Clinics in Surgery

Research Article
Published: 13 Dec, 2021

Ultra-Early Infection and High Death Risk of Sepsis in ICU Patients with Traumatic Brain Injure

Wang Guang-Sheng[1], Zhou Ye-Ting[2], Wang Shao-Dan[3], Zhai Xiao-Lei[4], Wang Yuan-Wei[1], Wang Ying[1], Zhou Jin-Jin[1], and Tong Dao-Ming[1]*

[1]Department of Neurology, Affiliated Shuyang Hospital, Xuzhou Medical University, China

[2]Department of Surgery, Affiliated Shuyang Hospital, Xuzhou Medical University, China

[3]Department of Intensive Care Medicine, Affiliated Shuyang Hospital, Xuzhou Medical University, China

[4]Department of Neurosurgery, Affiliated Shuyang Hospital, Xuzhou Medical University, China

Abstract

Background: There are few previous reports of ultra-early predicting infection and sepsis after Traumatic Brain Injury (TBI). This study is to assess ultra-early infection and death risk of sepsis following TBI.

Methods: We retrospectively enrolled TBI patients with first 3 h interval from trauma in an ICU of China (from January 2015 to December 2017). We used the SIRS criteria to screen infection, and used SOFA criteria to identify sepsis after TBI. An outcome measure mainly was mortality at first 48 h.

Results: A total of 263 TBI patients were included in our study. Among 152 (57.8%) ultra-early infected person, the time of trauma to infection onset was in 1 h (median, range, 0.5-3). Among 118 (44.9%) sepsis within initial 48 h after trauma, the time of median from trauma to sepsis was 10.0 h (range, 1-48). Mortality of sepsis in TBI at initial 48 h was in 67.6%. Cox regression demonstrated that lower GCS score (OR, 0.8; 95% CI, 0.729-0.865), higher SOFA score (OR, 1.1; 95% CI, 1.041-1.151), less ICU days (OR, 0.8; 95% CI, 0.729-0.832), requiring mechanical ventilation (OR, 2.1; 95% CI, 1.332-3.593), and unused antibiotics in initial 3 h (OR, 2.3; 95% CI, 1.213-3.772) were related to the risk of early death in TBI with sepsis.

Conclusion: Sepsis was 44.9% of TBI patients, with high mortality at initial 48 h, suggesting that TBI patients with ultra-early infection have to be used antibiotics within initial 0.5 h to 1 h in the ICU.

Keywords: Sepsis; Infection; Traumatic brain injury; Coma; Antibiotics: Outcome

Abbreviations

TBI: Traumatic Brain Injury; ICU: Intensive Care Unit: SIRS: Systemic Inflammatory Response Syndrome; AUC: Areas under the Curve; SOFA: Sequential sepsis-related Organ Failure Assessment; qSOFA: Quick SOFA

Background

In the United States, over 1.7 million patients have an acute Traumatic Brain Injury (TBI) annually. According to statistics, over 60% of patients with severe TBI die or survive with severe disabilities. Clinical evidence shows that sepsis is highly correlated with adverse prognosis and contributing to majority of deaths in TBI [1-3]. Recently, the incidence of TBI patients with high rate of infection has increased [4,5]. At the same time, the number of ICU patients with TBI with sepsis has been increasing [5]. The mortality for sepsis was 48.2% of patients in ICU [6], and the mortality rate at 1 year hospital discharge was up to 72.0% [7]. To control the frequent sepsis, a recent study indicated that rapid antibiotics treatment within the first 3 h of sepsis can reduce hospital mortality [8]. Moreover, early goal-directed therapy can lead time to administration of first dose of antibiotics [9]. To the best of our knowledge, TBI with sepsis is still a neglected global public health problem, and there are few previous reports of ultra-early predicting infection after TBI. Our hypothesis was that unused antibiotics treatment within initial 3 h in ICU would result in high risk sepsis and increased mortality. If this hypothesis is confirmed, an emergency antibiotics treatment into the ultra-early management of TBI patients would have benefits for reduced risk of sepsis and high mortality.

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Correspondence:
Tong Dao-Ming, Department of Neurology, Affiliated Shuyang Hospital, Xuzhou Medical University, No. 9, Yingbin Road, Shuyang, Jiangsu 223600, China, Tel: +86-15950634718; Fax: +86-0527-83557553; E-mail: tongdaoming@163.com

Received Date: *21 Oct 2021*
Accepted Date: *08 Dec 2021*
Published Date: *13 Dec 2021*

Citation:
Guang-Sheng W, Ye-Ting Z, Shao-Dan W, Xiao-Lei Z, Yuan-Wei W, Ying Wang, et al. Ultra-Early Infection and High Death Risk of Sepsis in ICU Patients with Traumatic Brain Injure. Clin Surg. 2021; 6: 3375.

Methods

Design, setting and patients

A study of data from a database of patients who had undergone TBI at the authors' institution was retrospectively performed between January 2015 and December 2017. All procedures were performed by the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of Affiliated Shuyang Hospital of Xuzhou Medical University (2015-0001). Informed consent was obtained from the relatives of patients.

We identified patient who was over age of 18, with a TBI or with ultra-early infection. Moreover, most of the patients who were performed a brain CT scans were also underwent a thorax or abdominal CT scans on admission. The time for ultra-early infection events are defined as the time for infection is within 3 h of the trauma event onset to the emergency care in the ICU. Thus, in our data, all patients were selected ≤ 3 h from trauma onset to the moment of the medical monitored in the ICU.

Inclusion criteria for sepsis after TBI

Based on sepsis is at least over one acute organ failure caused by infection. In this study population, almost all patients had an acute brain failure due to sudden TBI events at initial. Thus, the inclusion criteria for sepsis after TBI had to include the following criteria: (1) a sepsis has to present one or more organ failure with evidence of extracranial infection or Systemic Inflammatory Response Syndrome (SIRS) criteria ≥ 2; (2) a brain failure not be explained by alone TBI other than with a secondary sepsis. We excluded those who were over 3 h from symptoms onset to the ICU. We also excluded the TBI patients in who did not have data due to death within first 3 h or transport out of the ICU.

Screening of infection and organ failure

We considered that the SIRS is the original intention of sepsis' definition, and resent studies have confirmed that the SIRS was significantly superior to the qSOFA for predicting infection/sepsis [10,11]. Thus, we used the SIRS criteria ≥ 2 to identify infection events within first 0.5 h to 1 h in ICU, The SIRS criteria is showed as follows: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) tachypnea greater than 20 respirations per minute or PCO2 less than 32 mmHg; (4) white blood cell count >12.0 × 10^9/L or <4.0 × 10^9/L, or >10% band forms.

A SOFA score was calculated for organ failure following TBI in ICU, and it was assessed during 24 h to 72 h or later. A SOFA score ≥ 2 was defined as acute organ failure for a specialized organ [12]. Using SOFA standard to evaluate brain failure was the following: GCS scores of 10 to12 indicated a slight brain failure (SOFA=2), and GCS scores of <6 indicated a severe brain failure (SOFA=4). In this population, most patients at initial were suddenly in coma (a GCS score <8 or a motor function score of GCS<6) due to acute TBI. Therefore, we had to use that a SOFA score of ≥ 2 did not be explained by alone TBI other than MODS with septic brain failure. The SOFA criterion for extracranial organ is shown as follow. Respiratory failure: PaO_2/FiO_2 ≤ 300; Cardiovascular failure: Hypotension (systolic pressure <90 mmHg or decrease >40 mmHg or mean arterial pressure <65 mmHg); Liver failure: Total serum bilirubin >2 mg/dL; Renal failure: creatinine >171 uml/L; Coagulation: Platelet count ≤ 100 × 10^9/L.

Data collection

The data collection of our study was included as follow: the demographics, time of injury to infection, injury mechanism, intracranial pathological finding of CT scans, initial GCS scores, vital sign data, laboratory data, SOFA score, time starting antibiotic treatment, mechanical ventilation, surgical procedure, length of ICU stay, and outcomes.

The primary outcome measure was mortality at the first 48 h. The second outcome measure was mortality at 60 days. Neurological outcome was evaluated following the Glasgow Outcome Scale (GOS) [13]. The authors (TDM and WSD) were to assess the outcomes. In order to assessment the outcomes, survival state was confirmed by the medical records. If the patient died after discharge, the information was obtained from his family. Follow-up was in October 2017 to February 2018. According to the inclusion criteria for sepsis after TBI, the patients were divided to TBI with sepsis group and TBI without sepsis group for statistic analysis.

Statistical methods

All statistical analyses were performed using a SPSS 10.0 computerized statistics package. Data are expressed by mean ± Standard Deviation (SD) and medians (IQR) or percentages. The baseline variables were compared by z tests or t tests. The Areas under ROC Curve (AUC) were measured by the ultra-early data for infection in ICU. If the univariate analysis were significant, a logistic-regression model was used to estimate the Odds Ratios (OR) and 95% Confidence Intervals (CIs). A Cox proportional model was used to determine the risk of death events. Kaplan-Meier curves were computed and compared with use of the log-rank test. A p-value <0.05 was considered statistically significant.

Results

A total of 356 head-injured patients (over 18 years old) were admitted during this period. We excluded those TBI patients with >3 h from onset to ICU (N=15), without medical data due to death within first 3 h (N=57), and transport out of the ICU (N=21). Finally, 263 TBI patients were included in our study (Figure 1).

The data of TBI patients are described in the Table 1. Most patients (193 out of 263) were males, with mean age of 54 years

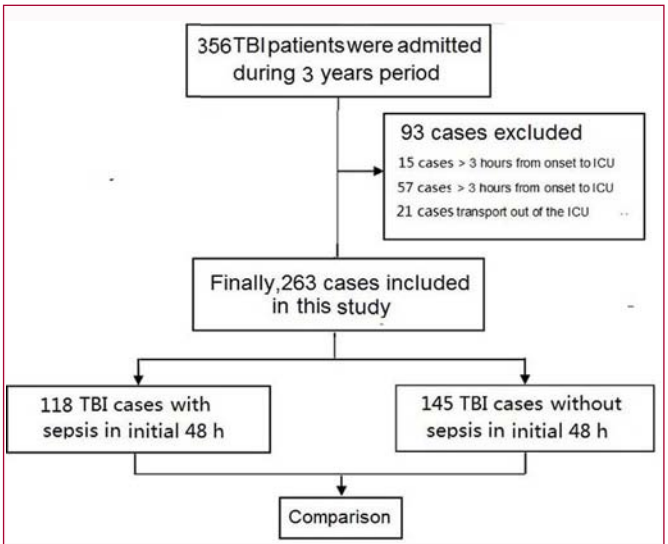

Figure 1: Study profile.

Table 1: Baseline characteristics of 263 patients with TBI in ICU.

Baseline characteristics	Value
Sex, n. (%)	
Male	193 (73.4)
Female	70 (26.6)
Age, year (mean ± SD)	54 ± 16.4
Median time from injury to ICU (hours, range) 1 (3.0)	
Injure Mechanism	
Road traffic collisions, n. (%)	155 (58.9)
Falls, n. (%)	108 (41.1)
Cycling falls, n. (%)	38 (35.2)
Falls from same level, n. (%)	30 (27.8)
Falls from height, n. (%)	26 (24.1)
Falls from Epilepsy, n. (%)	2 (0.1)
Median GCS score on admission, (range)	6 (3-8)
3-4 score, n. (%)	123 (46.8)
5-6 score, n. (%)	36 (13.7)
7-8 score, n. (%)	104 (39.5)
Head CT scan findings, n. (%)	
Subarachnoid hemorrhage, n (%)	244 (92.8))
Contusions, n. (%)	177 (67.3)
Subdural hematoma, n (%)	146 (55.5)
Intracerebral hemorrhage, n (%)	134 (51.0)
Epidural hematoma, n (%)	115 (43.7)
Other, n. (%)	57 (21.7))
Ultra-early infection events	152 (57.8)
Community-acquired pneumonia, n. (%)	79 (52.0)
Community-acquired skin/wound, n. (%)	68 (44.7)
Unknown, n. (%)	5 (3.0)
Positive body fluid culture, n (%)§	73 (48.0)
Median time from onset to infection (h, range)	1.0 (3)
From onset to infection within 0.5 hour, n (%)	6 (3.9)
From onset to infection within 0.5-1 hour, n (%)	121 (79.6)
From onset to infection within 1-2 hours, n (%)	13 (8.6)
From onset to infection within 2-3 hours, n (%)	12 (7.9)
Median time from trauma to sepsis (h, range)	10.2 (0.5-48)
Onset to sepsis within 0.5 hour, n (%)	0 (0.0)
Onset to sepsis within 1-3 hour, n (%)	23 (19.5)
Onset to sepsis within 3-24 hours, n (%)	74 (62.7)
Onset to sepsis within 24-48 hours, n (%)	21 (17.8)
Time of starting antibiotic treatment of 136 sepsis events	
Using antibiotic treatment within initial 3 h, n (%)	20/136 (14.4)
Starting antibiotics after 4 h on admission, n (%)	83/136 (61.0)
No using antibiotics within initial 3 h, n (%)	116/136 (85.3)
Sepsis-associated multiple organ failure, n (%)	109/136 (80.1)
Acute respiratory failure, n (%)	118/136 (87.0)
Sepsis associated brain failure, n (%)	114/136 (83.7)
Septic shock, n (%)	59/136 (43.7)
Acute renal failure, n (%)	35/136 (25.6)
Acute hepatic failure, n (%)	32/136 (23.7)
DIC, n (%)	2/136 (0.15)
Traditional mannitol treatment, n (%)	263 (100.0)
Intubated/mechanical ventilation, n (%)	212 (80.6)
Craniectomy, n. (%)	210 (79.8)

ICU: Intensive Care Unit; TBI: Traumatic Brain Injury; §: Including blood culture, sputun culture, and urine culture

Table 2: The results of univariate analysis in ICU TBI patients with sepsis and without sepsis in initial 48 hours (n=263).

Variable	TBI with sepsis in initial 48 h (118)	TBI without sepsis In initial 48h (n=145)	*P* Value
Male gender, n (%)	86 (72.9)	110 (75.9)	0.67
Age, (years, mean ± SD)	55.6 ± 16.4	53.5 ± 16.7	0.325
Median time from injury to ICU, (h, range)	1.1 (2.5)	1.1 (2.5)	0.39
GCS score, (mean ± SD)	5.0 ± 1.9	6.5 ± 2.8	<0.001
MAP, (mmHg, mean ± SD)	101.3 ± 29.3	100.7 ± 27.0	0.879
Respiratory rate, (breaths/min, mean ± SD)	21.0 ± 10.8	18.7 ± 7.1	0.039
Body temperature, (°C, mean ± SD)	36.6 ± 7.9	36.7 ± 9.5	0.961
Heart rate,(beats/min, mean ± SD)	91.0 ± 21.0	88.7 ± 22.8	0.371
leukocyte count, (× 10^9/l, mean ± SD)	16.0 ± 6.4	13.0 ± 4.7	<0.001
SIRS. (median, range)	3.4 (4.0)	1.9 (4.0)	0
Blood glucose, (mmol/l, mean ± SD)	9.7 ± 3.4	9.2 ± 3.6	0.205
Blood lactic acid, (mmol/l, mean ± SD)	3.5 ± 2.6	3.0 ± 2.4	0.175
C-reactive protein,(mg/L, mean ± SD)	119 ± 19.7	108 ± 27.3	0.043
SOFA score, (mean ± SD)	5.9 ± 2.5	2.2 ± 3.1	<0.001
ICU days, (mean ± SD)	6.1 ± 6.2	3.8 ± 4.7	0.001
No using antibiotic in initial 3 hours, n (%)	107 (90.7)	118 (81.4)	0.035
Requiring mechanical ventilation, n (%)	107 (90.7)	105 (72.4)	0
Craniectomy in initial 48 hours, n (%)	46 (39.0)	60 (41.4)	0.706
Mortality in initial 48 hours, n (%)	92 (67.6)	26 (20.5)	0

ICU: Intensive Care Unit; TBI: Traumatic Brain Injury; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential [Sepsis-Related] Organ Failure Assessment; GCS: Glasgow Coma Scale

(range, 18 to 91 years). Among 152 (57.8%) ultra-early infection, the median time of trauma to infection onset was an hour (range, 0.5-3). Among 118 (44.9%) sepsis events within initial 48 h after trauma onset, the time of trauma to sepsis was 10.0 h (median, range, 1-48). Using SIRS criteria for ultra-early predicting infection in TBI patients showed that the AUC was 0.773 (95% CI, 0.708-0.837), sensitivity 97%, specificity 39% (Figure 2). The prevalence peak of sepsis was within 3 h to 24 h (62.7%.74/118) after trauma onset, while only 19.5% of sepsis occurred within initial 3 h (Table 1). The time of starting antibiotic treatment due to unknown this ultra-early infection was delayed: only 14.4% case within initial 3 h used antibiotics treatment; 61.0% of the patients were in 4 h later on admission. Thus, unused antibiotics treatment within initial 3 h was in 85.3% of the patients.

Univariate analysis in ICU patients with TBI with sepsis and without sepsis in initial 48 h is presented in the Table 2. We found that GCS score (5.4 ± 2.3 *vs.* 6.3 ± 2.8, p=0.003), SIRS criteria (2 *vs.*

Table 3: Logistic regression analysis to identify the early predictors factors in TBI patients with sepsis.

Variable	OR	95% CI for OR	*p* value
GCS score	0.7	0.636-0.859	0.000
SIRS	2.1	1.556-2.705	0.000
SOFA score	1.5	1.361-1.736	0.000

GCS: Glasgow Coma Scale; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential [Sepsis-Related] Organ Function Assessment

Table 4: Cox regression analysis in TBI patient with sepsis.

Variable	OR	95% CI for OR	*p* value
No using antibiotic within initial 3h	2.2	1.213-3.772	0.007
GCS score	0.8	0.729-0.865	0.000
SOFA score	1.1	1.041-1.151	0.000
ICU days	0.8	0.729-0.832	0.000
Requiring mechanical ventilation	2.1	1.332-3.593	0.002

TBI: Traumatic Brain Injury; GCS: Glasgow Coma Scale; SOFA: Sequential [Sepsis-Related] Organ; ICU: Intensive Care Unit

1, p<0.001), WBC (15.9 ± 6.1 *vs.* 12.7 ± 4.8, p<0.001), respiratory rate (21.3 ± 10.4 *vs.* 18.1 ± 6.9, *p*=0.003), ICU days (6.5 ± 6.1 *vs.* 3.0 ± 4.1, p<0.001), C-reactive protein (119 ± 19.7 *vs.* 108 ± 27.3, p<0.05), SOFA scores (6.2 ± 2.6 *vs.* 1.4 ± 2.0, p<0.001), and unused antibiotic in initial 3 h had significantly differences between the two groups. The respective mortality in TBI patients with sepsis was significantly higher (67.6% *vs.* 20.5%, p<0.001) at initial 48 h than that those without sepsis.

When these significant factors are selected into logistic regression model, only lower GCS score (OR, 0.7; 95% CI, 0.6-0.9), SIRS ≥ 2 (OR, 2.1; 95% CI, 1.6-2.7), and higher SOFA score (OR, 1.5; 95% CI, 1.4-1.7) were related to the predicting factors for TBI patients with sepsis (Table 3).

Based on Kaplan-Meier that included TBI with or without septic events within 48 h, the Log Rank for worse survival was significantly related to TBI patients with sepsis events (Log Rank, 8.0; *p*<0.005) (Figure 3).

By Cox regression model analysis, the independent factors of mortality in TBI patients with sepsis were related to lower GCS score (OR, 0.8; 95% CI, 0.729-0.865, *p*<0.001), higher SOFA score (OR, 1.1; 95% CI, 1.041-1.151, *p*<0.001), less ICU days (OR, 0.8; 95% CI, 0.729-0.832, *p*<0.001), requiring mechanical ventilation (OR, 2.1; 95% CI, 1332-3.593, p<0.005), and unused antibiotics in first 3 h (OR, 2.2; 95% CI, 1.213-3.772, *p*<0.001) (Table 4).

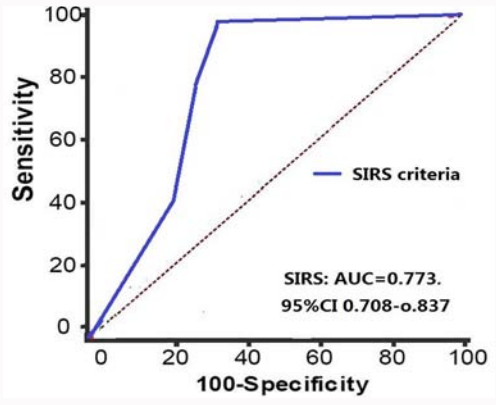

Figure 2: Using SIRS criteria for ultra-early predicting infection in TBI patients within initial 3 hours from trauma onset to the ICU showed that the AUC was 0.773 (95% CI, 0.708-0.837), sensitivity 97%, specificity 39%.

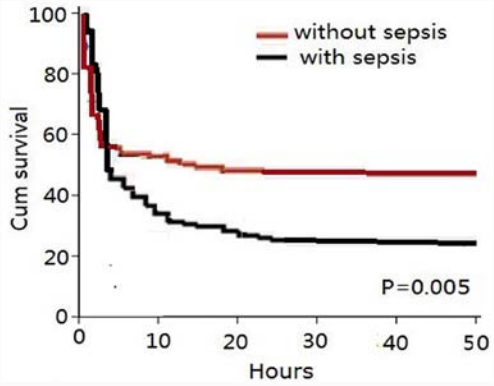

Figure 3: Kaplan-Meier survival curves that included TBI patients with and without sepsis events within 48 hours, the Log Rank for worse survival was significantly associated with TBI patients with sepsis events (Log Rank, 8.0; *p*<0.005).

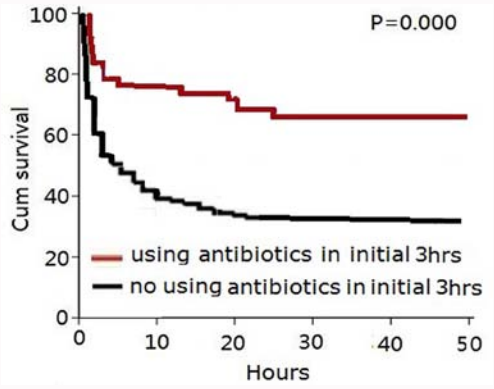

Figure 4: Kaplan-Meier survival curves showed that included TBI patients with and without undergo antibiotic treatment within the first 3 hours following trauma. The Log Rank for worse survival was significantly associated with TBI patients who did not undergo antibiotic treatment within the first 3 hours (Log Rank, 15.0; *p*<0.001).

By Kaplan-Meier survival curves analysis, the TBI patients who did not use antibiotics within the first 3 h following trauma were related to worse outcomes when compared with those who had used antibiotics in the first three hours. The Log Rank for worse survival was significantly related to TBI patients without using antibiotics in the first three hours (Log Rank, 15.0; *p*<0.001) (Figure 4).

During 60 days after admission, we diagnosed 18 cases with sepsis, which was not predicted by ultra-early using SIRS criteria. Finally, among 263 patients, we diagnosed 136 (51.7%) sepsis events. The MODS was the most common manifestation (109/136). Of them, septic organ failure at the top of the list was acute respiratory failure (87%), followed by septic brain failure (83.7%), septic shock (33.7%) (Table 3). During 60 days follow-up, the GOS score of 1 was higher in TBI patients with sepsis than that those without sepsis (73.2% *vs.* 55.9%, *p*=0.005).

Discussion

Although the prevalence of infection in TBI patients was high [2,4,14] and the risk of TBI with sepsis increased from 10% in 1992 [15] to 75% in 2012 [5], the ultra-early risk for infection is unclear previously. In this study, the SIRS criteria were used to screen the infection events, which were clearly shown that the prevalence of

infection within initial 3 h among TBI patients was up to 57.8%. While 44.9% of sepsis events in TBI patients who had a median time from onset to infection only 1.0 h were diagnosed by jointing SIRS and SOFA criteria, and the prevalence peak of sepsis was within 3 h to 24 h after trauma onset. By multivariate logistic regression analysis, our study confirmed that low GCS score, SIRS ≥ 2, and high SOFA score were related to predicting factors for TBI patients with sepsis.

We found that the mortality of sepsis at initial 48 h following TBI was in 67.6%. Interestingly, we found that craniectomy did not differ between the groups with or without sepsis, but an increase risk of death of greater than 8.0 fold was observed in TBI patients with sepsis compared to those without sepsis based on an unregulated risk analysis within 48 h.

To the best of our knowledge, patients with TBI show that bad outcome is due to massive direct parenchymal injury, but this is not the only pathophysiology. The insulted brain further get injured by secondary sepsis may exacerbate ischemic brain injury that would lead to a high rate of poor outcome [15-17]. Especially in patients with multiple organ failure may be induced to aggravate brain injure even further [18]. And the development of MODS is related a dysregulated inflammatory mechanisms [18]. Therefore, our study indicated that the secondary sepsis contributed to a high risk of death in TBI patients.

Moreover, Cox regression analysis revealed that the risk factors for worse survival in sepsis after TBI were related to the decreased GCS scores, less ICU days, requiring mechanical ventilation, increased SOFA scores, and unused antibiotics within initial 3 h. Though the effect of the decreased GCS scores, less ICU days, requiring mechanical ventilation, and increased SOFA scores on outcome have been recognized [19-22], this study showed that unused antibiotics in initial 3 h was associated with a higher risk on outcome. Therefore, ultra-early antibiotics treatment has to be performed for improving outcomes.

Although rapidly antibiotics treatment for sepsis is need [23,24], one recent study indicated the time of rapid administration of antibiotics for sepsis is within 3 h after SIRS onset [8]. Importantly, we found that the ultra-early infection events were within 0.5 h to 1 h after TBI. However, most of patients in the first three hours following trauma was not treated with antibiotics, leading to an over 15-fold increase in the risk of death due to sepsis. Therefore, these findings indicate that the "golden hour" of rapid administration of antibiotics for sepsis has to be used the antibiotic IV added into the first bottle of liquid within the initial 1.0 h in the ICU.

Some restrictions must be taken into account. First, excluding some patients with TBI in this set may be created an overestimation of incidence of sepsis, but the highest sepsis rate of 75% in patients with TBI on an ICU has been reported [5]. In addition, some studies confirmed that septic patients were associated with subcortical ischemic lesions [25,26] and microabscesses [27]. Therefore, it is very important that TBI patients with sepsis should be performed a brain MRI scan and CSF analysis, however, these examination in this study were rarely performed. Thus, our data about the prevalence of septic brain dysfunction can be under-estimated.

Conclusion

We found that secondary sepsis which had an ultra-early infection event was 44.9% of TBI patients, and with the mortality at initial 48 h was 67.6%. These findings suggest that TBI patients with ultra-early infection have to be treated with antibiotics within 0.5 h to1 h of infection/SIRS.

Ethics Approval and Consent to Participate

Approval was provided by the Institutional Review Board of the Shuyang People's Hospital, China.

Authors' Contribution

TDM and ZYT were responsible for the study concept and design. TDM, WSD, ZXI, WGS, and WYW were responsible for data acquisition and analysis. TDM, WGS, WYW were responsible for drafting the manuscript. All authors read and approved the final manuscript.

Acknowledgement

We would like to thank everyone who contributed to the study, namely, the nurses and physicians who recorded the patient data and the related senior experts for reviewing the medical records in the ICU.

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