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Research Article

The effects of marijuana use prior to traumatic brain injury on survival

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ABSTRACT

Background: Legalization of recreational marijuana throughout the United States has been associated with increased emergency department visits involving marijuana and its metabolites, tetrahydrocannabinol (THC) and cannabinoids. We investigated the relationship between marijuana use and outcomes after all levels of traumatic brain injury (TBI) from a large multi-center regional dataset.

Methods: A retrospective review of de-identified patient data from twenty-six regional hospitals, was performed to identify adult patients with mild, moderate, and severe TBI between January 2012 and December 2018, a toxicology screen, and drug screen results. Included patients were divided into four subgroups: 1) No Drugs, 2) THC, 3) Other drugs (one or more drugs not including THC), and 4) THC + Other drugs. The primary outcome was mortality at discharge, while secondary outcomes included days in intensive care unit (ICU), length of hospital stay (LOS), and days on a ventilator.

Results: A total of 3,237 patients (median age 46 years [range: 18–97 years]; 31.9% female [1029/3,227]) met the inclusion criteria. Patients in the No Drugs group had significantly higher mortality rates at discharge than the THC ($p = 0.0046$), Other Drugs ($p = 0.0307$), and THC + Other Drugs groups ($p = 0.0441$). On multiple logistic regression, drug status was found not to be an independent predictor of mortality at discharge, while age, Glasgow Coma Scale (GCS), days in the ICU, Injury Severity Score (ISS), LOS, and days on a ventilator were independent predictors.

Conclusions: Patients positive for one or more drugs, including marijuana, had significantly lower mortality at discharge than those with no drugs; however, after controlling for confounding variables, drug status was not found to be an independent predictor of mortality at discharge. Therefore, our results indicate no survival benefit for any level of TBI with concomitant drug use, including marijuana, in contrast to recent studies.

Level of Evidence: [Level III Prognostic and Epidemiological Study] - Prognostic.

1. Introduction

During the last 25 years, 33 US states and the District of Columbia have decriminalized, medicalized, and legalized marijuana (tetrahydrocannabinol (THC) and cannabinoids (CBD)), which has been followed by a dramatic increase in marijuana use among Americans [1]. As marijuana use has become more widespread, emergency department (ED) visit rates have increased from 51 to 73 visits per 100,000 population ≥ 12 years old for cannabis-only use [2]. Marijuana use has been implicated as a risk factor for all types of trauma, including motor vehicle collisions [3].

Recently, a positive THC screen for adult patients with a traumatic brain injury (TBI) was reported to be associated with decreased mortality rates [4]. A 3-year retrospective review of data at a Level 1 trauma center included 446 patients sustaining TBI with a toxicology screen, and after adjusting for differences between study cohorts, a positive THC screen was found to be independently associated with survival after TBI [4]. The aim of this study is to further investigate the relationship

Abbreviations: Cannabinoid, CBD; Emergency Department, ED; Glasgow Coma Scale, GCS; Injury Severity Score, ISS; Intensive Care Unit, ICU; Length of Stay, LOS; NORTR, Northern Ohio Regional Trauma Registry; Traumatic Brain Injury, TBI; Tetrahydrocannabinol, THC.

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between a positive THC toxicology test and outcomes after brain injury by utilizing a large multi-center dataset derived from twenty-six regional hospitals, including three Level 1 and five Level 3 trauma centers.

2. Methods

2.1. Study population

After obtaining Institutional Review Board approval, de-identified patient data was collected from the Northern Ohio Regional Trauma Registry (NORTR) of all trauma patients with mild, moderate, and severe TBI from January 1, 2012 and December 31, 2018. This data was retrospectively reviewed and screened for patients who met the following inclusion criteria: TBI, age $\geq$ 18 years, a toxicology screen, drug screen results, and documented data regarding outcome at discharge. Pediatric patients (age $<$ 18 years) and patients without toxicology screen or results and discharge outcomes were excluded.

Included patients were divided into four groups: 1) No Drugs – patients with a negative toxicology test; 2) Other Drugs – patients with positive toxicology for one or more illicit or prescription drugs other than THC, including amphetamines, benzodiazepines, cocaine, opiates, phencyclidine, barbiturates, methamphetamine, ecstasy, methadone, oxycodone, and tricyclic antidepressants; 3) THC – patients with positive toxicology for THC and negative for all other drugs; 4) THC + Other Drugs – patients with positive toxicology for THC and any of the other drug classes previously mentioned.

2.2. Study variables

Patient variables included age, gender, ethnicity, Glasgow Coma Scale (GCS), Injury Severity Score (ISS), complications, and mechanism of injury. Mechanism of injury was sorted into the following six categories based on ICD-10: 1) injuries related to physical assault or struck by or against an object (hereafter, "Assault/Struck"), 2) fall/ground impact-related injuries (hereafter, “Fall”), 3) gunshot wound (hereafter, “GSW”), 4) injuries to pedestrians from vehicle collisions or bicycle accidents (hereafter, "Pedestrian"), 5) injuries to vehicle operator, including motor vehicle collisions, motorcycle collisions, other vehicle collisions, and other motorized bicycle collisions (hereafter, “Vehicle”), and 5) other injuries including TBIs of unspecified origin and those that were rarely reported ($n < 25$), including burns, injuries from being cut/stabbed/pierced, machinery-related accidents, and suffocation. Outcome variables included ventilator days, days in intensive care unit (ICU), length of hospital stay (LOS), and mortality at discharge.

2.3. Statistical analyses

Statistical analyses include Fisher’s exact test for comparisons of dichotomous data between groups [5]. Odds ratios and 95% CIs were also computed using the Woolf logit method. The Kruskal-Wallis test was used to compare mean ranks of background characteristics and outcomes between groups [6]. The Kruskall-Wallis test was performed instead of standard parametric one-way analysis of variance to provide robust comparisons of distributions that accounts for departures from normality. To aid in interpretation of significant differences, comparisons of continuous and ordinal-scale variables were also reported as median differences (MDs). A correlation matrix showing the strength and direction of correlation between pairs of covariates was generated using Spearman’s rank correlation test via the ‘corrplot’ package in R [7]. Spearman’s rank correlation was used to provide a more robust measurement of correlation in the face of high leverage outliers and nonlinear relationships between covariates [8]. Multiple logistic regression was used to identify predictors of discharge mortality rates using age, gender, GCS, ICU days, LOS days, ventilator days, and ISS [9]. In addition, the multiplicative interactions of several of these variables were included as covariates; these interactions included: 1) LOS:ICU days, 2) LOS:ventilator days, 3) ICU days:ventilator days, and 4) GCS:ISS. Interaction terms are provided to account for the relatively large correlation between these pairs of covariates. Due to the long-tailed distributions (non-normal) of several variables, logarithmic transformations were applied as necessary to shrink the influence of high leverage data points (outliers). Odds ratios from multiple regressions were computed to aid in interpretation of significant outcomes. P-values from multiple logistic regression were computed using Wald’s test [10]. To execute the logistic regressions, multiple imputation by chained equations using predictive mean matching was performed to account for missing data in GCS, ISS, LOS, ICU stay, and ventilator days. Multiple imputation was performed using the ‘mice’ package in R [11]. The proportion of the variance in mortality data explained by the predictor variables was evaluated with pseudo-R^2 values for univariate regressions and adjusted pseudo-R^2 values for multivariate regressions (adjusted for the number of predictors in the model and only increasing R^2 if new terms improve the model more than would be expected by chance). Model performance in correctly classifying whether patients survived or died was evaluated by the area under the receiver operating characteristic curve (AUC). In all cases, p-values ≤ 0.05 were considered significant. Statistics were performed in RStudio (Version 1.2.5033).

3. Results

3.1. Study population

3,237 patients were included in the analysis with a median age of 46 (IQR: 30–60; range: 18–97) and 31.8% (1,029/3,237) were female patients. Based on toxicology test results, 1,680 patients (52.2%) were in the No Drugs, 889 patients (27.5%) in Other Drugs, 370 patients (11.4%) in THC, and 289 patients (2.9%) in THC + Other Drugs groups (Table 1). Summary statistics of all patient characteristics by group are shown in Table 1; distributions of each patient characteristic by group are also shown visually in Supplementary Figs. 1-9.

The No Drugs group had a significantly higher number of females than the THC group (OR = 1.53 [95% CI: 1.18 to 1.99], $p = 0.001$), and the Other Drugs group had a significantly higher number of females than the THC + Other Drugs group (OR = 1.82 [95% CI: 1.38 to 2.40], $p < 0.001$). There were no other statistically significant differences between sex distributions between groups. Comparisons of sex between groups are shown in Table 2.

The No Drugs group was significantly older than the THC (MD = 20.0 years, $p < 0.001$), Other Drugs (MD = 7.0 years, $p < 0.001$), and THC + Other Drugs groups (MD = 20.0 years, $p < 0.001$). The Other Drugs group was significantly older than the THC group (MD = 13.0 years, $p < 0.001$) and the THC + Other Drugs group (MD = 13.0 years, $p < 0.001$). There were no differences in age between any of the other groups (Table 3).

Results from multiple comparison tests of ranked data showed that there were no statistically significant differences in GCS scores or ISS scores between any of the groups (Table 3). However, the No Drugs group had a significantly longer LOS compared to the THC + Other Drugs group (MD = 1.0 days, $p = 0.005$). The Other Drugs group also had a significantly longer LOS (MD = 1.0 days, $p = 0.002$) compared to the THC + Other Drugs group (Table 3).

There were no differences in complication rates between any of the groups ($p = 0.609$). With the exception of rates of Pedestrian causes of TBI, which was not significantly different between any of the groups ($p = 0.630$), all other causes of TBI had significant differences between individual groups. Multiple comparison tests for complication rates and cause of TBI are shown in Supplementary Tables 1 and 2, respectively.

3.2. Mortality at discharge

The No Drugs group had significantly higher mortality than the THC group (OR = 2.29 [95% CI 1.25 to 4.19], $p = 0.005$), the Other Drugs

Table 1
Patient Characteristics by Group.

Characteristic	No Drugs (n = 1680)	Other Drugs (n = 889)	THC (n = 370)	THC + Other Drugs (n = 298)	P value
Age	51.45 ± 20.35	45.95 ± 17.67	35.99 ± 14.28	35.74 ± 12.94	<0.001
Female	538 (32.02%)	319 (35.88%)	87 (23.51%)	85 (28.52%)	<0.001
GCS*	15 (13–15) [3–15]	15 (12–15) [3–15]	15 (12–15) [3–15]	15 (12–15) [3–15]	0.771
≤8	249 (17.82%)	149 (20.61%)	60 (20.41%)	46 (19.17%)	.
9–12	68 (4.88%)	39 (5.39%)	14 (4.76%)	15 (6.25%)	.
≥13	1080 (77.31%)	535 (74.00%)	220 (74.83%)	179 (74.58%)	.
ISS*	10 (5–17) [1–75]	9 (5–17) [1–75]	9 (5–17) [1–75]	9 (5–17) [1–50]	0.018
≤8	643 (38.39%)	383 (43.13%)	143 (38.65%)	137 (46.28%)	.
9–15	454 (27.10%)	240 (27.03%)	111 (30.00%)	77 (26.01%)	.
16–24	331 (19.76%)	147 (16.55%)	77 (20.81%)	42 (14.19%)	.
≥25	247 (14.74%)	118 (13.29%)	39 (10.54%)	40 (13.51%)	.
ICU days*	1 (0–3) [0–40]	1 (0–3) [0–33]	1 (0–3) [0–29]	1 (0–2) [0–32]	0.208
LOS days*	3 (1–6) [0–366]	3 (1–6) [0–169]	2 (1–5) [0–42]	2 (1–4) [0–50]	0.001
Ventilator days*	0 (0–2) [0–47]	0 (0–3) [0–33]	0 (0–2) [0–34]	0 (0–2) [0–29]	0.928
Complications*	301 (82.02%)	152 (81.28%)	56 (78.87)	53 (85.48%)	0.609
Cause of TBI					
Assault/Struck	107 (6.37%)	75 (8.45%)	43 (11.62%)	45 (15.10%)	<0.001
Fall	685 (40.77%)	317 (35.70%)	77 (20.81%)	76 (25.50%)	<0.001
GSW	20 (1.19%)	9 (1.01%)	6 (1.62%)	10 (3.36%)	0.035
Vehicle	722 (42.98%)	402 (45.27%)	198 (53.51%)	132 (44.30%)	<0.001
Pedestrian	50 (2.98%)	26 (2.93%)	12 (3.24%)	5 (1.70%)	0.630
Other	96 (5.71%)	59 (6.64%)	34 (9.19%)	30 (10.07%)	0.010

Data are mean ± SD, n (%), or median (IQR) [range]. P-values were computed via Kruskall-Wallis test or Fisher's exact test with Freeman-Halton's extension. Multiple comparison tests of each variable by group are shown elsewhere.
GCS = Glasgow Coma Scale; GSW = Gunshot wound; ICU = Intensive Care Unit; ISS = Injury Severity Score; LOS = Length of stay; THC = Tetrahydrocannabinol
*Missing data present (see Supplementary Material for additional information on available sample sizes and patient populations)

group (OR = 1.50 [95% CI 1.04 to 2.15], p = 0.031), and the THC + Other Drugs group (OR = 1.84 [95% CI 1.00 to 3.38], p = 0.044). There were no significant differences in mortality at discharge between THC + Other Drugs and THC (OR = 1.23 [95% CI 0.64 to 2.37], p = 0.634) and THC and THC + Other Drugs (OR 0.81 [95% CI 0.36 to 1.82], p = 0.678). Comparisons of mortality at discharge between groups are shown in Table 4.

A correlation matrix using Spearman's rank correlation is shown in Fig. 1. Based on the output of the correlation matrix, the overall impact of effects from multicollinearity were likely, with a relatively large degree of correlation between nearly all covariates; as such, interaction terms between several covariates were included in the multiple logistic

Table 2
Comparisons of Sex by Group.

Sex by Drug Status Drug Status Group	F	M	Total	Odds Ratio	95% CI	P value
No Drugs Other Drugs	538 319	1142 570	1680 889	0.84	0.71 to 1.00	0.053
No Drugs THC	538 87	1142 283	1680 370	1.53	1.18 to 1.99	0.001
No Drugs THC + Other Drugs	538 85	1142 213	1680 298	1.18	0.90 to 1.55	0.250
Other Drugs THC	319 87	570 283	889 370	1.82	1.38 to 2.40	<0.001
Other Drugs THC + Other Drugs	319 85	570 213	889 298	1.82	1.38 to 2.40	<0.001
THC THC + Other Drugs	87 85	283 213	370 298	0.77	0.54 to 1.09	0.155

THC = Tetrahydrocannabinol; M = Male; F = Female; CI = Confidence Interval

regression (see Methods for a list of included interaction terms). Due to the high frequency of missing data (2,550/3,237, 78.8%) complications were not included as a covariate in the regression model.

On multiple logistic regression, increasing age, ISS, and ventilator days were shown to be significant independent predictors of mortality; conversely, decreasing GCS, LOS, and ICU stay were significantly associated with mortality. Increases in the interaction terms LOS:ventilator days and ICU:ventilator days were also associated with higher odds of mortality. Sex, cause of TBI, and drug status were not independent predictors of mortality at discharge (Table 5). The adjusted pseudo-R^2 of the regression model was 0.617 ($p < 0.001$) and had an AUC value of 0.961 (Fig. 2).

Most importantly, drug status was not found to be an independent predictor of mortality at discharge. In contrast with results from multivariate regression, univariate logistic regressions are shown in Supplementary Table 3. While drug class appears to be associated with mortality on univariate regression, with all groups having significantly lower odds of mortality compared to the No Drugs group (p = 0.006), these differences were not shown when adjusting for other important patient characteristics. Therefore, our analysis provides no evidence to suggest that THC reduces mortality rate in TBI patients.

4. Discussion

This study demonstrates that, while patients with a positive toxicology for one or more drugs, including THC, had significantly lower mortality at discharge when compared dichotomously to patients with No Drugs (negative toxicology), upon multiple logistic regression analysis this differential mortality was not found. Once other factors, including age, GCS, ICU stay, ISS, LOS, and ventilator days, were taken into account, our multiple logistic regression indicated drug status is not an independent predictor of mortality at discharge. Race, sex, and cause of TBI were also not shown to be independent predictors of mortality at discharge, while age, GCS, ICU days, ISS, LOS days, and ventilator days were identified as independent predictors of mortality at discharge.

The neuroprotective effects of THC after experimental TBI has been demonstrated in preclinical studies. Wei et al. demonstrated THC treatment in a rat model of TBI alleviated brain edema, attenuated cell apoptosis, and improved neurobehavioral function, potentially due to an upregulation of NFE2-related factor, a transcription factor that regulates the cellular antioxidant response following TBI [12]. Other mechanisms

Table 3
Comparisons of Ranked Data by Group.

	Mean rank 1	Mean rank 2	Mean Rank Diff.	n1	n2	Z	P value
Age							
No Drugs vs. Other Drugs	1837	1599	237.3	1680	889	6.12	<0.001
No Drugs vs. THC	1837	1098	738.4	1680	370	13.76	<0.001
No Drugs vs. THC + Other Drugs	1837	1098	738.3	1680	298	12.57	<0.001
Other Drugs vs. THC	1599	1098	501.1	889	370	8.67	<0.001
Other Drugs vs. THC + Other Drugs	1599	1098	501.0	889	298	8.01	<0.001
THC vs. THC + Other Drugs	1098	1098	−0.1	370	298	0.001	>0.999
Length of Stay (days)							
No Drugs vs. Other Drugs	1637.0	1662.0	−25.5	1676	889	0.67	>0.999
No Drugs vs. THC	1637.0	1545.0	91.7	1676	369	1.73	0.498
No Drugs vs. THC + Other Drugs	1637.0	1442.0	194.7	1676	296	3.36	0.005
Other Drugs vs. THC	1662.0	1545.0	117.2	889	369	2.06	0.237
Other Drugs vs. THC + Other Drugs	1662.0	1442.0	220.3	889	296	3.57	0.002
THC vs. THC + Other Drugs	1545.0	1442.0	103.1	369	296	1.44	0.905
ICU (days)							
No Drugs vs. Other Drugs	1341.0	1388.0	−47.7	1403	728	1.40	0.967
No Drugs vs. THC	1341.0	1321.0	19.8	1403	316	0.43	>0.999
No Drugs vs. THC + Other Drugs	1341.0	1283.0	58.1	1403	244	1.12	>0.999
Other Drugs vs. THC	1388.0	1321.0	67.5	728	316	1.34	>0.999
Other Drugs vs. THC + Other Drugs	1388.0	1283.0	105.8	728	244	1.92	0.330
THC vs. THC + Other Drugs	1321.0	1283.0	38.4	316	244	0.60	>0.999
Ventilator (days)							
No Drugs vs. Other Drugs	934.6	936.9	−2.3	921	545	0.09	>0.999
No Drugs vs. THC	934.6	951.3	−16.7	921	227	0.46	>0.999
No Drugs vs. THC + Other Drugs	934.6	956.8	−22.2	921	185	0.56	>0.999
Other Drugs vs. THC	936.9	951.3	−14.4	545	227	0.37	>0.999
Other Drugs vs. THC + Other Drugs	936.9	956.8	−19.9	545	185	0.47	>0.999
THC vs. THC + Other Drugs	951.3	956.8	−5.5	227	185	0.11	>0.999
GCS							
No Drugs vs. Other Drugs	1340.0	1311.0	29.3	1397	723	0.95	>0.999
No Drugs vs. THC	1340.0	1313.0	27.6	1397	294	0.64	>0.999
No Drugs vs. THC + Other Drugs	1340.0	1319.0	21.7	1397	240	0.46	>0.999
Other Drugs vs. THC	1311.0	1313.0	−1.7	723	294	0.04	>0.999
Other Drugs vs. THC + Other Drugs	1311.0	1319.0	−7.6	723	240	0.15	>0.999
THC vs. THC + Other Drugs	1313.0	1319.0	−5.9	294	240	0.10	>0.999
ISS							
No Drugs vs. Other Drugs	1660.0	1561.0	99.7	1675	888	2.59	0.058
No Drugs vs. THC	1660.0	1614.0	46.3	1675	370	0.87	>0.999
No Drugs vs. THC + Other Drugs	1660.0	1521.0	139.0	1675	296	2.37	0.106
Other Drugs vs. THC	1561.0	1614.0	−53.4	888	370	0.93	>0.999
Other Drugs vs. THC + Other Drugs	1561.0	1521.0	39.3	888	296	0.63	>0.999
THC vs. THC + Other Drugs	1614.0	1521.0	92.6	370	296	1.28	>0.999
Complications							
No Drugs vs. Other Drugs	341.5	345.3	−3.8	367	187	0.27	>0.999
No Drugs vs. THC	341.5	337.7	3.8	367	71	0.18	>0.999
No Drugs vs. THC + Other Drugs	341.5	361.8	−20.3	367	62	0.94	>0.999
Other Drugs vs. THC	345.3	337.7	7.6	187	71	0.34	>0.999
Other Drugs vs. THC + Other Drugs	345.3	361.8	−16.5	187	62	0.71	>0.999
THC vs. THC + Other Drugs	337.7	361.8	−24.1	71	62	0.88	>0.999

Comparisons were made using the Kruskal-Wallis test. GCS = Glasgow Coma Scale; ICU = Intensive Care Unit; ISS = Injury Severity Score; LOS = Length of stay; THC = Tetrahydrocannabinol; CI = Confidence Interval

of the neuroprotective properties of THC in the setting of TBI have been demonstrated by Braun et al., who found that the administration of a selective CB2R agonist increased macrophage anti-inflammatory polarization, reduced edema development, enhanced cerebral blood flow, and improved neurobehavioral outcomes in models of TBI [13]. Additionally, Gao et al. found THC improved neurological function and reduced brain water content in rats after TBI by enhancing autophagy activation and attenuating oxidative stress and apoptosis by modulating the mitochondrial apoptotic pathway [14].

Despite these positive preclinical studies, clinical literature examining the effect of THC on TBI is limited to two single-center studies. Nguyen et al. performed a 3-year retrospective study at a Level 1 trauma center, which included patients sustaining TBI with a toxicology screen. After adjusting for differences between study cohorts, a positive THC screen was found to be independently associated with survival after TBI [4]. Additionally, a 5-year retrospective study of a trauma database by O'Phelan et al. indicated alcohol and methamphetamine use was associated with decreased mortality after TBI, and reported that patients who tested positive for methamphetamine were more likely to test positive for THC, and hypothesized the synergistic effects of methamphetamine and THC may have contributed to overall lower mortality in this cohort [15]. Our study found that comparisons between toxicology groups did show patients positive for one or more drugs, including THC, had significantly lower mortality at discharge than patients with no drugs; however, after controlling for confounding variables, drug status was not found to be an independent predictor of mortality at discharge. Since our dichotomous comparisons align with the findings of Nguyen et al., we can confirm the presence of a correlation between THC and lower mortality, but our multiple logistic regression model shows this correlation could be attributed to other patient characteristics and variables. Nguyen et al. completed a regression of THC, age, mechanisms of injury, ethnicity, gender, alcohol>0.08%, and ISS, while our model used age, gender, GCS, ICU days, LOS days, ventilator days, ISS, and complications. Of note, the Nguyen et al. study also dichotomized independent predictors such as ISS, while our study included the full range of values on logistic regression whenever possible. Intentionally

Table 4
Comparisons of Mortality at Discharge by Group.

Mortality by Drug Status Drug Status Group	Dead	Alive	Total	Odds Ratio	95% CI	P value
No Drugs Other Drugs	116 42	1564 847	1680 889	1.50	1.04 to 2.15	0.031
No Drugs THC	116 12	1564 370	1680 382	2.29	1.25 to 4.19	0.005
No Drugs THC + Other Drugs	116 12	1564 298	1680 310	1.84	1.00 to 3.38	0.044
Other Drugs THC	42 12	847 370	889 382	1.53	0.80 to 2.94	0.227
Other Drugs THC + Other Drugs	42 12	847 298	889 310	1.23	0.64 to 2.37	0.634
THC THC + Other Drugs	12 12	370 298	382 310	0.81	0.36 to 1.82	0.678

THC = Tetrahydrocannabinol; CI = Confidence Interval

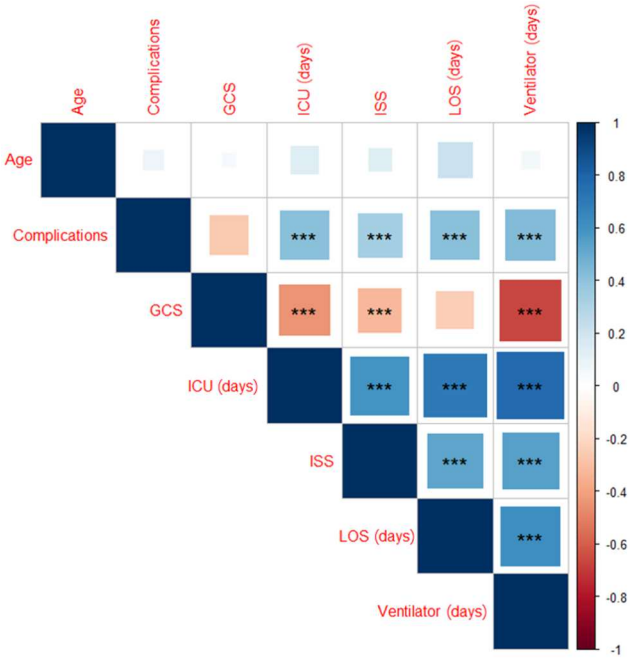

Fig. 1. Correlation Matrix using Spearman's rank correlation. Complications vs. ICU days (r = 0.416); Complications vs. ISS (r = 0.336); Complications vs. LOS days (r = 0.417); Complications vs. Ventilator days (r = 0.438); GCS vs. ICU days (r = -0.446); GCS vs. ISS (r = -0.327); GCS vs. Ventilator days (r = -0.663); ICU days vs. ISS (r = 0.594); ICU days vs. LOS days (r = 0.707); ICU days vs. Ventilator days (r = 0.774); ISS vs. LOS days (r = 0.530); LOS days vs. Ventilator days (r = 0.612). Blue represents positive correlations and red symbolizes inverse correlations. *p < 0.05, **p < 0.01, ***p < 0.001. GCS = Glasgow Coma Scale; ISS = Injury Severity Score; LOS = Length of stay. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dichotomizing data and including on regression can have important consequences which may lead to imprecise conclusions [16]. Indeed, we showed ISS was a strong predictor of mortality at discharge when including it as an ordered factor (i.e. non-dichotomized). Although the difference between ISS score among the different drug classes was not significant at the α = 0.05 level on univariate analysis, it is likely that these differences at least moderately contributed to the high mortality rates among the No Drugs group. While it is unclear how well the logistic regression model was performed in the Nguyen et al. study since no summary effect size was reported, our multiple logistic regression model explained a large proportion of the variability in discharge mortality rates (McFadden's Pseudo R^2 = 0.617; p < 0.001) and was shown to reliably predict discharge mortality (AUC = 0.961). It should also be noted that a large proportion of patients included in our study had mild TBIs (e.g., ISS ≤ 8), whereas the Nguyen et al. study defined TBI as Abbreviated Injury Scale scores ≥ 4 and had a greater proportion of severe cases with ISS ≥ 16. As such, it is possible that the potential survival benefit of THC is only observed in patients with more severe injuries, if at all. Further investigation on a patient cohort with an adequate sample size of patients with TBI, possibly stratified by severity, is required to elucidate any neuroprotective effects of THC in such a patient population.

Table 5
Multivariate logistic regressions, regressing patient characteristics against mortality.

Variable	Odds Ratio	95% CI	P value
(Intercept)	7.87e-4	6.74e-5; 7.80e-3	<0.011
Drug Group	.	.	.
(ref = No Drugs)	.	.	.
THC	1.06	0.45; 2.33	0.897
Other Drugs	0.82	0.48; 1.39	0.471
THC + Other Drugs	0.61	0.24; 1.45	0.280
Age	1.05	1.03; 1.06	<0.001
Male sex (ref = female)	0.83	0.50; 1.39	0.475
Log(GCS)	0.31	0.13; 0.70	0.005
Log(ISS)	12.90	6.67; 25.64	<0.001
Log(GCS):Log(ISS)	0.89	0.67; 1.17	0.396
Log(LOS)	0.23	0.12; 0.44	<0.001
Log(ICU)	0.35	0.15; 0.76	0.010
Log(Ventilator)	15.78	6.89; 38.06	<0.001
Log(LOS):Log(ICU)	0.86	0.54; 1.36	0.529
Log(LOS):Log(Ventilator)	0.40	0.25; 0.64	<0.001
Log(ICU):Log(Ventilator)	2.27	1.47; 3.46	<0.001
Cause of TBI	.	.	.
(ref = Assault/Struck)	.	.	.
Fall	0.94	0.38; 2.55	0.891
GSW	1.76	0.45; 7.09	0.420
Vehicle	0.49	0.20; 1.31	0.134
Pedestrian	1.31	0.30; 5.41	0.710
Other	0.84	0.30; 2.52	0.752
SUMMARY	**Pseudo-R^2**	**AUC**	**P value**
	0.617	0.961	<0.001

5. Limitations

Several limitations of this study should be noted. Primarily, the study was retrospective in nature, and some potentially relevant data was lacking for this patient population, including clinical course and surgical treatment. Missing data on several different patient characteristics represents another drawback of our study. Our patient population is also heavily skewed toward more mild cases of TBI (e.g., ISS < 16); a more evenly distributed sample with a larger number of moderate-severe TBI cases would provide a more sensitive analysis on the impact of TBI severity on mortality. Additionally, past drug history was not collected, making it impossible to distinguish between chronic and acute drug use. Limitations in toxicology screens may have given positive THC screening results even for patients who had not been actively intoxicated or recently used before TBI, if they had used THC in the recent past (4.6 to 15.4 days) [17].

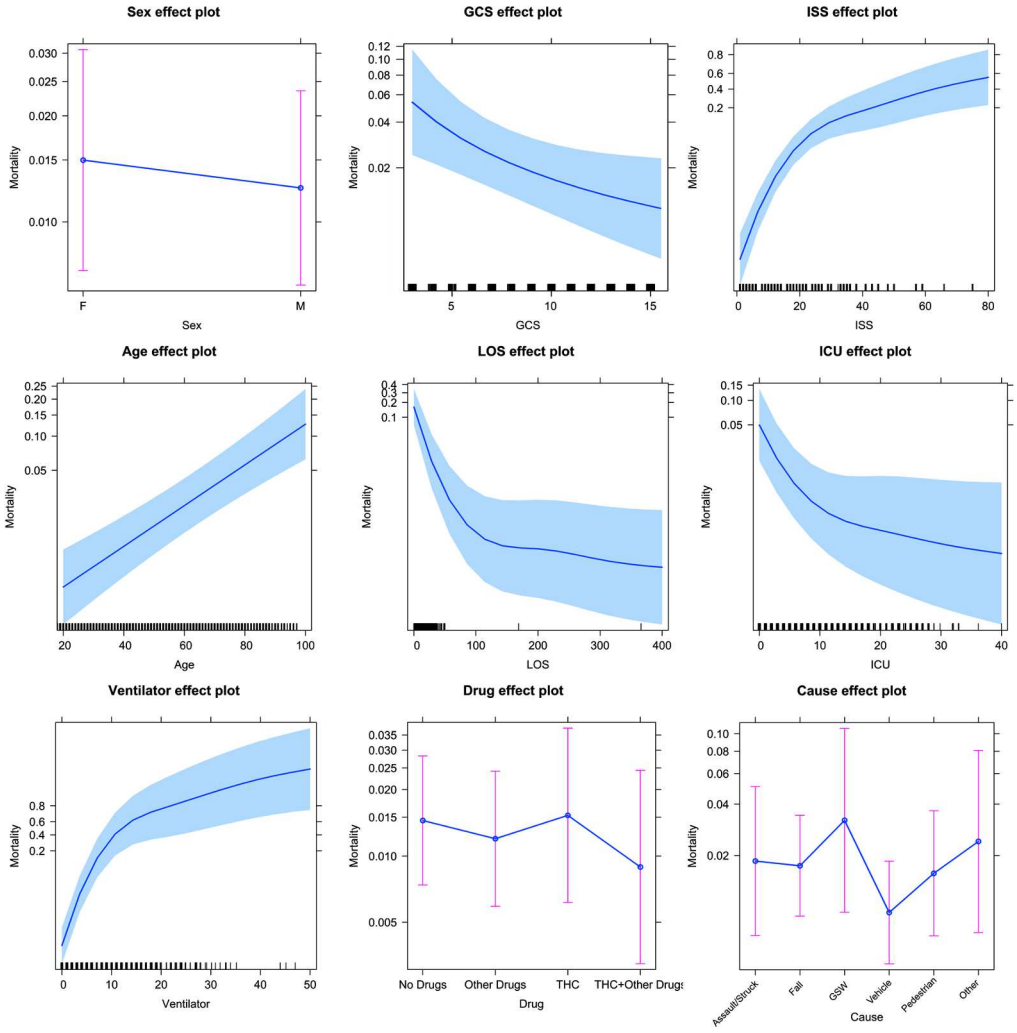

Fig. 2. Bivariate plots of predicted probabilities of mortality across individual predictors. Results are adjusted to probability distributions from the output of multivariate regression model. Shaded areas represent 95% confidence intervals. GCS = Glasgow Coma Scale; GSW = Gunshot Wound; ISS = Injury Severity Score; LOS = Length of stay; THC = Tetrahydrocannabinol.

6. Conclusion

We have found that after mild, moderate, and severe TBI, a positive THC screening was not an independent predictor of mortality at discharge when controlling for confounding variables. While the neuroprotective effects of marijuana in the setting of TBI have been demonstrated in preclinical studies, further research is needed to fully understand the relationship between marijuana and its metabolites and mortality outcomes in a clinical setting.

CRediT authorship contribution statement

John J. Leskovan: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing - review & editing. **Puja D. Patel:** Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **John Pederson:** Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Aaron Moore:** Investigation, Methodology, Writing - review & editing. **Amer A. faneh:** Investigation, Methodology, Writing - review & editing. **Laura R. Brown:** Investigation, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inat.2021.101139.

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