inflation factor (VIF). When $VIF > 2$, Pearson's correlation was calculated, and if $r > 0.6$ between the variables, the one with the highest Wald statistic was included in the multivariable analysis [18]. For assessing the goodness of fit for the model, the model Chi-square was assessed and the Hosmer & Lemeshow, Cox & Snell and Nagelkerke statistics were calculated.

To include the maximum number of cases in the multivariable logistic regression, missing values for vital signs

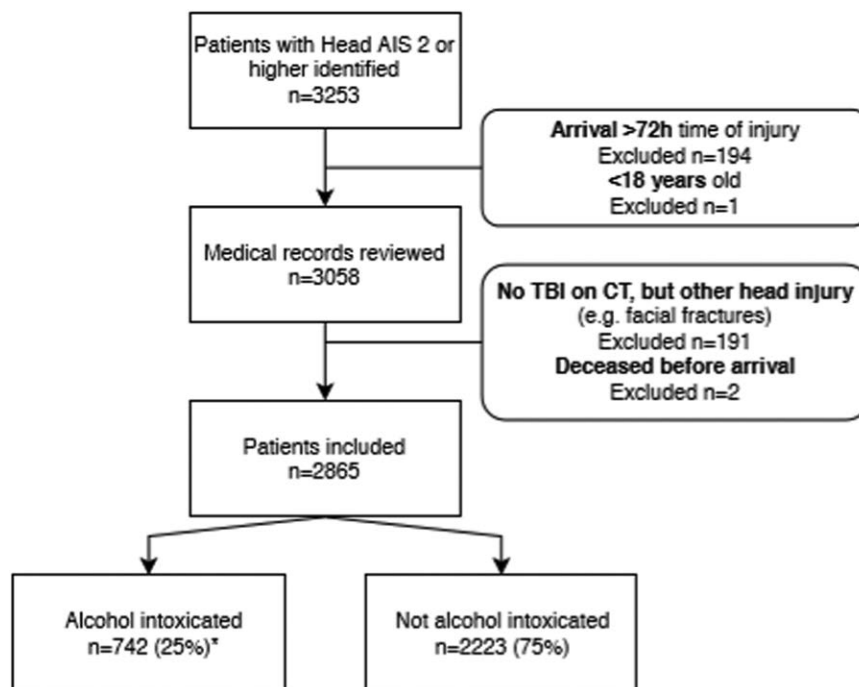
and INR were imputed using multiple imputation with 50 iterations. A second analysis was conducted in a similar fashion with alcohol intoxication subdivided by BAC groups. To test the strategy for the assessment of alcohol intoxication, a sensitivity analysis was conducted for the adjusted OR of in-hospital mortality, excluding cases where BAC was not measured. A second sensitivity analysis was conducted including only cases with isolated TBI to test if the conclusions would be altered by polytrauma cases. To evaluate if the results would be influenced by a considerable amount of time between time of injury and presentation in the ED, a third sensitivity analysis was executed without patients who were transferred from an outside hospital.

Statistical analysis was performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, New York, USA). The institutional review board approved the study and waived informed consent.

Results

In total, 2865 sTBI patients were included for analysis (Fig. 1). Of these, 715 (25%) suffered from alcohol intoxication. For 77 patients without elevated BAC, alcohol intoxication was nevertheless reported. The group of TBI patients with alcohol intoxication was younger (mean age 46 vs 68 years), more often male and had more frequently a social history of alcohol or polysubstance

Fig. 1



Flowchart of patient selection. *638 patients with positive blood alcohol concentration and 77 with suspicion of alcohol intoxication. In 31 patients with negative blood alcohol concentration, there was a clear description about alcohol intoxication at the time of injury more than 8 h prior to the alcohol measurement. These patients were included in the 'alcohol intoxicated' group.

abuse, compared to the group without alcohol intoxication. Their mechanism of injury was more often violence related and they had more often skull fractures and epidural hemorrhages. They also arrived in the ED with a lower GCS and a lower percentage had an elevated INR. The severity of the injuries, characterized by head AIS, ISS and Rotterdam CT score, did not differ between groups (Table 2).

In-hospital mortality

The overall in-hospital mortality rate was 14% (387 patients). Patients with alcohol intoxication had lower mortality (8.4%) than the other patients (15%) (Table 3). The unadjusted OR for mortality in patients with alcohol intoxication was 0.51 (95% CI, 0.38–0.68). Bivariate analysis demonstrated that age, comorbidity index, trauma mechanism, injury severity, and vital parameters were potentially associated with in-hospital mortality ($P < 0.05$) (Table 4). Age and CCI were suspected for collinearity, as was for head AIS and ISS. Therefore, only CCI and head AIS were included in the multivariable analysis.

After adjustment for these variables in a multivariable logistic regression analysis, with a Hosmer and Lemeshow's R^2 of 0.45 ($P = 0.90$), alcohol intoxication at time of TBI was no longer associated with in-hospital mortality (adjusted OR 0.72; 95% CI, 0.48–1.09).

In an additional analysis (appendix 1, supplement digital content 1, <http://links.lww.com/EJEM/A287>) including alcohol intoxication grouped by BAC level, the adjusted OR for low BAC was 0.97 (95% CI, 0.43–1.20), for moderate BAC the adjusted OR was 0.48 (95% CI, 0.23–0.99), and it was 0.75 (95% CI, 0.38–1.49) for high BAC. In a sensitivity analysis (appendix 2, supplement digital content 1, <http://links.lww.com/EJEM/A287>), including only 1476 patients with measured BAC, the adjusted OR for in-hospital mortality was 0.72 (95% CI, 0.44–1.17) in patients with alcohol intoxication. For the different BAC groups, the adjusted ORs did not differ more than 0.04 from the ORs in the analysis in appendix 1, supplement digital content 1, <http://links.lww.com/EJEM/A287>. In the second sensitivity analysis [appendix 3, supplement digital content 1, <http://links.lww.com/EJEM/A287>] including only isolated TBI cases ($n = 2118$ (74%)) the unadjusted OR for in-hospital mortality for alcohol intoxication was 0.45 (95% CI, 0.31–0.64) and the adjusted OR was 0.71 (95% CI, 0.41–1.24). The third sensitivity analysis (appendix 4, supplement digital content 1, <http://links.lww.com/EJEM/A287>) excluding patients who were transferred, the ORs for in-hospital mortality in alcohol intoxication were comparable with unadjusted OR 0.42 (95% CI, 0.28–0.63) and adjusted OR 0.57 (95% CI, 0.29–1.11).

Secondary endpoints

There was no difference in length of hospital stay. More patients with alcohol intoxication had a neurosurgical

Table 2 Description of traumatic brain injury patients with and without alcohol intoxication

	Intoxicated patients	Not intoxicated patients
	<i>n</i> =715	<i>n</i> =2150
Patient baseline		
Age, mean (SD)	46 (17)	68 (21)
Male gender, <i>n</i> (%)	571 (80)	1217 (57)
Race Caucasian, <i>n</i> (%)	516 (72)	1753 (82)
CCI, median (IQR)	1 (0–2)	4 (1–5)
SH of alcohol abuse, <i>n</i> (%)	420 (59)	218 (10)
SH of polysubstance abuse, <i>n</i> (%)	138 (19)	157 (7.3)
Mechanism of injury, <i>n</i> (%)		
Fall	416 (58)	1594 (74)
Assault (blunt)	103 (14)	61 (2.8)
Gunshot/penetrating	9 (1.3)	27 (1.3)
Motor vehicle traffic	172 (24)	353 (16)
Other	15 (2.1)	115 (5.3)
Type of head injury, <i>n</i> (%) ^a		
Cerebral contusion	264 (37)	472 (22)
Subarachnoid hemorrhage	454 (64)	1248 (58)
Subdural hemorrhage	433 (61)	1340 (62)
Epidural hemorrhage	117 (16)	157 (7.3)
Other intracranial hemorrhage	120 (17)	350 (16)
Skull fracture	355 (50)	629 (29)
Intracranial injury NFS	94 (13)	253 (12)
Other TBI	3 (0.4)	7 (0.3)
Injury severity		
Isolated TBI, <i>n</i> (%)	527 (74)	1589 (74)
Head AIS, median (IQR)	4 (4–5)	4 (4–5)
ISS, median (IQR)	21 (17–26)	21 (16–26)
Rotterdam CT score, median (IQR)	2 (1–2)	2 (1–2)
Vital signs upon arrival		
GCS, median (IQR)	14 (6–15)	15 (12–15)
GCS high (>12), <i>n</i> (%)	426 (61)	1551 (75)
GCS intermediate (8–12), <i>n</i> (%)	78 (11)	151 (7.2)
GCS low (<8), <i>n</i> (%)	200 (28)	382 (18)
Heart rate, mean (SD)	87 (19)	83 (20)
SBP in mmHg, mean (SD)	137 (24)	148 (30)
Body temperature °C, mean (SD)	36.4 (0.60)	36.4 (0.65)
INR ≥1.5, <i>n</i> (%)	47 (6.6)	378 (18)

AIS, Abbreviated Injury Score; CCI, Charlson Comorbidity Index; GCS, Glasgow Coma Scale; NFS, not further specified; SH, social history; ISS, Injury Severity Score; INR, International Normalized Ratio; TBI, traumatic brain injury.

^aMost patients had multiple types of TBI.

intervention and a larger proportion was admitted to the ICU compared to the other patients (Table 2). Upon hospital discharge, the discharge destination differed ($P < 0.01$): patients who suffered from alcohol intoxication at the time of injury mostly went home (51 vs 32%), whereas the other patients were more often referred to inpatient rehabilitation facilities.

In a subgroup of 122 patients who were discharged to an affiliated inpatient neurorehabilitation facility, the functional outcome measured with the GOS-E after 1 year of follow-up was not different for patients with alcohol intoxication at the time of injury (28 patients, 23%).

Discussion

In this study that included 2865 patients with severe TBI that presented in the ED, there was no independent association between alcohol intoxication and in-hospital mortality. In contrast to these findings, other studies have shown alcohol intoxication to be associated with reduced in-hospital mortality rates [6–8,19–22].

Table 3 Outcomes of traumatic brain injury patients with and without alcohol intoxication

	Alcohol intoxicated	Not alcohol intoxicated	P value	Effect size ^b
	n=715	n=2150		
In-hospital mortality, n (%)	60 (8.4)	327 (15)	<0.01	0.51 (0.38 to 0.68)
30-day mortality, n (%)	62 (8.7)	347 (16)	<0.01	0.49 (0.37 to 0.66)
ICU admission, n (%)	386 (54)	1047 (49)	0.02	1.24 (1.04 to 1.46)
ICU length of stay in days, mean (SD)	3.0 (5.6)	3.5 (5.9)	0.04	0.50 (0.02 to 0.98)
Hospital length of stay in days, mean (SD)	9.0 (12)	8.8 (12)	0.65	0.24 (-0.78 to 1.25)
Neurosurgical intervention, n (%)	174 (24)	392 (18)	<0.01	1.44 (1.18 to 1.77)
GOS-E after 1 year, median (IQR) ^a	6 (4–8)	5.5 (3–7)	0.13	0.43 (-0.22 to 1.52)
Discharge destination				
Eloped/left AMA, n (%)	14 (2.1)	12 (0.7)	<0.01	3.56 (1.64 to 7.73)
Home, n (%)	330 (50)	571 (31)	<0.01	2.37 (1.99 to 2.82)
Home with services, n (%)	105 (16)	324 (18)	0.80	0.97 (0.76 to 1.23)
Skilled nursing facility, n (%)	9 (1.4)	150 (8.2)	<0.01	0.17 (0.09 to 0.33)
In-patient rehab, n (%)	184 (28)	703 (39)	<0.01	0.71 (0.59 to 0.86)
Hospice, n (%)	1 (0.20)	43 (2.4)	<0.01	0.07 (0.01 to 0.50)
Other, n (%)	12 (1.8)	20 (1.1)	0.10	1.82 (0.88 to 3.74)

^aSubgroup of 123 patients included in the TBIMS database.

^bFor categorical data by odds ratio, for continuous data by mean difference with 95% confidence intervals.

AMA, against medical advice; GOS-E, Glasgow Outcome Scale-Extended; IQR, interquartile range; TBI, traumatic brain injury.

Table 4 Odds ratios for in-hospital mortality, n=2865

	Unadjusted OR	95% CI	Wald	P value	Adjusted OR	95% CI	Wald	P value
Alcohol intoxication yes/no	0.51	0.38–0.68	21	<0.01	0.72	0.48–1.09	2.38	0.12
Patient baseline								
Age ^a	1.02	1.01–1.03	51	<0.01	–	–	–	–
Male gender	1.02	0.82–1.27	0.03	0.87	–	–	–	–
Caucasian race	0.88	0.68–1.13	1.0	0.31	–	–	–	–
CCI	1.20	1.15–1.23	52	<0.01	1.59	1.45–1.74	97.8	<0.01
Mechanism of injury								
Fall	1.30	1.02–1.66	4.35	0.04	0.75	0.49–1.15	0.58	0.18
Assault (blunt)	0.19	0.08–0.47	13.1	<0.01	0.41	0.13–1.26	0.18	0.12
Gunshot/penetrating	6.67	3.44–12.9	31.5	<0.01	2.59	0.93–7.17	4.57	0.07
Motor vehicle traffic	0.92	0.70–1.23	0.31	0.58	–	–	–	–
Other	0.41	0.20–0.84	5.91	0.02	0.52	0.20–1.34	1.50	0.18
Injury severity								
Head AIS	4.9	4.0–5.9	241	<0.01	2.19	1.72–2.80	36.2	<0.01
ISS ^a	1.1	1.1–1.1	149	<0.01	–	–	–	–
Rotterdam CT score	3.1	2.8–3.5	460	<0.01	2.30	2.02–2.62	136	<0.01
Vitals upon arrival								
GCS high (>12)	Reference	–	–	–	Reference	–	–	–
GCS intermediate (8–12)	3.85	2.63–5.64	47.7	<0.01	2.81	1.75–4.51	18.5	<0.01
GCS low (<8)	9.90	7.68–12.8	313	<0.01	6.68	4.56–9.79	100	<0.01
Temperature <36°C	2.55	1.97–3.32	49.5	<0.01	1.63	1.13–2.34	7.24	0.01
Heart rate >100 beats/min	1.76	1.37–2.26	20.0	<0.01	2.07	1.46–2.92	15.1	<0.01
SBP <100 mmHg	3.33	2.19–5.06	31.7	<0.01	3.13	1.71–5.74	9.48	<0.01
INR ≥1.5	3.01	2.35–3.85	75.6	<0.01	1.74	1.24–2.44	8.46	<0.01

^aNot included in multivariable regression because of collinearity.

$R^2=0.45$ (Hosmer & Lemeshow) $P=0.90$, 0.28 (Cox & Snell), 0.52 (Nagelkerke). Model $\chi^2(1)=850$, $P<0.01$.

AIS, Abbreviated Injury Score; CI, confidence interval; CCI, Charlson Comorbidity Index; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; OR, odds ratio; SBP, systolic blood pressure; INR, international normalized ratio.

However, the findings of Chen *et al.* suggested that the presumed protective effect of alcohol in many clinical studies may owe to confounding bias by ISS and cause and intent of trauma [10]. Indeed, when adjusted for all available potential confounding factors any statistical significance was lost. An alternative explanation for the loss of an association between alcohol and mortality could be reduced statistical power. This is unlikely; however, because of the number of included cases exceeds the minimal generally accepted sample size for the amount of predictors by far [23]. Also, the odds ratios for in-hospital mortality and BAC did not demonstrate a

consistent dose-response relationship, both in the unadjusted and adjusted analyses, serving as further proof of the lack of an association.

Nevertheless, the patients with alcohol intoxication were more frequently admitted to the ICU, which is possibly related to the lower GCS on arrival in this group, warranting closer clinical observation. There was also a significantly higher proportion of patients undergoing a neurosurgical intervention for TBI. This could be related to the type of injury because the intoxicated patients more often had skull fractures and epidural hemorrhages.

Also, the statistically significant younger age of the intoxicated group could have influenced the neurosurgical decision making [24].

Limitations

This study has several limitations: the first is the lack of BAC measurements for the entire population. Although an effort was made to correctly classify patients as with alcohol intoxication and without intoxication by extensively reviewing the medical records, for some patients this remains an assumption. However, the sensitivity analysis, including only cases with measured BAC, did not lead to different conclusions about the association of alcohol intoxication with the sTBI endpoints. The second limitation refers to the assumption that BAC upon arrival corresponded with BAC at the time of injury. Individual differences in alcohol physiology were impossible to account for in the retrospective observational data. In addition, there was insufficient data available about the exact time between injury and alcohol measurement. Also, the studied center is a tertiary referral center serving a wide area. This may have caused longer times between injury and presentation in the ED, potentially causing false-negative BAC results in a selected group of patients who suffered from alcohol intoxication at the time of injury, but metabolized the alcohol before it could be measured in the ED. A large proportion of the patients in the ED were actually transferred from an outside hospital. It could be that those sTBI patients, who survived longer transportation times, were less severely injured. This could have resulted in lower mortality in the no-intoxication group, masking a possible beneficial association with alcohol. On the other hand, in the sensitivity analysis excluding transferred patients, the conclusions did not change. A third limitation is the lack of data to draw conclusions about the influence of alcohol intoxication on outcomes after discharge from the hospital, such as neurological function, return to work status and mortality. Although long-term outcomes detection presents a formidable research challenge, some previous studies described a beneficiary effect of alcohol [9,22]. These long-term outcomes are particularly meaningful for the majority of patients who survive the initial hospital admission for sTBI and, therefore warrants further investigation.

Conclusion

In this retrospective study, there was no independent association between alcohol intoxication and higher in-hospital mortality in emergency patients with severe TBI. It did not confirm the findings of other studies that suggested a neuroprotective effect of alcohol to sTBI. In the important challenge of improving outcomes for sTBI patients, alcohol is not likely to provide therapeutic options.

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The institutional review board approved the study and waived informed consent for individual participants included in the study.

Conflicts of interest

There are no conflicts of interest.

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