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ORIGINAL ARTICLE

Risk factors for sepsis in Korean trauma patients

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Abstract
Purpose Sepsis in severely injured patients is one of the leading causes of death in hospitals. The incidence of and risk factors for sepsis after trauma have been studied outside, but not within Korea. Therefore, this study investigated the incidence of sepsis and the independent risk factors for sepsis in moderately to severely injured patients in Korea.
Methods The electronic medical records of patients who visited the emergency department from January 2010 to December 2012 were reviewed retrospectively. Patients older than 18 years of age with an Injury Severity Score (ISS) greater than or equal to nine points were included.
Results A total of 183 patients met the study inclusion criteria. The median ISS was 14 (range 9–17) points and 15 (8 %) patients developed sepsis. The patients' age [adjusted OR, 1.053; 95 % confidence intervals (CI), 1.015–1.094], ISS (adjusted OR, 1.114; 95 % CI, 1.046–1.187), and emergency surgery (adjusted OR, 3.727; 95 % CI, 1.051–13.221) were independent risk factors for post-traumatic sepsis.
Conclusions Among the risk factors identified in the literature, our research confirmed only the patients' age and ISS as risk factors for sepsis after trauma, and, additionally, identified emergency surgery as a risk factor in Korean patients. Therefore, trauma patients who have any of the risk factors mentioned above have a high risk of post-traumatic sepsis, which requires certain precautionary clinical measures.

Keywords Injury · Risk factor · Sepsis · Trauma

Introduction

As first aid and hospital procedures for the management of trauma patients have developed, the overall mortality of injured patients has become lower in recent years [1–3]. However, mortality in severely injured patients who survive after initial resuscitation is still high if trauma-related complications such as sepsis or multiple organ dysfunction syndrome (MODS) occur [4]. Moreover, these complications are closely related to the death of trauma patients in the intensive care unit (ICU) [5].

Sepsis in severely injured patients is one of the leading causes of death in the later stage of trauma; therefore, early recognition of the risk factors for injury-related complications may help to reduce mortality in the ICU. It is necessary to know what factors are related to the development of post-traumatic sepsis.

There are several studies of the incidence of and risk factors for sepsis after trauma in settings outside Korea [4–7], but there have been no studies of this type in Korea. The proportion of cases of blunt trauma among patients experiencing severe trauma is high, while the incidence of penetrating injury is relatively low in Korea. Due to these differences in the type of injuries sustained, the results of studies of post-traumatic sepsis in Korea may be different from those of other studies.

In this study, we investigated the incidence of sepsis among trauma-related complications. We also identified

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independent risk factors for post-traumatic sepsis in Korea and compared these results with those of other studies.

Patients and methods

Study population

This study included trauma patients who visited the emergency department in Korea University Ansan Hospital from January 2010 to December 2012. Patients who were admitted to the ICU with traumatic injury and who were aged 18 years or older were included in this study. Patients were excluded after chart review if they presented with an Injury Severity Score (ISS) <9, or if they died within 72 h of admission since this made it impossible to identify the development of sepsis.

Definitions

Sepsis was defined as the presence (probable or documented) of infection, together with systemic manifestation of infection [8, 9]. Infection was defined as a clinical infection source such as pneumonia, urinary tract infection, wound infection or bacteremia, meaning positive blood cultures, which were thought not to be contaminated. Systemic manifestation was defined by the presence of at least three systemic inflammatory response syndrome (SIRS) criteria. Mild and moderate to severe injury was defined by an ISS of $\leq$15 and >15, respectively. Emergency surgery was defined as operative procedures that were performed within 24 h of presentation to the emergency room (ER).

Methods

The patients' electronic medical records were reviewed retrospectively. The data collected were age, gender, vital signs, presence of shock at ER presentation (systolic blood pressure <90 mmHg), type of injury, results of blood tests on admission, Glasgow Coma Scale (GCS) score, ISS (which was calculated using the final diagnosis at discharge), incidence of transfusion, amount of transfused packed red blood cells (pRBC) and fresh frozen plasma (FFP), incidence of mechanical ventilation and incidence of emergency surgery. The development of sepsis and mortality were evaluated as outcomes.

Statistical analysis

Data are presented as medians $\pm$ interquartile range for continuous variables and as percentages with 95 % confidence intervals for incidence rates. Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables were applied to the comparison of two groups. A multivariable analysis was performed by stepwise logistic regression with the predictors associated with sepsis. The variables that were potential predictors for post-traumatic sepsis were selected from the results obtained in our study and other previous studies. Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered significant.

Results

During the study period, 211 patients with traumatic injury were admitted to the ICU. Of these eligible patients, 28 were excluded if: they were under 18 years old ($n = 4$), any data were missing ($n = 3$), they presented with ISS <9 ($n = 16$), or if they died within 72 h of admission ($n = 5$). Therefore, a total of 183 patients were enrolled in this study (Fig. 1).

Patients had a median age of 45 (35–58) years and 127 (69.4 %) were male. Blunt injury was present in 165 (90.2 %) patients. The median ISS was 14 (9–17) points and 15 (8 %) patients developed sepsis. Emergency surgery was performed on 44 (24 %) patients. The median duration of hospital stay was 18 (11–31) days. Of the total of 183 patients, 5 (2.7 %) patients died during hospitalization. The patient demographics and characteristics are summarized in Table 1.

Univariable analysis was performed in sepsis and non-sepsis groups (Table 2). The age was higher, but not significantly so in the group of patients with sepsis (55 vs. 46, $p = 0.051$). There were no sex differences in either group (male; 66.7 vs. 69.6 %, $p = 0.775$). Patients with sepsis showed a high ISS (22 vs. 15, $p = 0.006$) and were injured more severely, as indicated by an ISS greater than 15 (80.0 vs. 47.0 %, $p = 0.016$). Hypotension in the ER was similar in both groups (6.7 vs. 9.5 %, $p = 1.000$). All patients with sepsis suffered blunt trauma (blunt; 100.0 vs. 89.3 %, $p = 0.369$). Post-traumatic sepsis was significantly associated with the incidence of transfusion (60.0 vs. 32.7 %, $p = 0.047$), with septic patients receiving, in particular, significantly higher rates of transfusion of pRBC (5 vs. 0, $p = 0.017$) and FFP (2 vs. 0, $p = 0.011$) units. However, the massive transfusion rate was not significantly different between groups (6.7 vs. 6.5 %, $p = 1.000$). There was a trend towards increased emergency surgical treatment in patients with sepsis, but this was not significantly different between groups (46.7 vs. 22.0 %, $p = 0.053$). Five patients died, with one in the sepsis group and the other 4 in the non-sepsis group. The mortality rate was not significantly different between groups (6.7 vs. 2.4 %, $p = 0.370$).

A multivariable analysis was performed by stepwise logistic regression with a total of seven variables. The

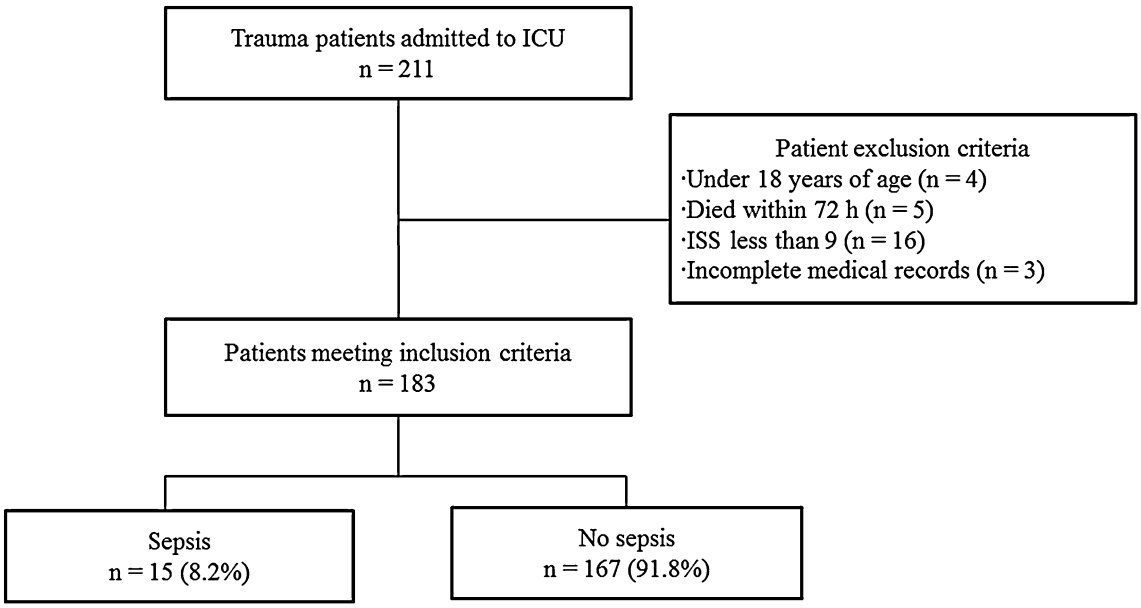

Fig. 1 Flow diagram of patient enrollment

Table 1 Demographics and clinical characteristics of study patients

	Number ($N = 183$)	Median (quintile)
Age (years; median)		45 (35–58)
Male (%)	127 (69.4)	
Injury type		
Blunt (%)	165 (90.2)	
Penetrating (%)	18 (9.8)	
GCS score (score; median)		15 (14–15)
ISS (score, median)		14 (9–17)
SBP (mmHg; median)		130 (110–145)
Shock[a] (%)	17 (9.3)	
Sepsis (%)	15 (8.2)	
Pneumonia (%)	6 (3.3)	
Urinary tract infection (%)	4 (2.2)	
Wound infection (%)	3 (1.6)	
Uncertain[b] (%)	4 (2.2)	
Emergency surgery[c] (%)	44 (24.0)	
Prophylactic antibiotics (%)	176 (96.2)	
Length of hospital stay (days; median)		18 (11–31)
Mortality (%)	5 (2.7)	

ISS Injury Severity Score, *GCS* Glasgow Coma Scale, *SBP* systolic blood pressure, *ER* emergency room

[a] SBP < 90 mmHg at the ER

[b] Bacteremia of uncertain origin

[c] Operative procedures within 24 h of ER presentation

variables that were analyzed as potential predictors of sepsis were ISS, incidence of transfusion, amount of transfused pRBC and FFP, selected from our study, and age, gender, and emergency surgery, selected from previous studies. The following variables were found to be independent risk factors for post-traumatic sepsis: age, ISS, and emergency surgery. These results are presented in Table 3.

Discussion

It is known that there are three time-separated peaks in the incidence of post-traumatic death [10, 11]. The first deaths occur within 1 h of the immediate response to the trauma. The second deaths occur within 24 h of trauma, from severe head injuries or hypovolemic shock. Even if patients survive these two stages, a third peak in the incidence of death occurs due to other complications such as MODS or sepsis. Hence, in order to reduce the incidence of post-traumatic death, there is a need for appropriate approaches to these three stages. This is especially true for the third peak of death, the incidence of which tends to be the subject of much attention from those investigating trauma.

According to the 2007–2008 National Trauma Data Bank, the incidence of sepsis in patients with moderate to severe injury is 1.4 % [12]. The occurrence of sepsis during post-traumatic events was found to be 2 % in Osborn et al. [4], while Wafaisade et al. [7] indicated that 10 % of trauma patients developed sepsis. The incidence of post-traumatic sepsis ranged from 1.4 to 14.4 % in previous research [12, 13]. One reason for such differences in the occurrence rate of post-traumatic sepsis is thought to be the differences in the injury severity in the patients in each study. The patients in our research had an ISS of 9 or more, with an average ISS of 14. Among these patients, 8 % developed

Table 2 Comparison of clinical characteristics and outcomes in septic and non-septic patients

Variable	Sepsis $n = 15$ (8.2 %)	No sepsis $n = 167$ (91.8 %)	p
Age (years; median)	52 (41–77)	44 (35–55)	0.051
Male (%)	10 (66.7)	117 (69.6)	0.777
Blunt trauma (%)	15 (100.0)	149 (89.3)	0.369
GCS score (score; median)	15 (10–15)	15 (14–15)	0.095
ISS (score; median)	18 (16–29)	14 (9–17)	0.005*
ISS ≥ 15 (%)	12 (80.0)	79 (47.0)	0.016*
SBP (mm Hg; median)	132 (110–152)	130 (110–144)	0.404
Shock[a] (%)	1 (6.7)	16 (9.5)	1.000
Heart rate (beats/min; median)	92 (86–104)	84 (74–96)	0.075
Hemoglobin[b] (g/dL; median)	13.1 (12.2–14.4)	14.2 (12.7–15.1)	0.287
WBC[b] (nL^{-1}; median)	12.6 (9.6–17.8)	11.7 (8.6–15.3)	0.539
Platelets[b] (nL^{-1}; median)	281 (235–314)	271 (217–323)	0.627
Prothrombin time[b] (INR; median)	12.3 (11.3–13)	12 (11.6–12.6)	0.598
Transfusion[c] (%)	9 (60.0)	55 (32.7)	0.047*
pRBC (units; median)	5 (0–7)	0 (0–3)	0.017*
FFP (units; median)	2 (0–12)	0 (0–0)	0.011*
Massive transfusion[d] (%)	1 (6.7)	11 (6.5)	1.000
Emergency surgery[e] (%)	7 (46.7)	37 (22.0)	0.053
Mechanical ventilation (%)	2 (13.3)	10 (6.0)	0.256
Hospital days (days; median)	107 (31–138)	17 (10–27)	<0.001*
Mortality (%)	1 (6.7)	4 (2.4)	0.370

GCS Glasgow Coma Scale, *ISS* Injury Severity Score, *SBP* systolic blood pressure, *ER* emergency room, *WBC* white blood cells, *INR* international normalized ratio, *pRBC* packed red blood cells, *FFP* fresh frozen plasma

* $p < 0.05$

[a] SBP < 90 mmHg at ER

[b] Blood tests on admission

[c] Transfused in ER and ICU

[d] Transfused over 10 pRBC units for 24 h

[e] Operative procedures within 24 h of ER presentation

sepsis. The incidence of sepsis in other studies with similar ISS were found to be similar to those in our study.

Despite the fact that, recently, overall mortality in severely injured patients is decreasing, there is no improved outcome in patients with post-traumatic sepsis [5]. According to Osborn et al., in patients with post-traumatic sepsis, the mortality rate is 23.1 %, while Wafaisade et al. indicated that the mortality rate is 19.5 %, suggesting that post-traumatic sepsis patients possess a higher mortality rate than non-traumatic sepsis patients. However, in our study, there were five deaths, whereby one patient died on the 22nd day of hospitalization due to sepsis and multi-organ failure, and the other four patients died due to progression of brain edema after traumatic cerebral hemorrhage. This mortality rate was relatively low, such that there was only one case of death caused by sepsis, and thus this study

Table 3 Independent risk factors for sepsis after trauma (multivariable analysis using a stepwise logistic regression model with backward variable selection)

Variable	Odds ratio (95 % confidence intervals)	p
Age	1.053 (1.015–1.094)	0.006*
ISS	1.114 (1.046–1.187)	0.001*
Emergency surgery[a]	3.727 (1.051–13.221)	0.042*

The logistic regression model was performed with seven variables (age, gender, ISS, transfusion, pRBC, FFP, emergency surgery)

ISS Injury Severity Score, *pRBC* packed red blood cells, *FFP* fresh frozen plasma

* $p < 0.05$

[a] Operative procedures within 24 h of ER presentation

[b] Transfused in ER and ICU

failed to establish the correlation between death and occurrence of sepsis in moderately to severely injured patients.

Osborn et al. reported the risk factors for sepsis as male gender, ISS, Revised Trauma Score (RTS), and GCS score. In Wafaisade et al., the risk factors were age, male gender, the presence of comorbidity, GCS score, ISS, Abbreviated injury $\text{scale}_{\text{thorax}}$ (AIS), number of injuries, amount of transfused pRBC, number of surgeries, and laparotomy. However, our study was only able to confirm some of these risk factors reported by other researchers. This may be due to differences in the number of patients, trauma mechanism (most of which were blunt injury), and the severity of injury (median ISS was 14 in our study).

In the present study, it was found that age was an independent risk factor for the development of sepsis. Age is also strongly correlated with sepsis development in non-trauma patients, as well as in trauma patients [14]. As patients' age increases, differences appear in their health status, and consequently there are increased comorbidities, which contribute to the failure to establish effective and adequate defense mechanisms in the early stages of trauma [15].

Trauma in itself affects a patient's immune system and this is highly correlated to the severity of the Trauma [10, 11, 16–21]. The ISS can be used as an index that reflects the severity of the trauma, and indeed we confirmed that there was a greater occurrence of sepsis in moderately to severely injured patients with an ISS greater than 15, and that ISS was an independent risk factor for post-traumatic sepsis in multivariable analysis.

Some authors have indicated that allogenic transfusion is the cause of post-traumatic infection and SIRS after injury [6, 22]. It is known that the contaminating leukocytes and the inflammatory mediators within blood units are associated with these reactions. In Moore et al. [23], the complications after trauma were related to blood transfusion in a dose-dependent relationship. In our research, pRBC or FFP transfusion quantities were assessed in relation to the occurrence of sepsis using univariable analysis. However, multivariable logistic regression analysis did not identify these quantities as significant independent risk factors for sepsis.

The injury in the early stage of trauma acts as the 'first hit' to a patient's immune system. Subsequently, the infection, ischemia, reperfusion and surgery that occur after trauma facilitate the pro-inflammatory response and work as a 'second hit' to a patient's immune system. These inflammatory responses to injury and the consecutive post-traumatic immunosuppression have been well studied in numerous experimental and clinical studies. As mentioned above, early surgical procedures in trauma patients can stress and affect the immune system, in addition to the effect of the primary injury, thereby aggravating various complications [10]. It was reported in Tschoeke et al. [18] that surgical procedures during the early stages of trauma may facilitate a pro-inflammatory immune response by increasing the plasma concentration of the inflammatory markers IL-6 and sTREM-1. Additionally, it was argued that the combined effect of the 'first hit' and 'second hit', by producing hyper-inflammation or immunosuppression, creates an environment that can facilitate various complications. In this research, it was clinically confirmed that early surgery conducted within 24 h of traumatic injury may increase the risk of sepsis. This is highly meaningful in determining the treatment pathways for patients with severe traumatic injury in emergency settings.

As discussed above, the occurrence of post-traumatic sepsis is not only associated with patient characteristics but also has a complex association with trauma-related factors. It has been found that sepsis or MODS after trauma are associated with the patient's immune system [16]. Trauma in itself affects the patient's immune system and this early immune response is normally a protective mechanism following injures. However, an inappropriate response of the immune system seems to be responsible for organ dysfunction and increased susceptibility to infection [17]. Therefore, in order to develop appropriate treatment strategies for trauma patients, the degree of correlation between the risk factors identified and the corresponding immune response must be taken into consideration.

There are several limitations to this study. First, it includes only 15 patients who developed post-traumatic sepsis; hence, only some of the risk factors that were assessed to be relevant in other larger studies were measured. Second, despite the general acceptance that the development of sepsis after trauma is the main cause of death in severely injured patients, there was only one patient who died from sepsis in the present study; hence we were not able to confirm whether post-traumatic sepsis was generally a cause of death in trauma patients in our setting. Third, it is suggested in the literature that the site(s) of injury may be a possible factor in the risk of sepsis; however, this was not determined in the present study. Finally, the present conclusions were determined on the basis of 3 years of retrospective records of one hospital, which may not be regarded as being representative of all Korean trauma patients; therefore, more extensive research is warranted.

Conclusions

According to the results of this study, 15 (8 %) patients among mild to severe injury (ISS $\geq$ 9) developed sepsis. Among the risk factors for sepsis that were relevant in other studies, our research confirmed age and ISS and additionally identified emergency surgery as risk factors. If trauma patients possess any of these risk factors, there is a high

risk of post-traumatic sepsis, requiring certain precautionary clinical measures. An understanding of these risk factors may help to lower the mortality rate of moderately to severely injured patients.

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Compliance with ethical standards

The institutional review board for clinical research at Korea University Ansan Hospital approved the use of medical records for this retrospective study (No. AS14040).

Conflict of interest Jong-Hak Park, Sung-Hyuk Choi, Young-Hoon Yoon, Sung-Jun Park, Jung-Youn Kim and Han-Jin Cho declare that they have no conflict of interest.

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