Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Alcohol in Traumatic Brain Injury: Toxic or Therapeutic?

William Brigode, MD, Caitlin Cohan, MD, Genna Beattie, MD, and Gregory Victorino, MD*

Department of Surgery, University of California-San Francisco, Oakland California

ARTICLE INFO

Article history:
Received 2 March 2019
Received in revised form
17 May 2019
Accepted 7 June 2019
Available online xxx

Keywords:
Trauma
Traumatic brain injury
Alcohol

ABSTRACT

Background: Alcohol (EtOH) poses a challenge in traumatic brain injuries (TBIs) given its metabolic and neurologic impact. Studies have had opposing results regarding mortality and complication rates in the intoxicated TBI patient. We hypothesized that trauma mechanism, brain injury severity, and blood alcohol concentration (BAC) would influence the impact of EtOH on mortality in TBI.

Methods: We performed a single-institution retrospective review of consecutive adult trauma patients tested for EtOH and a diagnosis of TBI. The primary outcome was mortality, and secondary outcomes included infectious complications. The primary analysis included univariate and multivariate regression comparing mortality between intoxicated and sober patients, at different values of BAC, different brain injury severities, and among mechanisms of trauma.

Results: Admission EtOH was assessed in 583 patients with TBI, with 256 testing positive for EtOH and 327 testing negative. Overall, EtOH was associated with lower mortality on univariate analysis (4.7% *versus* 8.9%, $P = 0.05$) but not on multivariate analysis ($P = 0.21$). There was no effect of EtOH on mortality when patients were stratified by brain injury severity or among penetrating trauma victims. However, EtOH was associated with lower overall infectious complications on univariate and multivariate regression. Finally, EtOH was predictive of mortality with an area under the receiver operator characteristic curve of 0.83.

Conclusions: We found that EtOH is not associated with mortality in the patient with TBI, suggesting no causative effect. However, EtOH showed some predictability of mortality based on a receiver operator characteristic analysis. Interestingly, EtOH was associated with lower infectious complications, suggesting an immunomodulatory effect of EtOH in TBI.

Introduction

Traumatic brain injury (TBI) is a significant burden to health care systems worldwide. Alcohol (ethanol or EtOH) plays a significant role in inciting traumatic events and alters the body's response to medical insults, both traumatic and non-traumatic. Although we know the pathophysiology of many disease processes, such as alcoholic encephalopathy, gastrointestinal cancers, cirrhosis, and pancreatitis, we do not have a clear understanding of the role EtOH plays in TBI. Of the

This paper was presented at the 14th Academic Surgical Conference in Houston, Texas on February 7, 2019.

* *Corresponding author*. Department of Surgery, 1411 E 31st Street, Oakland, CA 94602. Tel.: +1 419 206 2735; fax: 510-437-5127.
E-mail address: William.Brigode@alamedahealthsystem.org (W. Brigode).

0022-4804/$ – see front matter © 2019 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jss.2019.06.043

current literature, selected studies support an association of lower mortality in intoxicated TBI patients when compared with sober TBI cohorts.[1-11] Other studies question these results showing no association[12,13] or an association of EtOH with a higher mortality.[14]

The controversial association and mixed results have prompted significant clinical and laboratory research on EtOH and TBI. Pertinent clinical outcomes that have been studied include hospital length of stay (LOS), intensive care unit length of stay (ICU-LOS), and complication rates. Some studies suggest longer LOS in patients testing EtOH-positive (EtOH+) than EtOH-negative (EtOH−).[2] Others show equal[6] or shorter[8] LOS. Finally, complication rates have been mixed.[2,3,5-7,9] Perhaps most interesting is the effect of EtOH on infectious complications, such as sepsis,[2,3] pneumonia,[14,15] and urinary tract infection (UTI),[14] as EtOH has been shown to augment the immune response *in vitro*, but these studies show mixed effects *in vivo*.

The heterogeneity of outcomes has prompted reasoning with metabolic, immunologic, and cell-signaling hypotheses to explain the differences in outcomes. Much laboratory research has been done to elucidate the mechanism of the potential protective effect of EtOH. EtOH has been suggested to decreasing the cerebral glycemic metabolic rate[16] and attenuating the hyperthermic response to TBI.[17] The immunologic effect of EtOH may include downregulation of inflammatory cytokines and chemokines, such as IL-1β, TNF-α,[18] and IL-6.[19] Other discoveries in EtOH physiology include that EtOH may decrease aquaporin leading to decreased brain water content,[20,21] altered Bcl-2 protein expression and changes in neuronal apoptosis,[22] ErbB tyrosine kinase–mediated cell signaling,[23] and changes in synaptophysin-mediated immunoreactivity.[24]

Despite the abundant research, controversy still exists over the effect of EtOH on TBI. Studies often include varying populations, making them difficult to compare and elicit the truth to EtOH physiology. They have different inclusion and exclusion criteria based on Abbreviated Injury Score (AIS) of the head and/or neck (AIS-H), the presence or absence of accompanying injuries, and the mechanism of trauma, making them hard to compare. Previous studies use various cutoffs for blood alcohol concentration (BAC), with some using the absence or presence of EtOH, a low *versus* high grouping at a non-zero BAC, or a spectrum of BAC ranges. Given the heterogeneity of study design, we aimed to isolate some of the patient factors that may lend insight into the confusing and contradictory previously published results. We hypothesized that the varying results may be due to the exact cutoff of BAC used to define intoxication, the exclusion of mild and/or moderate TBI, and the mechanism of trauma. We therefore

Table 1 – BAC tested *versus* untested patients.

Selected patient demographics and outcomes	Tested	Tested (%)	Untested	Untested %	P-value
	Mean (standard deviation)		Mean (standard deviation)		
	n/total		*n*/total		
Demographics					
Age	49.0 (18.8)		58.0 (24.7)		<0.001
Female	158/583	27.1%	286/720	39.7%	<0.001
Penetrating	25/583	4.3%	44/720	6.1%	0.14
Prehospital cardiac arrest	11/583	1.9%	21/720	2.9%	0.12
Loss of consciousness	357/452	79.0%	394/588	67.0%	<0.001
Trauma activation level					<0.001
Systolic blood pressure	137.9 (29.4)		138.4 (36.5)		0.77
Diastolic blood pressure	81.0 (16.7)		78.0 (21.6)		0.007
Heart rate	93.6 (21.8)		85.6 (23.4)		<0.001
Respiratory rate	17.1 (6.9)		17.5 (6.1)		0.22
Pulse oximetry	97.2 (6.1)		94.6 (17.1)		<0.001
Anisocoria	9/582	1.5%	7/717	1.0%	0.52
GCS	12.3 (3.8)		13.5 (3.2)		<0.001
Midline shift	61/575	10.6%	54/679	8.0%	0.10
AIS-H	2.7 (1.2)		2.5 (1.2)		<0.001
ISS	14.8 (11.8)		12.7 (11.4)		0.001
Outcomes					
Discharge GCS	13.8 (3.3)		13.8 (3.4)		0.77
LOS	8.5 (10.9)		5.4 (7.5)		<0.001
ICU LOS	7.7 (7.5)		6.2 (6.9)		0.027
Ventilator days	7.4 (7.7)		7.1 (8.2)		0.79
Mortality	41/583	7.0%	60/720	8.3%	0.38

analyzed our population across a range of BAC, across all severities of TBI, with TBI and multisystem trauma, and in all mechanisms that presented to our institution.

Methods

We performed a single-institution retrospective review from January 1, 2016, through June 30, 2018, of adult patients with trauma admitted to our busy urban level I trauma center with any measured BAC (including those measured to be zero) and a diagnosis of TBI. Exclusion criterion included patients in whom BAC was not assessed. The primary outcome assessed was mortality comparing EtOH+ and EtOH− patients at different threshold values of BAC. Secondary outcomes included discharge Glasgow Coma Scale (GCS), AIS-H, ventilator days, ICU LOS and hospital LOS, and mechanism subtypes.

Primary univariate analysis used paired *t*-tests to compare continuous data and chi-squared tests to compare categorical data for the EtOH+ and EtOH− populations. Multivariate regression was performed to assess for independence of patient characteristics influencing mortality, secondary outcomes, and complications. The initial model included each patient's entire set of prehospital and trauma-bay demographics with a *P*-value less than 0.5. After eliminating codependent variables from the initial model, we included the following variables into our ultimate model: sex, age, blunt *versus* penetrating trauma, the presence or absence of an automobile, the presence or absence of prehospital cardiac arrest, presentation systolic blood pressure, presentation oxygen saturation, presentation GCS, Injury Severity Score (ISS), AIS-H, the presence of a blown pupil on presentation, the presentation of midline shift on initial computed tomography, and BAC. Highly correlating covariables were examined, and the lesser variable of each pair was dropped from the final model. We then repeated the univariate and multivariate analyses across subgroups of AIS-H to assess the effect of EtOH on TBI severity. Likewise, we repeated univariate and multivariate analyses on individual trauma mechanisms.

We performed subgroup analysis by stratifying TBI by AIS-H severity. We divided TBI by individual AIS and presentation GCS. We then grouped brain injury severity as defined by previous studies. TBI severity is defined with AIS-H in previous studies as mild TBI: AIS-H = 1-2, moderate TBI: AIS-H = 3, and severe TBI: AIS-H = 4-5. TBI severity is defined with GCS in

Table 2 – Alcohol positive *versus* alcohol negative patients.

Selectedpatient demographics and outcomes	EtOH+	EtOH+ (%)	EtOH−	EtOH− (%)	*P*-value
	Mean (standard deviation)		Mean (standard deviation)		
	n/total		*n*/total		
Demographics					
Age	46.5 (16.8)		50.9 (20.1)		0.005
Female	59/256	23.0%	99/327	30.3%	0.31
Penetrating	12/256	4.7%	13/327	4.0%	0.67
Prehospital cardiac arrest	5/251	2.0%	6/327	1.8%	0.92
Loss of consciousness	160/203	78.8%	197/249	79.1%	0.94
Loss of consciousness time	6.9 (9.9)		3.7 (3.1)		0.23
Trauma activation level					0.61
Systolic blood pressure	134.5 (25.9)		140.5 (31.6)		0.014
Diastolic blood pressure	80.3 (15.6)		81.5 (17.6)		0.37
Heart rate	96.2 (20.0)		91.7 (22.9)		0.013
Respiratory rate	16.9 (5.9)		17.1 (7.5)		0.73
Pulse oximetry	97.4 (2.4)		97.1 (7.9)		0.52
Anisocoria					0.75
GCS	12.4 (3.7)		12.2 (3.9)		0.40
Midline shift	26/252	10.3%	35/323	10.8%	0.84
AIS-H	2.6 (1.2)		2.8 (1.3)		0.06
ISS	13.6 (11.1)		15.8 (12.3)		0.024
BAC	0.230 (0.110)		0.000 (0.000)		<0.001
Outcomes					
Discharge GCS	14.2 (2.7)		13.4 (3.7)		0.006
LOS	7.4 (10.4)		9.3 (11.3)		0.032
ICU LOS	6.7 (6.3)		8.4 (8.1)		0.090
Ventilator days	6.6 (5.7)		7.8 (8.6)		0.34
Mortality	12/256	4.7%	29/327	8.9%	0.050

previous studies as mild TBI: GCS = 13-15, moderate TBI: GCS = 9-12, and severe TBI: GCS = 3-8. Key groups were severe TBI, as in Tien *et al.* and Pandit *et al.*, and the combination of moderate and severe (AIS = 3-5,[2,3,6-13] and GCS = 3-12 as in the meta-analyses by Brennan *et al.* and Raj *et al.*). We also performed subgroup analysis among subgroups of trauma, first by penetrating *versus* blunt trauma, and second, by mechanism of blunt trauma.

Finally, to assess the effect of BAC, we created a receiver operator characteristic (ROC) and calculated the area under the receiver operator characteristic (AUROC) over the physiologic BAC range of 0.000 to 0.400 g/dL. The ideal cutoff was determined by the Youden index and the distance to the perfect classification. The Youden index, sensitivity plus specificity minus one. The perfect classification is at the point where specificity and sensitivity are both 100%.

Results

A total of 1303 patients were admitted during the 30-month period, of which 583 were assessed for BAC. The populations that were tested and also untested for EtOH had similar mortality rates (7.0% *versus* 8.3%, $P = 0.38$). The tested population was more likely male, was younger, and was more injured, with higher AIS-H and ISS. Tested patients presented with a slightly lower admission GCS, a longer hospital LOS, and a longer ICU LOS. The discharge GCS and number of ventilator days were similar (Table 1).

Of the 583 patients assessed for BAC, 327 were EtOH− and 256 were EtOH+. EtOH+ patients were more likely male, younger, and less injured, with lower ISS and a trend toward lower AIS-H (Table 2). The overall mortality was 7.0%. There was a lower mortality in the EtOH+ group than the EtOH− group (4.7% *versus* 8.9%, respectively; $P = 0.05$). The discharge GCS was higher in EtOH+ patients despite being similar at admission. The total LOS was shorter in EtOH+, with a trend toward lower ICU-LOS. The overall complication rate was similar at 20%. EtOH+ patients were more likely to go through withdrawal. However, EtOH− patients were more likely to have any infection, including ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), and a trend toward a significant association with sepsis (Table 3). Selected outcomes are provided in Figure 1.

Our multivariate regression model showed that age, penetrating trauma, prehospital cardiac arrest, presentation oxygen saturation, presentation GCS, ISS, the presence of a blown pupil on presentation, and the presentation of midline shift on initial (computed tomography) were all associated with increased mortality (Table 4). Using the same model for each of our secondary outcomes and complications, hospital LOS, ICU LOS, and discharge GCS, while improved in the intoxicated group on univariate analysis, were no longer associated with BAC (Table 5). Withdrawal was more common in the EtOH+ patient, and on multivariate analysis, BAC remained the most strongly associated factor for EtOH withdrawal. VAP was more likely in the EtOH+ group on univariate analysis, but BAC was not associated with VAP incidence in

Table 3 – Complications in the EtOH+ *versus* EtOH− populations.

Complication	EtOH+	EtOH+ (%)	EtOH−	EtOH− (%)	*P*-value
	Mean (standard deviation)		Mean (standard deviation)		
Any complication	53/256	20.7%	67/327	20.5%	0.95
Unplanned intubation	5/256	2.0%	10/327	3.1%	0.40
Unplanned ICU stay	1/256	0.4%	7/327	2.1%	0.071
Unplanned OR	1/256	0.4%	1/327	0.3%	0.86
CVA	1/256	0.4%	4/327	1.2%	0.28
EtOH withdrawal	15/256	5.9%	6/327	1.8%	0.010
Other EtOH complication	21/256	8.2%	8/327	2.4%	0.002
Cardiac arrest	6/256	2.3%	9/327	2.8%	0.076
VAP	2/256	0.8%	12/327	3.7%	0.024
ARDS	7/256	2.7%	15/327	4.6%	0.24
PE	1/256	0.4%	2/327	0.6%	0.71
AKI	2/256	0.8%	4/327	1.2%	0.60
All infections	3/256	1.2%	22/327	6.7%	0.001
CAUTI	0/256	0.0%	6/327	1.8%	0.03
CLABSI	0/256	0.0%	1/327	0.3%	0.38
Surgical infection	1/256	0.4%	2/327	0.6%	0.71
Sepsis	1/256	0.4%	7/327	2.1%	0.071
DVT	1/256	0.4%	3/327	0.9%	0.44
Other complication	15/256	5.9%	32/327	9.8%	0.08

CVA = cerebrovascular accident; PE = pulmonary embolism; AKI = acute kidney injury; CLABSI = central line associated blood stream infection; DVT = deep vein thrombosis; ARDS = acute respiratory distress syndrome.

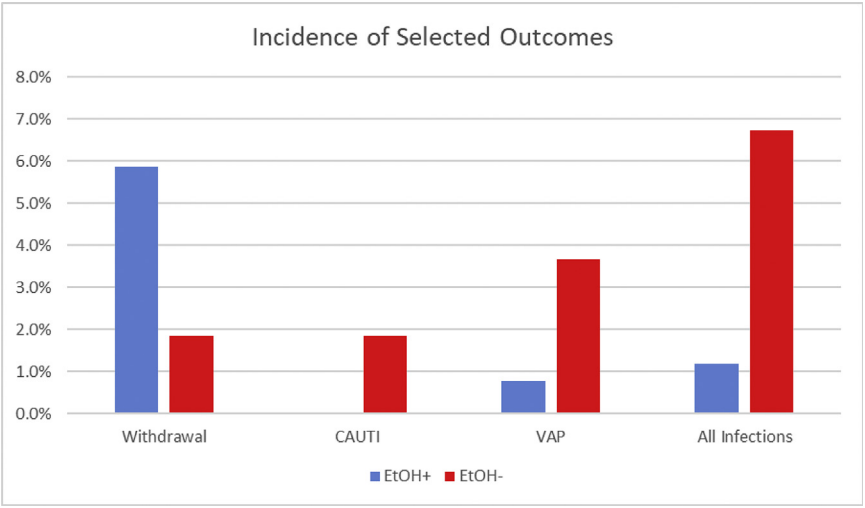

Fig. 1 – Univariate analysis of selected secondary outcomes. All statistically different ($P < 0.05$). (Color version of figure is available online.)

our multivariate model. However, BAC remained associated with a decreased rate of having any infection ($P < 0.05$), including CAUTI ($P < 0.05$).

Our subpopulation analysis among TBI severity revealed no differences whether on univariate or multivariate analysis and whether stratified by AIS-H (Fig. 2) or GCS (Fig. 3). Our final subgroup analysis was by stratifying mortality by mechanism (Fig. 4). Blunt trauma, most of our cohort, was significantly associated with mortality on univariate analysis. There was no subgroup of blunt trauma that was significantly associated with mortality. Our population showed an imbalance of EtOH association depending on the day of admission; 39.5% of EtOH+ patients presented on a weekend, compared to only 29.4% of EtOH− patients.

To evaluate the utility of BAC in predicting mortality, we created an ROC curve for BAC 0.000-0.375 g/dL at intervals of 0.025 g/dL. At BAC values of 0.400 g/dL and above, the ROC was below the line of no discrimination as there was only one death in patients with a BAC above 0.400 g/dL. We then calculated the AUROC to be 0.83. The Youden Index showed the best BAC thresholds for association with mortality were 0.0625 g/dL and 0.75 g/dL, which gave an equal Youden Index of 0.585. The point closest to the perfect classification (distance = 0.305) was at a BAC of 0.0875 g/dL. The legal limit of 0.08 g/dL gave a distance of 0.306 (Fig. 5).

Table 4 – Univariate *versus* multivariate analysis of variables associated with mortality.

Patient characteristic	Univariate analysis	Multivariate analysis
Prehospital cardiac arrest	<0.001	<0.001
Presentation GCS	<0.001	<0.001
Pulse oximetry	<0.001	<0.001
Penetrating trauma	<0.001	<0.001
Midline shift	<0.001	0.003
Anisocoria	<0.001	0.011
Age	0.20	0.011
ISS	<0.001	0.017
AIS-H	<0.001	0.14
BAC	0.03	0.21
Nonautomobile blunt trauma	0.83	0.34
Sex	0.75	0.36
SBP	0.37	0.47

Discussion

It is unclear whether EtOH is associated with better or worse outcomes in TBI. The early studies suggested a protective effect of EtOH on TBI by showing reduced mortality, whereas subsequent data disputed this effect. We hypothesized that the varying results may be due to the exact cutoff of BAC used to define intoxication, the exclusion of mild and/or moderate TBI, and the mechanism of trauma. We found that EtOH and BAC were associated with improved mortality on univariate analysis, but this association did not hold in our multivariate model.

Our result of univariate association of EtOH and mortality in the TBI population agrees with many of the single-institution studies. This comes with the limitation of statistically significant differences between the EtOH+ and EtOH− groups. The intoxicated patient averaged 5 y younger and was slightly more likely to be male. It is unclear if these statistical differences are clinically relevant or whether they account for any mortality difference in the populations. Our study has several key differences from the prior literature. First, our study included brain injured patients of all severities, whereas most previous studies limit their population to severe (AIS = 4-5 or GCS < 9) or moderate to severe (AIS = 3-5 or GCS < 13). Second, on multivariate analysis, BAC was not associated with mortality. This is unlike the largest published data from the National Trauma Data Bank,[9] which the presence or absence

Table 5 – P-values for BAC for outcomes.

Selected outcomes and complications	Univariate	Multivariate
Mortality	0.050	0.21
LOS	0.032	0.13
ICU LOS	0.09	0.09
Ventilator days	0.34	0.18
Discharge GCS	0.006	0.12
Any complication	0.95	0.41
Unplanned intubation	0.40	0.66
Unplanned ICU	0.07	0.26
Unplanned OR	0.86	0.69
CVA	0.28	0.90
EtOH withdrawal	0.010	0.002
Other EtOH complication	0.002	0.003
Cardiac arrest	0.76	0.76
VAP	0.024	0.20
ARDS	0.24	0.28
PE	0.71	0.65
AKI	0.60	0.78
Any infection	0.001	0.037
CAUTI	0.029	0.033
CLABSI	0.38	0.63
Surgical infection	0.71	0.78
Sepsis	0.07	0.30
DVT	0.44	0.23
Other complication	0.08	0.13

CVA = cerebrovascular accident; PE = pulmonary embolism; AKI = acute kidney injury; CLABSI = central line associated blood stream infection; DVT = deep vein thrombosis; ARDS = acute respiratory distress syndrome.

of alcohol remains statistically significant after stepwise logistic regression. In both studies, there are statistically significant differences in the composition of the tested and untested population. What we infer is the possibility of the treating providers nonrandomly testing for EtOH on individual patients. This bias at the patient level selects patients into the tested and nontested groups in a nonrandom fashion. Thus, the tested population is not representative of the total population.

Several studies support a clinical background for bias. Ronning *et al.*[25] showed that EtOH may artificially assign patients to a more severe GCS group. Stuke *et al.*[26] refute this idea by claiming that GCS in EtOH+ patients is within one point of EtOH– counterparts. Shahin *et al.*[27] show a greater improvement in GCS in EtOH+ (3 points) patients than EtOH– (1 point) patients when comparing the emergency room GCS and the best day 1 GCS. Our study shows a similar phenomenon, with similar presentation GCS, but with a difference on discharge (14.2 *versus* 13.4, $P = 0.01$). What remains unclear is the explanation for any bias. This may be an EtOH-mediated treatment effect or the artificial depression of GCS that intensifies physician treatment and causes post-selection bias between the groups. It may also be a treatment bias due to hospital and societal logistics; Fabbri *et al.*[28] note that positive BAC is associated with more injuries on weekends, thus shifting how injured patients are treated based on differences in weekend *versus* weekday hospital staffing and patient burden. Our population showed a similar imbalance with a higher proportion of EtOH+ admissions on the weekend, lending credence to this hypothesis.

Not reported in the literature but perhaps impacting outcomes in these populations are EtOH-related interventions. The institution of the Clinical Institute Withdrawal Assessment for Alcohol and related interventions may create a treatment bias. EtOH+ patients may be selected into a higher level of care with more frequent nursing assessments as a result of these protocols. The pharmacological interventions for EtOH withdrawal are neuromodulators that may alter the course of a patient's TBI. We were unable to characterize these differences in our population, but there was a significant difference in withdrawal rates between the cohorts. Of note, EtOH– patients went through withdrawal at a nonzero rate of 1.8%. It is unclear

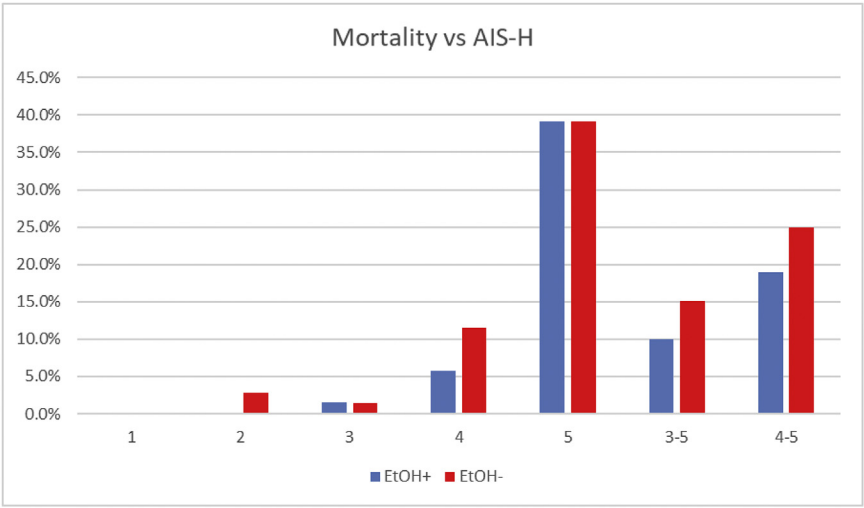

Fig. 2 – Mortality *versus* AIS-H. No statistical differences on multivariate analysis across each individual AIS-H or when grouped into groups of moderate-severe TBI (AIS-H 3-5) or severe TBI (AIS-H 4-5). (Color version of figure is available online.)

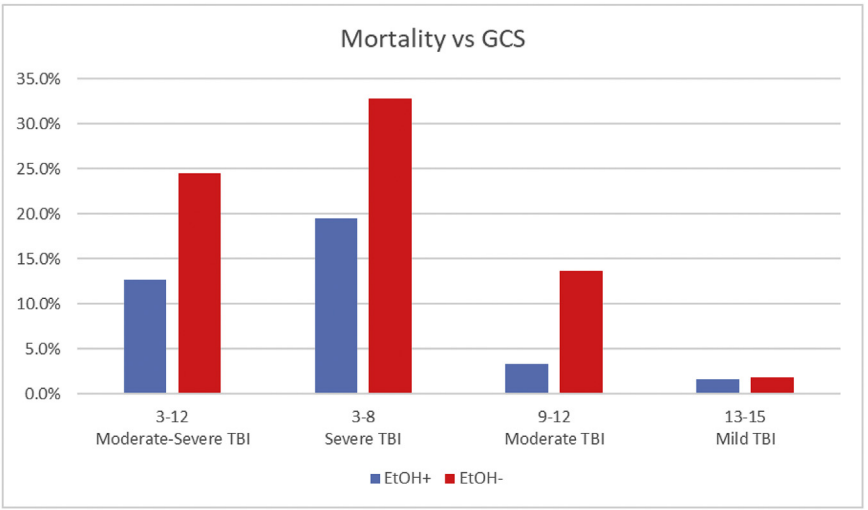

Fig. 3 – Mortality *versus* GCS. No statistical differences on the grouping of mild, moderate, severe, or the combination of moderate and severe TBI. (Color version of figure is available online.)

whether this is due to patients destined to withdraw testing negative or an overdiagnosis of suspected withdrawal. Anecdotally, there is a subset of the trauma population that present as a fall secondary to seizure secondary to withdrawal, which could represent a number of patients who test negative but would be diagnosed with EtOH withdrawal.

Several studies have shown differing techniques to improve upon the weaknesses of earlier studies. Chen *et al.*[13] used the National Trauma Data Bank and matched EtOH+ patients with EtOH− patients, found no difference in mortality between the groups, and concluded that the reduction in mortality of other studies is due to residual confounding. One study's population[6] was universally screened for EtOH based on the guidelines in their trauma system. This showed that patients with an isolated severe TBI and a BAC above 0.08 have a relative risk of mortality of 0.52 compared with the EtOH− subgroup. Universal EtOH screening reduces the selection bias of the treating physician. However, there remains a residual bias in the study, given that selection into the trauma system is based on prehospital triage criteria.

Our subgroup analysis was intended to validate our hypotheses that brain injury severity and trauma mechanism affected the association of EtOH and mortality. However, when TBI severity was stratified by AIS-H or by GCS, there were no significant mortality differences between the EtOH+ and EtOH− groups. We hypothesized that brain injury severity may cause a difference in mortality, as two key articles from the National Trauma Database showed contrasting results. One study[9] included moderate and severe TBI (AIS-H-3 and above) and showed reduced mortality in the EtOH+ group, whereas the other[14] only included severe TBI (AIS-H-4 and above). Our data showed that mortality was statistically

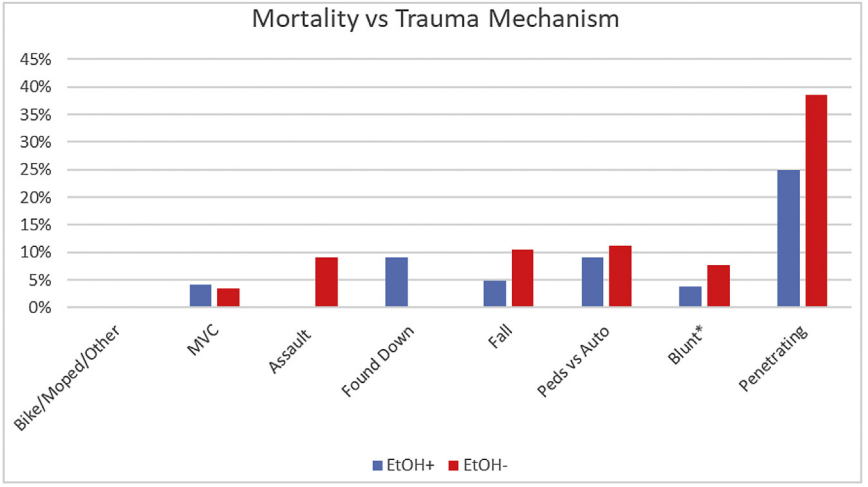

Fig. 4 – Mortality *versus* trauma mechanism. *Only subgroup for which EtOH was associated with mortality on univariate analysis ($P = 0.049$). No groups showed an association of EtOH and mortality on multivariate analysis. (Color version of figure is available online.)

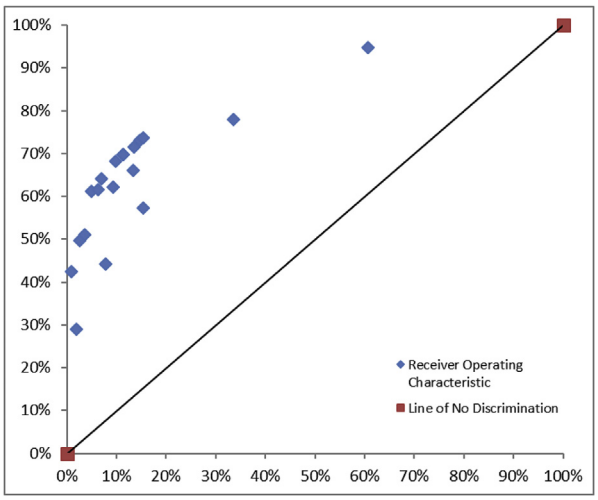

Fig. 5 – Receiver operating characteristic. AUROC = 0.83. (Color version of figure is available online.)

similar ($P > 0.05$) between the EtOH+ and EtOH− group across all TBI levels (Figs. 2 and 3). This disproves our hypothesis that only certain brain injury severities would have a protective effect of EtOH. However, our study was the first include mild TBI (AIS-H 1-2 and/or GCS 13-15), distinguishing it from the prior studies.

Another key difference in the design of previous studies was the isolation of blunt trauma from penetrating trauma. Given this difference, we hypothesized trauma mechanism may play a role in whether EtOH has a protective role or not. We thought that there may be specific mechanisms in which EtOH has minimal impact because the mechanism of trauma was so severe as to dominate EtOH's effect. Alternatively, some mechanisms may be so mild that mortality was too low to see an effect from EtOH. Like some previous studies, we showed that in a blunt trauma subgroup, EtOH was associated with lower mortality. However, this did not hold true for any of the subgroups of blunt trauma on either univariate or multivariate analysis. Although disproving our hypothesis, this is the first analysis of trauma mechanism as a basis for EtOH's effect on mortality.

Despite EtOH not being associated with mortality on the multivariate analysis, based on the univariate analysis, there is a baseline association with mortality. This allows for assessment of BAC as a predictor of mortality using a ROC. Over the clinically relevant range of BAC (0-0.375 g/dL), our data produced an AUROC of 0.83, suggesting that BAC may be predictive of mortality. In addition, our ROC analysis shows a range of BAC from 0.0675 to 0.0875 that are the strongest predictors. These values have the best sensitivity, specificity, and true positive rate, with a low false-positive rate. This is interesting because these are clinically relevant values that approximate the legal driving limit in the United States (0.08).

Although EtOH was not associated with mortality on multivariate regression, it remains interesting that EtOH was associated with lower overall infectious complications on univariate and multivariate regression and it was a significant factor associated with a lower CAUTI rate. Several studies show laboratory data in rats suggesting an immunomodulatory effect of EtOH exposure.[18,19] Wagner *et al.*[29] used clinical data to show EtOH+ had lower IL-6 and leukocyte counts; however, this did not bear out clinical improvements in mortality, sepsis, pneumonia, or acute respiratory distress syndrome. The other clinical data available do not clarify the situation (Table 6: Infectious complications in the literature) as there are data sets available showing either increased or decreased rates for the sepsis, pneumonia, and UTI, with numerous others showing no association.

Table 6 – Infectious complications as reported in the literature.

Complication	More frequent in EtOH+	Less frequent in EtOH-
Sepsis	Salim[2]	Lustenberger
Pneumonia	Pandit	Hadjibashi
UTI	Pandit	This study

Conclusion

Alcohol's effects on TBI remain a quandary. EtOH is likely not a causative agent for survival, given our multivariate analysis. However, EtOH has an association with improved mortality on univariate analysis, which makes for an interesting predictor of survival as based on our ROC analysis, especially when a BAC of 0.08 is used as a cutoff. Mortality in the TBI population is dominated by patient characteristics such as advanced patient age, higher ISS, penetrating mechanism of trauma, prehospital cardiac arrest, presentation, and GCS. Interestingly, EtOH was associated with decreased rates of CAUTI and overall infections in our cohort, suggesting a possible protective effect against infectious complications secondary to EtOH's effect on the immune system.

Acknowledgment

Authors' contributions: W.B. contributed to concept, study design, data analysis, manuscript writing, and manuscript editing. C.C. contributed to concept, study design, and data analysis. G.B. contributed to concept, study design, and data analysis. G.V. contributed to concept, study design, and manuscript editing.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article. This study was unfunded by any private or governmental organization.

REFERENCES

1. O'Phelan K, McArthur DL, Chang CWJ, et al. The impact of substance abuse on mortality in patients with severe traumatic brain injury. *J Trauma*. 2008;65:674–677.
2. Salim A, Teixeira P, Ley EJ, et al. Serum ethanol levels: predictor of survival after severe traumatic brain injury. *J Trauma*. 2009;67:697–703.
3. Lustenberger T, Inaba K, Barmaras G, et al. Ethanol intoxication is associated with a lower incidence of admission coagulopathy in severe traumatic brain injury patients. *J Neurotrauma*. 2011;28:1699–1706.
4. Tien HCN, Tremblay LN, Rizoli SB, et al. Association between alcohol and mortality in patients with severe traumatic head injury. *Arch Surg*. 2006;141:1185–1191.
5. Raj R, Skrifvars MB, Kivisaari R, et al. Acute alcohol intoxication and long-term outcome in patients with traumatic brain injury. *J Neurotrauma*. 2015;32:95–100.
6. Talving P, Plurad D, Barmparas G, et al. Isolated severe traumatic brain injuries: association of blood alcohol levels with the severity of injuries and outcomes. *J Trauma*. 2010;68:357–362.
7. Berry C, Salim A, Alban R, et al. Serum ethanol levels in patients with moderate to severe traumatic brain injury influence outcomes: a surprising finding. *Am Surg*. 2010;76:1067–1070.
8. Berry C, Ley EJ, Margulies DR, et al. Correlating the blood alcohol concentration with outcome after traumatic brain injury. *Am Surg*. 2011;77:1416–1419.
9. Salim A, Ley EJ, Cryer HG, et al. Positive serum ethanol level and mortality in moderate to severe traumatic brain injury. *Arch Surg*. 2009;144:865–871.
10. Brennan JH, Bernard S, Cameron PA, et al. Ethanol and isolated traumatic brain injury. *J Clin Neurosci*. 2015;22:1375–1381.
11. Raj R, Mikkonen ED, Siironen J, et al. Alcohol and mortality after moderate to severe traumatic brain injury: a meta-analysis of observational studies. *J Neurosurg*. 2016;124:1684–1692.
12. Shandro JR, Rivara FP, Wang J, et al. Alcohol and risk of mortality in patients with traumatic brain injury. *J Trauma*. 2009;66:1584–1590.
13. Chen CM, Yi H-Y, Yoon Y-H, et al. Alcohol use at time of injury and survival following traumatic brain injury: results from the National Trauma Data Bank. *J Stud Alcohol Drugs*. 2012;73:531–541.
14. Pandit V, Patel N, Rhee P, et al. Effect of alcohol in traumatic brain injury: is it really protective? *J Surg Res*. 2014;190:634–639.
15. Hadjibashi AA, Berry CB, Ley EJ, et al. Alcohol is associated with a lower pneumonia rate after traumatic brain injury. *J Surg Res*. 2012;173:212–215.
16. Kelly DF, Kozlowski DA, Haddad E, et al. Ethanol reduces metabolic uncoupling following experimental head injury. *J Neurotrauma*. 2000;17:261–272.
17. Taylor AN, Romeo HE, Beylin AV, et al. Alcohol consumption in traumatic brain injury: attenuation of TBI-induced hyperthermia and neurocognitive deficits. *J Neurotrauma*. 2002;19:1597–1608.
18. Gottesfeld Z, Moore AN, Dash PK. Acute ethanol intake attenuates inflammatory cytokines after brain injury in rates: a possible role for corticosterone. *J Neurotrauma*. 2002;19:317–326.
19. Goodman MD, Makley AT, Campion EM, et al. Preinjury Alcohol exposure attenuates the neuroinflammatory response to traumatic brain injury. *J Surg Res*. 2013;184:1053–1058.
20. Katada R, Nishitani Y, Honmou O, et al. Expression of aquaporin-4 augments cytotoxic brain edema after traumatic brain injury during acute ethanol exposure. *Am J Pathol*. 2012;180:17–23.
21. Wang T, Chou DY, Ding JY, et al. Reduction of brain edema and expression of aquaporins with acute ethanol treatment after traumatic brain injury. *J Neurosurg*. 2013;118:390–396.
22. Min H, Wei-Guo L, Liang W, et al. Influence of acute ethanol intoxication on neuronal apoptosis and Bcl-2 protein expression after severe traumatic brain injury in rats. *Chin J Traumatol*. 2013;15:136–139.
23. Chandrasekar A, Olde Heuvel F, Wepler M, et al. The neuroprotective effect of ethanol intoxication in traumatic brain injury is associated with the suppression of ErbB signaling in parvalbumin-positive interneurons. *J Neurotrauma*. 2018;24:1–18.
24. Rureci E, Dashti R, Tanriverdi T, et al. Acute ethanol intoxication in a model of traumatic brain injury: the Protective role of moderate doses demonstrated by immunoreactivity of synaptophysin in hippocampal neurons. *Neurol Res*. 2004;24:108–113.
25. Ronning P, Gunstad PO, Skaga N-O, et al. The impact of blood ethanol concentration on the classification of head injury in traumatic brain injury. *Brain Inj*. 2015;29:1648–1653.
26. Stuke L, Diaz-Arrastia R, Gentilello LM, et al. Effect of alcohol on Glasgow coma Scale in head-injured patients. *Ann Surg*. 2007;245:651–655.
27. Shahin H, Gopinath SP, Robertson CS. Influence of alcohol on early Glasgow Coma Scale in head-injured patients. *J Trauma*. 2010;69:1176–1181.
28. Fabbri A, Marchesini G, Morselli-Labate AM, et al. Positive blood alcohol concentration and road accidents. A prospective study in an Italian emergency department. *Emerg Med J*. 2002;19:210–214.
29. Wagner N, Akbarpour A, Mors K, et al. Alcohol intoxication reduces systemic interleukin-6 levels and leukocyte counts after severe TBI compared with not intoxicated TBI patients. *Shock*. 2016;46:261–269.