ORIGINAL ARTICLE

Sepsis in Traumatic Brain Injury: Epidemiology and Outcomes

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ABSTRACT: ***Background:*** Traumatic brain injury (TBI) is a leading cause of death and disability. Risk factors for in-hospital mortality include older age, co-morbidity, and TBI severity. Few studies have investigated the role of sepsis in individuals with TBI. ***Methods:*** We studied adult patients with TBI admitted to intensive care over a 5-year period. Patient characteristics were identified by linking clinical and administrative databases. Charts of individuals with TBI and sepsis were manually reviewed. Predictors of ICU and hospital mortality were identified using logistic regression modeling. ***Results:*** Four hundred eighty-six individuals with TBI were admitted to intensive care. Sixteen (3.3%) developed sepsis. Pneumonia was the most common source (94%). *Staphylococcus aureus* was the most common pathogen (75%). ICU lengths of stay (LOS) (12.2 days [interquartile range (IQR) 4.4–23.5] versus 3.7 days [IQR 1.7–8.2]; $p < 0.001$) and hospital LOS (28.0 days [IQR 11.8–41.4] versus 15.3 days [IQR 5.0–30.9]; $p = 0.017$) were longer in patients with TBI and sepsis. Sepsis was not associated with ICU (adjusted odds ratio [aOR] 0.51; 95%CI 0.12–2.27; $p = 0.38$) or hospital (aOR 0.78; 95% CI 0.21–2.96; $p = 0.78$) mortality, though age (aOR 1.02; 95% CI 1.00–1.04; $p = 0.014$ for hospital mortality), severe TBI (aOR 3.71; 95% CI 1.52–9.08; $p = 0.004$ for ICU mortality and 4.10; 95% CI 1.95–8.65; $p < 0.001$ for hospital mortality), and APACHE II score (aOR 1.19; 95% CI 1.11–1.28; $p < 0.001$ for ICU mortality and 1.22; 95% CI 1.14–1.31; $p < 0.001$ for hospital mortality) were. ***Conclusion:*** Sepsis in patients with TBI was not associated with mortality; however, sepsis was associated with increased health care utilization (ICU and hospital LOS).

RÉSUMÉ : Épidémiologie et évolution de l'état de santé de patients atteints de septicémie à la suite d'un traumatisme crânio-cérébral. ***Contexte*** **:** Les traumatismes crânio-cérébraux (TCC) sont une des principales causes de décès et d'invalidité. Parmi les facteurs de risque de mortalité hospitalière, on peut inclure un âge avancé, le fait d'être atteint d'une maladie concomitante et le niveau de gravité d'un TCC. Cela étant, peu nombreuses sont les études qui se sont intéressées à l'impact de la septicémie chez des individus victimes d'un TCC. ***Méthodes*** **:** Nous avons analysé les cas de patients adultes victimes de TCC ayant été admis aux soins intensifs, et ce, au cours d'une période de cinq ans. Les caractéristiques de ces patients ont été identifiées en reliant des bases de données cliniques et administratives. Les dossiers de patients à la fois victimes de TCC et ayant été atteints de septicémie ont été par la suite passés en revue. Fait à souligner, nous avons obtenu des prédicteurs de mortalité hospitalière et de mortalité survenue aux soins intensifs en ayant recours à une modélisation de régression logistique. ***Résultats*** **:** Au total, 486 individus victimes de TCC ont été admis aux soins intensifs ; 16 d'entre eux, soit 3,3 %, ont été atteints d'une septicémie. Le fait de souffrir de pneumonie s'est révélé la source de septicémie la plus courante (94 %) tandis que le staphylocoque doré est apparu comme le pathogène le plus commun (75 %). La durée de séjour des patients admis aux soins intensifs (12,2 jours [EI 4,4 – 23,5] contre 3,7 jours [EI 1,7 – 8,2] ; $p < 0,001$) et hospitalisés (28,0 jours [EI 11,8 – 41,4] contre 15,3 jours [EI 5,0 – 30,9] ; $p = 0,017$) s'est ainsi avérée plus longue chez les patients victimes de TCC et atteints de septicémie. Bien que la septicémie n'ait pas été associée à la mortalité de ceux admis aux soins intensifs (RCA 0,51 ; IC 95 % 0,12 – 2,27 ; $p = 0,38$) ou à l'hôpital (RCA 0,78 ; IC 95 % 0,21 – 2,96 ; $p = 0,78$), il reste cependant que l'âge (RCA 1,02 ; IC 95 % 1,00 – 1,04 ; $p = 0,014$ pour la mortalité hospitalière), des TCC de nature grave (RCA 3,71 ; IC 95 % 1,52 – 9,08 ; $p = 0,004$ pour la mortalité aux soins intensifs et RCA 4,10; IC 95 % 1,95 – 8,65 ; $p < 0,001$ pour la mortalité hospitalière) et les scores obtenus au système de classification APACHE II (RCA 1,19 ; IC 95 % 1,11-1,28 ; $p < 0,001$ pour la mortalité aux soins intensifs et RCA 1,22 ; IC 95 % 1,14 – 1,31 ; $p < 0,001$ pour la mortalité hospitalière) l'ont été. ***Conclusion*** **:** Le développement de la septicémie chez des patients victimes de TCC n'a pas été associé à une mortalité accrue. Cela dit, ce syndrome d'infection et d'inflammation a été associé à une utilisation plus importante de ressources hospitalières, que ce soit le recours à des soins intensifs et une durée de séjour accrue.

Keywords: Sepsis, Infection, Traumatic brain injury, Outcomes

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Introduction

In the USA, the incidence of traumatic brain injury (TBI) of all severity is 579 per 100,000 persons, equating to roughly 1.7 million cases of TBI per year.[1] Estimates of TBI in Canada range between 22 and 52 per 100,000 persons.[2] TBI is one of the leading causes of death and disability in the USA, with

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roughly 30% of all injury-related deaths involving TBI.[1] Approximately 25% of patients who acquire TBI die – with 17% dying at the site of injury and 6% in an acute care setting.[1]

In-hospital death rates following TBI vary widely, with estimates ranging between 4% and 28%.[3,4] Epidemiologic studies have identified a number of risk factors for in-hospital mortality following TBI, including older age, race, number of medical co-morbidities, total number of other traumatic injuries, and TBI severity.[5–7] Imaging classification systems such as the Marshall CT classification,[8] the Rotterdam CT score,[9] the Stockholm CT score,[10] and the Helsinki CT score[11] are all validated in predicting outcomes in patients with TBI. Clinical biomarkers including glial fibrillary acidic protein and S100B have also shown promise in the prognostication of patients with TBI.[12]

Nosocomial complications in patients with TBI are myriad and include venous thromboembolism, postoperative complications, healthcare-acquired infections, and sepsis. Patients with acute neurologic injury are at higher risk of developing respiratory failure and ICU-acquired sepsis, when compared with other critically injured patients.[13] To date, few studies have investigated the role of sepsis in patients with TBI.[7,14,15]

In this study, our objectives were to: (a) describe the epidemiology of sepsis in our TBI cohort and (b) to determine whether sepsis was associated with increased mortality or healthcare utilization in patients with TBI. We hypothesized that patients with TBI and sepsis would have increased mortality and longer hospital lengths of stay (LOS), when compared with TBI patients without sepsis.

Materials and Methods

We conducted a retrospective, observational, single-center study. The Research Ethics Board at the University of Alberta approved the study and obviated the need for informed consent (study number Pro00071672). STROBE guidelines for reporting of observational studies were followed.[16]

Inclusion Criteria

All adult patients (aged 18 or greater) with TBI admitted to the University of Alberta Hospital general and neurosurgical ICUs from January 1, 2012, to December 31, 2016, were included in the study.

Patients with TBI were identified using *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, Canada (ICD-10-CA) codes using the Data and Health Information Resources-Alberta Health Services Data Reporting Repository (DIMR-AHSDRR).[17] ICD-10-CA codes used to identify patients with TBI included S06 (S06.0–S06.1), S06.2 (S06.25–S06.26), S06.3 (S06.35–S06.36, S06.4–S06.6, and S06.9).

Patient characteristics including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Glasgow Coma Scale (GCS) score, Sequential Organ Failure Assessment (SOFA) score, ICU admission date, ICU discharge date, hospital discharge date, and ICU and hospital mortality were identified using an ICU medical information system (TRACER). Severe TBI was defined as GCS ≤ 8.

ICD-10-CA codes were furthered used to identify patients with TBI and sepsis. ICD-10-CA codes used to identify sepsis included A40 (A40.0–A40.3 and A40.8–A40.9), A41 (A41.0–A41.4), A41.5 (A41.50–A41.52 and A41.58), A41.8 (A41.80 and A41.88), A41.9, B37.7, R57.2, and R65.1. Charts of patients with TBI and sepsis were then manually reviewed for medical co-morbidities, sepsis source, and microbial etiology. For timing, the development of sepsis was defined as the time of in-hospital antibiotic prescription.

Statistical Analysis

Baseline characteristics of the cohort were expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate, for continuous variables. Categorical variables were expressed as a number and percentage.

Non-parametric tests (Mann–Whitney U) were used to determine differences between TBI patients with and without sepsis for continuous variables (as all were non-normal in distribution). Chi-square and Fisher's exact tests were used to compare categorical variables. Tests were two-tailed with an alpha of 0.05. Univariate logistic regression was performed to test for associations with mortality and reported as unadjusted odds ratios (OR). Variables of clinical significance and those with p-values ≤ 0.1 in univariate analyses were included in multivariable logistic regression modeling to evaluate the association with mortality. Adjusted odds ratios (aOR), 95% confidence intervals (95% CI), and p-values were generated to quantify the magnitude and precision of the estimate. Statistical analyses were performed using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY).

Results

A total of 486 patients with TBI were identified. Baseline characteristics can be found in Table 1. Of note, most patients were young males and had severe TBI (49%). In the entire cohort, 363 patients (74.7%) required intubation and mechanical ventilation. Median LOS in the ICU was 3.9 days (IQR 1.7–8.6) and in-hospital was 15.7 days (IQR 5.1–31.8). Eighty-six (17.7%) patients with TBI died in the ICU, while 119 (24.5%) with TBI died in the hospital.

Of the 486 patients with TBI, 16 (3.3%) developed sepsis (Table 1). All 16 patients were male, with 13 patients (81.3%) requiring intubation and mechanical ventilation. One patient of the 16 septic patients (6.3%) developed septic shock while in the ICU. Pneumonia was the predominant source of sepsis (94%, Table 2). Additional sources included skin and soft-tissue infection, colitis, and urinary tract infection. *Staphylococcus aureus* was the most commonly identified pathogen (Table 2, 12; 75%) – of which nine were methicillin-sensitive (MSSA) and three were methicillin-resistant (MRSA). Co-morbidities were rare, with alcohol use disorder being the most common (31%, Table 2). Eleven of 16 (68.8%) patients with TBI and sepsis had isolated head injuries, while the remaining 5 (31.2%) had additional traumatic injuries including long-bone fractures (three patients), pneumothorax (two patients), intra-abdominal injury (two patients), and hemothorax (one patient). Median time to the development of sepsis was 4.9 days (IQR 1–6).

Univariate comparisons between septic and non-septic TBI cohorts (Table 1) did not reveal significant differences in age, APACHE II score, or TBI severity. The percentage of males in the septic cohort, however, was higher compared to the non-septic cohort. SOFA scores were also higher in the septic

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Table 1: Baseline characteristics and univariate analyses examining associations with sepsis in TBI patients

	All patients ($n = 486$)	Sepsis no ($n = 470$)	Sepsis yes ($n = 16$)	p value
Age (median years, IQR)	45 (28–60)	45 (28–60)	43 (27–64)	0.91
Sex (male, %)	370 (76.1)	354 (75.3)	16 (100)	**0.023**
APACHE II (median, IQR)	17 (13–24)	17 (12–24)	20 (16–27)	0.075
GCS (median, IQR)	9 (4–13)	9 (4–13)	6 (3–11)	0.19
Severe TBI (%)	239 (49.2)	228 (48.5)	11 (68.8)	0.11
SOFA (median, IQR)	6 (4–9)	6 (4–8)	8 (7–11)	**0.001**
ICU LOS (median days, IQR)	3.9 (1.7–8.6)	3.7 (1.7–8.2)	12.2 (4.4–23.5)	**<0.001**
Hospital LOS (median days, IQR)	15.7 (5.1–31.8)	15.3 (5.0–30.9)	28.0 (11.8–41.4)	**0.017**
ICU mortality (%)	86 (17.7)	83 (17.7)	3 (18.8)	0.91
Hospital mortality (%)	119 (24.5)	114 (24.3)	5 (31.3)	0.52

APACHE = Acute Physiology and Chronic Health Evaluation; GCS = Glasgow Coma Score; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; SOFA = Sequential Organ Failure Score; TBI = traumatic brain injury. Severe TBI defined as GCS ≤ 8.
Bold values indicate statistical significance.

cohort (8 [IQR 7–11]) versus the non-septic cohort (6 [IQR 4–8]). While ICU and hospital mortality did not differ between groups, ICU LOS was longer in the septic group (12.2 days [IQR 4.4–23.5]) versus 3.7 days [IQR 1.7–8.2] in those without sepsis. Furthermore, hospital LOS was also longer in the septic group (28.0 days [IQR 11.8–41.4]), as compared with the group without sepsis (15.3 days [IQR 5.0–30.9]).

Univariate analyses revealed that severe TBI, APACHE II, and SOFA scores were associated with increased ICU mortality (Table 3). Similarly, severe TBI, APACHE II, and SOFA scores, in addition to age and sex, were all associated with increased hospital mortality (Table 4). Sepsis was not associated with mortality.

Multivariable logistic regression confirmed that sepsis was not a predictor of ICU (aOR 0.51, 95% CI 0.12–2.27, $p = 0.38$, Table 5) or hospital (aOR 0.78, 95% CI 0.21–2.96, $p = 0.78$, Table 6) mortality. Older age (aOR 1.02, 95% CI 1.00–1.04, $p = 0.04$, for hospital mortality), severe TBI (aOR 3.71, 95% CI 1.52–9.08, $p = 0.004$, for ICU mortality and 4.19, 95% CI 1.95–8.65, $p < 0.001$, for hospital mortality), and higher illness acuity (aOR 1.19 per point in APACHE II score, 95% CI 1.11–1.28, $p < 0.001$, for ICU mortality and 1.22, 95% CI 1.14–1.31, $p < 0.001$, for hospital mortality) were independently associated with mortality (Tables 5 and 6).

Discussion

This retrospective study of patients with TBI admitted to intensive care over a 5-year period did not demonstrate a significant association between the development of sepsis and ICU or hospital mortality. This is in contrast to the findings of Selassie *et al.* who demonstrated, in the largest study investigating the role of sepsis in TBI to date, that sepsis was associated with an increased risk of in-hospital death.[7]

In another study investigating the impact of non-neurological complications in patients with severe TBI, Corral *et al.* demonstrated that septic shock (but not sepsis) was associated with an increased risk of hospital mortality.[15] Similarly, in a retrospective analysis of 175 patients with TBI and sepsis, severe sepsis, or septic shock, Cardozo Junior *et al.* showed that only septic shock (and again, not sepsis) was associated with an increased risk of patient mortality.[14]

In our analysis, we did not discriminate between sepsis and septic shock. Though our study is similar in size to that of Corral *et al.* and Cardozo Junior *et al.*, it is challenging to make comparisons between the studies, given a number of key differences. In the study by Corral *et al.*, only patients with severe TBI (defined as GCS < 9 in their analysis) were included in their analysis, whereas our cohort included mostly (49%), but not solely, patients with severe TBI. Furthermore, the percentage of patients who developed sepsis in our study (3.3%) were markedly lower compared with their study (75%; which seems very high). While Cardozo Junior *et al.* did include patients with varying degrees of TBI, they subcategorized patients with a diagnosis of TBI into those with sepsis, severe sepsis, and septic shock in their analysis.

The percentage of patients who developed sepsis in our study, as mentioned earlier, were surprisingly low (3.3%), but similar to the incidence (1.0%) reported by Selassie *et al.*[7] Sellasie *et al.*, however, had a much larger sample size, with a total of 41,395 patients, and higher statistical power. As such, we believe our study was underpowered to detect an association between sepsis and mortality even if one does exist.

In keeping with other epidemiologic studies of TBI,[5–7] we found that TBI severity and illness acuity (as measured by the APACHE II score) were independent predictors of both ICU and hospital mortality. Age was also an independent predictor for hospital mortality. In addition, ICU and hospital LOS were

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Table 2: Co-morbidities, sepsis source, and microbial etiology in TBI patients with sepsis

Patient ID	Co-morbidities	Sepsis source	Cultures
TBI-1	PUD, MRSA cellulitis, ETOH abuse	Pneumonia	MRSA (sputum)
TBI-2	None	Pneumonia	MSSA (sputum)
TBI-3	Depression, ETOH abuse	SSTI	MSSA (skin, blood)
TB1-4	None	Pneumonia, colitis	HI (sputum), C diff (stool)
TBI-5	DMI, ETOH abuse	Pneumonia	HI (sputum, blood)
TBI-6	Hypothyroidism, lung CA	Pneumonia, UTI	MSSA (sputum), SM (sputum), EC (urine)
TBI-7	ETOH abuse	Pneumonia	MSSA (sputum)
TBI-8	None	Pneumonia	MSSA (sputum)
TBI-9	ETOH abuse	Pneumonia	BC (sputum, blood)
TBI-10	SCZ, IVDU	Pneumonia	MSSA (sputum, blood)
TBI-11	None	Pneumonia	MSSA (sputum)
TBI-12	None	Pneumonia	MRSA (sputum), PA (sputum)
TBI-13	None	Pneumonia	MSSA (sputum)
TBI-14	HTN, BPH, DMII, AD	Pneumonia	MSSA (sputum)
TBI-15	Retinitis pigmentosa	Pneumonia	MP (sputum)
TBI-16	None	Pneumonia	MRSA (sputum)

AD = Alzheimer's disease; BC = Bacillus cereus; BPH = benign prostatic hypertrophy; CA = cancer; C diff = *Clostridium difficile*; DMI = diabetes mellitus type I; DMII = diabetes mellitus type II; EC = *Escherichia coli*; ETOH = ethanol; HI = *Haemophilus influenzae*; HTN = hypertension; IVDU = intravenous drug use; MP = *Mycoplasma pneumoniae*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PA = *Pseudomonas aeruginosa*; PUD = peptic ulcer disease; SCZ = schizophrenia; SSTI = skin and soft-tissue infection; SM = *Serratia marcescens*; UTI = urinary tract infection.

Table 3: Univariate logistic regression analyses for ICU mortality in patients with TBI

ICU mortality	Unadjusted OR (95% CI)	*p* value
Age	1.01 (0.99–1.02)	0.19
Sex	0.63 (0.37–1.04)	0.07
Severe TBI	14.5 (6.8–30.8)	**<0.001**
APACHE II	1.26 (1.20–1.33)	**<0.001**
SOFA	1.42 (1.31–1.55)	**<0.001**
Sepsis	1.08 (0.30–3.86)	0.91

Bold values indicate statistical significance.

significantly longer in patients who developed sepsis, when compared with patients who did not develop sepsis.

In patients who developed sepsis the putative source was almost exclusively pulmonary (94%) and the microbial etiology

Table 4: Univariate logistic regression analyses for hospital mortality in patients with TBI

Hospital mortality	Unadjusted OR (95% CI)	*p* value
Age	1.02 (1.01–1.03)	**<0.001**
Sex	0.49 (0.31–0.77)	**0.002**
Severe TBI	11.9 (6.7–21.3)	**<0.001**
APACHE II	1.30 (1.23–1.36)	**<0.001**
SOFA	1.40 (1.29–1.51)	**<0.001**
Sepsis	1.42 (0.48–4.17)	0.52

Bold values indicate statistical significance.

Table 5: Multivariable logistic regression analyses for ICU mortality in patients with TBI

Variable	aOR (95% CI)	*p* value
Age	1.00 (0.98–1.02)	0.96
Sex	1.12 (0.57–2.21)	0.74
Severe TBI	3.71 (1.52–9.08)	**0.004**
APACHE II	1.19 (1.11–1.28)	**<0.001**
SOFA	1.08 (0.95–1.22)	0.25
Sepsis	0.51 (0.12–2.27)	0.38

Bold values indicate statistical significance.

Table 6: Multivariable logistic regression analyses for hospital mortality in patients with TBI

Variable	aOR (95% CI)	*p* value
Age	1.02 (1.00–1.04)	**0.014**
Sex	0.74 (0.39–1.39)	0.35
Severe TBI	4.10 (1.95–8.65)	**<0.001**
APACHE II	1.22 (1.14–1.31)	**<0.001**
SOFA	1.02 (0.91–1.15)	0.69
Sepsis	0.78 (0.21–2.96)	0.78

Bold values indicate statistical significance.

was mostly *Staphylococcus aureus* (75%). The median time to the development of sepsis was 4.9 days. In the 15 patients who developed pneumonia, 6 (40%) did so within 2 days of admission, suggesting a community-acquired pneumonia. The remaining nine developed pneumonia after 2 days of admission (range 3–20 days), implying hospital acquisition. Mechanistically, it remains unclear as to why head-injured patients appear to preferentially develop *Staphylococcus aureus* pneumonia, though the addition of blunt trauma[18,19] and/or pre-colonization of the nares by *Staphylococcus aureus*[20] are established risk factors.

According to the Canadian Institute for Health Information, the daily cost of an ICU admission in Canada is substantial, with

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an average cost per day of $3592.[21] Notably, this value increases to $4186 in teaching ICUs across Canada. Moreover, patients with TBI are particularly costly to the healthcare system. This is evidenced by a Canadian study that demonstrated that the mean acute care cost of patients with TBI was $19,083.[22] Similarly, a European study by Raj *et al.* showed that in patients with TBI, the mean university hospital cost was €19,568.[23] Taken together, and in the context of the present study, sepsis has the potential to dramatically increase ICU-associated healthcare costs for a given patient with TBI.

Despite its strengths, our study has a number of limitations. Although we included patients from multiple ICUs, the study was performed at a single center and, thus, may not be generalizable. Also, the use of an administrative database and the use of ICD-10-CA codes may have resulted in misclassification (for either sepsis and/or TBI). Moreover, our study was comparatively small, and likely underpowered to show an association between sepsis and mortality. In addition, APACHE II and SOFA scores were collected at the time of admission and may not have been truly reflective of illness and/or organ dysfunction at the time of sepsis diagnosis. And as with all observational studies, we were not able to infer causality, only associations. Lastly, there exists the possibility of residual confounding despite risk adjustment.

Conclusions

In this study, sepsis was rare in patients with TBI admitted to ICU, with an incidence of 3.3%. In those who did develop sepsis, pneumonia was the most common source and *Staphylococcus aureus* was the predominant pathogen. In keeping with previous studies, older age, TBI severity, and higher illness acuity were independently associated with mortality. Sepsis in patients with TBI was not associated with increased mortality; however, it was associated with increased healthcare utilization (ICU and hospital LOS).

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Conflict of Interest

The authors have no conflicts of interest to declare.

Statement of Authorship

DA designed the study, performed the chart review, and drafted the manuscript. DJK revised the manuscript. WIS designed the study, performed the statistical analysis, and revised the manuscript.

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