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Severe Traumatic Head Injury Affects Systemic Cytokine Expression

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Abstract

Background—The neuroimmunologic effect of traumatic head injury remains ill-defined. This study aimed to characterize systemic cytokine profiles among traumatically injured patients to assess the effect of traumatic head injury on the systemic inflammatory response.

Study Design—Over five years, 1,022 patients were evaluated from a multi-institutional trauma immunomodulatory database (TIMD). Patients were stratified by presence of severe head injury (SHI, Head ISS ≥ 4, n=335) versus non-severe head injury (NHI, Head ISS ≤ 3, n=687). Systemic cytokine expression was quantified by ELISA within 72 hours of admission. Patient factors, outcomes, and cytokine profiles were compared by univariate analyses.

Results—SHI patients were more severely injured with higher mortality despite similar ICU infection and ventilator associated pneumonia (VAP) rates. Expression of early pro-inflammatory cytokines, IL-6 ($p<0.001$) and tumor necrosis factor (TNF)-α ($p=0.02$), were higher among NHI patients, while expression of immunomodulatory cytokines, interferon-γ ($p=0.01$) and IL-12 ($p=0.003$), was higher in SHI patients. High TNF-α levels in NHI patients were associated with mortality ($p=0.01$), increased mechanical ventilation ($p=0.02$), and development of VAP ($p=0.01$). Alternatively, among SHI patients, high IL-2 levels were associated with survival, decreased mechanical ventilation, and absence of VAP.

Conclusions—The presence of severe traumatic head injury significantly alters systemic cytokine expression and exerts an immunomodulatory effect. Early recognition of these profiles may allow for targeted intervention to reduce patient morbidity and mortality.

Keywords

Head Injury; Cytokine; Mortality; Infection; Outcomes

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INTRODUCTION

Trauma related injuries remain the fifth leading cause of death in the United States, accounting for approximately 125,000 deaths annually.[1] Of traumatic deaths, motor vehicle accidents serve as the mechanism of injury in 23% of all injury-related fatalities and totaled nearly 42,000 deaths in 2007.[1] Moreover, among those age ≤ 45, trauma remains the leading cause of morbidity and mortality, and many trauma-related deaths are associated with traumatic head injuries.[1]

Traumatic head injury (THI) related deaths encompass a broad range of injuries and insults. The relationship between death and THI has been associated with individual Glasgow Coma Scale (GCS) scores as mild (GCS 13-15), moderate (9-13), and severe (3-8) THI have substantial differences in neurologic recovery and disability.[2] Traumatic head injury typically occurs in two stages, primary and secondary brain injury, based on mechanism and timing. Primary injury refers to the initial damage caused by the inciting event, resulting in either focal or diffuse damage and is typically diagnosed radiographically.[3, 4] Secondary brain injury is the result of neuroinflammation, occurring days to weeks after the initial traumatic event. This secondary injury results from cerebral inflammation, blood-brain barrier (BBB) dysfunction, and an up regulation of immunoinflammatory processes including cerebral and systemic cytokine cascades.[5, 6]

Cytokines are cell-signaling peptides secreted by systemic immune cells and central nervous system (CNS) cells, which act to provide intercellular communication. Following traumatic injuries both pro- and anti-inflammatory cytokines cascades are activated, include the interleukin (IL) family, tumor necrosis factor (TNF), interferons (IFN), and various growth factors.[7] Cytokine release is a necessary, important and highly complex process that helps recruit neutrophils, B cells and T cells, platelets and other factors to areas of injury and damage.[8, 9] However, it is often an unrecognized imbalance in pro- and anti-inflammatory cytokine expression that ultimately results in the initiation of an unrecoverable physiologic state. Thus, understanding systemic cytokine expression profiles for various patient populations holds tremendous clinical potential in aiding clinicians with early goal-directed therapy. While select patient series have highlighted systemic cytokine profiles in critically ill and injured patients,[10] the specific impact of severe THI on the human neuroinflammatory response and resultant cytokine expression profiles remains ill-defined.

The purpose of the present study was to characterize systemic cytokine profiles among traumatically injured patients to assess the effect of traumatic head injury on the systemic inflammatory response. These data were then used to correlate systemic cytokine expression with patient morbidity and mortality in order to identify clinically significant associations to assist with early goal directed therapy.

MATERIALS AND METHODS

Study Design

This study was approved by the Institutional Review Board (IRB) at both the University of Virginia, including a waiver for informed patient consent, and Vanderbilt University, which required an assent from a surrogate prior to data collection and informed patient consent for all cases of resolved critical illness. A retrospective review of the multi-institutional Trauma Immunomodulatory Database (TIMD) was performed to extract patient records for those sustaining traumatic injuries for the study period October 2001 to May 2006. TIMD is a prospectively collected database developed collaboratively between the University of Virginia Medical Center and Vanderbilt University Medical Center Departments of Surgery.

Patients and Subject Enrollment

Patient data for those ≥ 18 years of age of both genders and all races who were admitted to either surgical or trauma intensive care units (ICU) were entered into TIMD. Patients with traumatic injuries met the principal inclusion criteria for this study. Trauma patients were stratified according to presence or absence of a severe traumatic head injury. Severe head injury (SHI) was defined as any head injury eliciting an injury severity score (ISS) head score ≥ 4. Patient characteristics, including demographics, traumatic injury related details, and co-morbid disease, systemic cytokine profiles, and outcomes were analyzed to determine the influence of severe traumatic head injuries.

Data Collection and Variable Definitions

TIMD data collection was performed by trained, full-time research personnel, consisting of clinically trained nurses, nurse practitioners, and physicians assistants. Collected data was gathered through review of patient medical records as well as personal interviews of patients, families and patient healthcare providers. Baseline patient demographics, co-morbid disease states, hospital and ICU discharge data, and in-hospital complication and death related details were entered into the secure, password-protected TIMD computer database. Data collected was used to calculate the ISS,[11] and the Glascow Coma Scale (GCS) score at the time of admission or initial presentation. In-hospital mortality reflects all patient deaths from any cause prior to hospital discharge.

Patient infections, excluding catheter related infections, were defined according to standard United States (US) Centers for Disease Control and Prevention (CDC) definitions and guidelines.[12] Accordingly, pneumonia was diagnosed with the presence of systemic evidence of infection, production of sputum, isolation of a predominant organism, development of a new or changing infiltrate or effusion on chest roeentography, or growth of > 100,000 colony-forming units (CFU) on quantitative culture via endotracheal aspiration or >10,000 CFU via bronchoalveolar lavage (BAL). Bacteremia or blood-stream infections were diagnosed with isolation of organisms for any single blood culture using aspectic sample collection techniques, except for coagulase-negative *Staphylococcus epidermidis,* which required positive growth from two separate positive blood cultures. Urinary tract infections occurred in the presence of either >100,000 organisms/ml of urine or >10,000 organisms/ml with symptoms. Catheter-related infections included those with >15 colonies with the semi-quantitative roll plate technique in the setting of clinical infection with possible but not necessary positive blood culture with the same organism. Catheter tips cultures were obtained after removal from patients with either persistently elevated or rising white blood cell (WBC) counts or in those with body temperature > 38.5°C. Skin, soft tissue, wound, and peritoneal infections occurred in those with culture-positive results when available or were diagnosed clinically.

Cytokine Quantification and Analysis

Systemic cytokine levels were obtained from patient serum samples collected within 72 hours of inpatient admission, with nearly half collected within the first 24 hours of admission. For each patient, a 10-ml blood sample was collected via peripheral venopuncture or via access of a central venous line. Collected blood samples were immediately centrifuged and the plasma was separated and stored at −70°C prior to analysis. Subsequent enzyme linked immunosorbent assay (ELISA) techniques were utilized to determine systemic cytokine concentrations. The ELISA-based Luminex^{100} system© (Miraibio, Inc., Alamdea, CA) was utilized to analyze all patient samples. Cytokine assessment included serum concentrations of pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-12, interferon-gamma (INF-gamma), tumor necrosis factor-alpha (TNF-alpha), granulocyte-macrophage colony-stimulating factor (GM-CSF)) and anti-inflammatory

cytokines (IL-4 and IL-10) as well as the chemokines IL-8 and IL-5. Minimum cytokine detectibility was defined as 2.7 pg/mL.

Statistical Analysis

All statistical methodology was designed to test the null hypothesis that outcomes and serum cytokine concentrations following traumatic injuries are not significantly different despite the presence of severe traumatic head injury. Standard statistical significance was set to an alpha <0.05. All study outcomes and data comparisons were established *a priori* before data collection. Missing data for all variables of interest underwent sequential case-wise deletion to obtain a complete dataset for subsequent analysis.

Descriptive statistics for all variable comparisons were calculated using appropriate univariate hypothesis tests. Categorical variables are expressed as within group percentages and were compared for independent samples using either the Pearson's χ^2 or Fisher's Exact test. Continuous variables are expressed as either mean ± standard deviation (SD) or median [interquartile range] depending upon overall variable distribution. Independent sample single factor analysis of variance (ANOVA) was used for parametric data comparisons, while the Mann Whitney *U* test was used for all non-parametric data comparisons. Calculated test statistics were used to derive all reported two-tailed *p*-values. Predictive Analytics SoftWare (PASW) with complex sampling module software, version 18.0.0 (IBM Corporation, Somers, NY) was used for all data manipulation and statistical analyses.

RESULTS

Patient Characteristics

A total of 1,022 patients were included in this study. All patients had complete cytokine data. Upon patient stratification, 335 (32.8%) trauma patients had the presence of a severe head injury, and 687 (67.2%) had no severe head injury (NHI). Patient demographics, characteristics, trauma profiles, and critical care interventions are detailed in Table 1. SHI patients were younger and more commonly male. No significant differences were noted between study groups with respect to race and ethnicity. Regarding patient co-morbid disease, NHI patients more commonly presented with underlying pulmonary disease (p=0.01) and autoimmune disease (p=0.01), while incremental clinical differences existed between groups for other co-morbid disease states. Overall, SHI patients were more severely injured with higher median ISS scores (34 vs. 25, p<0.001), and as expected had significantly higher Head and Neck ISS component scores (p<0.001) as well as lower median GCS scores upon admission (6 vs. 9, p<0.001). Alternatively, NHI patients presented with a higher prevalence of penetrating trauma (14.2% vs. 6.3%, p<0.001). As a result, nearly all SHI patients were treated with mechanical ventilation (97.9%); however, duration of ventilation, incidence of tracheostomy placement and the provision of blood product transfusions was higher for NHI patients.

Patient Outcomes Associated with Presence of Severe Head Injury

Among patient outcomes (Table 2), hospital mortality was significantly higher (13.4% vs. 9.3%, p<0.04) for SHI patients. However, no significant differences were observed between study groups with respect to composite ICU infection rates, median number of ICU infections, incidence of ventilator associated pneumonia, or median ICU or total hospital lengths of stay.

Systemic Cytokine Profiles and Cytokine Differences Between Survivors and Decedents

Table 3 displays baseline cytokine profiles for trauma patients with and without severe head injuries. Expression of early pro-inflammatory cytokines, IL-6 (p<0.001) and tumor necrosis

factor (TNF)-α (p=0.02), were higher among NHI patients, while expression of immunomodulatory cytokines, interferon-γ (p=0.01) and IL-12 (p=0.003), was higher in SHI patients. To examine the impact of cytokine profiles on patient mortality, univariate analyses were performed for the outcome of death among both SHI and NHI patients (Table 4). Among both SHI and NHI patients, high systemic IL-4 levels were observed for decedents. In addition, higher expression of IL-6, -8 and TNF-alpha levels were associated with mortality for NHI patients.

Cytokine Profiles Associated with Duration of Mechanical Ventilation and Ventilator Associated Pneumonia

Additional analyses were performed to identify suspected differences in systemic cytokine expression profiles as a function of duration of mechanical ventilation and the onset of ventilator associated pneumonia (Tables 5 and 6, respectively). These analyses demonstrated that significant differences in select cytokines existed among both SHI and NHI patients. Among NHI patients overall IL-8 and TNF-alpha levels varied across categories of mechanical ventilation duration (≤3 days vs. 4-6 days vs. ≥ 7 days). Furthermore, high TNF-α levels in NHI patients were associated increased mechanical ventilation (p=0.02), and development of VAP (p=0.01). Alternatively, among SHI patients, high IL-2 levels were associated with survival, decreased mechanical ventilation, and absence of VAP. In addition, higher IL-8 and IL-10 levels were noted in SHI patients that developed VAP compared to those without VAP development.

DISCUSSION

In the present study, we have presented novel data related to patient outcomes and systemic cytokine profiles among traumatically injured patients to comment upon the neuroimmunologic effect of traumatic head injuries on the systemic inflammatory response. Using data collected from a multi-institutional cohort of patients, these results corroborate prior reports of the negative effect that severe head injuries have on trauma patient outcomes and extend the discussion of these outcomes to demonstrate significant associations with varied cytokine responses. Specifically, these data suggest that significant differences exist in cytokine levels among both SHI and NHI patients, and that among both pro- and anti-inflammatory cytokines, IL-4, -6 and TNF-α levels are associated with hospital mortality. Further differences were noted for IL-2 and TNF-α levels with respect to duration of mechanical ventilation and the development of ventilator associated pneumonia. Overall, these results provide useful clinical insight to be incorporated into existing clinical algorithms for the treatment of trauma patients with and without severe head injuries.

Patient outcomes in the present study are in agreement with other trauma series. Regarding patient mortality, the 13.4% mortality observed for severe head injury patients in this series favors comparatively to other series with documented mortality rates of 30% for severe traumatic brain injury.[13] The mortality rate observed in this series reflects the exclusion of patients not surviving to 48 hours. The most common in-patient complication following severe THI is infection, owing to invasive monitoring, prolonged ICU length of stay, mechanical ventilation, and post-traumatic immunosuppression.[14] Rates of systemic infection following isolated severe head injury in reported series is as high as 50-65%,[15-17] which is higher than the 48% composite incidence rate of infections in the present series. Although rates of ventilator associated pneumonia were not significantly different between SHI and NHI patients in this series, several other studies have found significantly higher rates of respiratory infections compared to other anatomic locations following severe head injury. Consistent with previous findings of increased infections with increased severity of head trauma, Hoyt et. al. revealed 74% of infections in their THI patients were respiratory infections among patients with mean GCS 6.8,[10] while other series have documented

respiratory infections comprising approximately 30-45% of all infectious complications.[15-17]

Historically, the brain was considered an "immunologically privileged organ", lacking the ability to elicit an inflammatory immune response.[3, 4, 18] This was attributed to the presence of the BBB; however, it is now recognized that endothelial permeability following THI results in transmigration of systemic immune cells including neutrophils, monocytes, and lymphocytes.[5] Concurrent with migrant immune cells into the CNS, resident cells including astrocytes, microglia, and neurons are activated and up-regulated and subsequently secrete inflammatory mediators such as cytokines, chemokines, cytotoxic proteases, and oxygen radicals.[3, 5, 6, 18] This neuroinflammatory environment results in secondary brain injury from cell death, tissue damage, and neurodegeneration. Furthermore, despite the clear neurotoxic character of certain cytokines, recognition has recently been given to select neuroprotective functions.[7, 19] Thus, the dual role of cytokines highlights the complexity and multifaceted interactions that exist among cytokine cascades, and indicates a potential for neuromodulatory therapies in the future.

The most significant results of this study, therefore, are the unique differences noted in systemic cytokine expression profiles, which corroborate results of select human and animal studies. As demonstrated herein, alterations in cytokine expression following THI exist and have been noted for several cytokines, including IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α, and transforming growth factor-β.[7, 13, 20-25] Interleukin-1 (IL-1) is one of the most studied cytokines and classically described as a pro-inflammatory cytokine. In multiple rodent models, an IL-1 receptor antagonist has been shown to reduce neurodegeneration, contusion volume, and prevent cognitive deficits when administered in either an intracerebroventricular or subcutaneous route.[26, 27] Similar to the present study, interleukin-6 (IL-6) is found in elevated levels following THI and is a significant mediator of fever, tachycardia, and the acute phase response.[13] In one noted study, while significantly lower than cerebrospinal fluid (CSF) levels following THI, serum levels of IL-6 peaked two days after non-head injury related trauma and a considerable acute-phase response was observed.[13] Interleukin-6 has demonstrated neuroprotective effects as it has been shown to stimulate nerve growth factor, and aid in survival and differentiation of neurons.[28-30] Further, TNF-α is a potent pro-inflammatory cytokine and functions much like IL-1 activating a multitude of additional cytokine and chemokine cascades.[7] [Lenzlinger, 2001] Consistent with our results, both animal and human studies reveal that TNF-α is significantly up regulated following THI and released by numerous resident cells in the CNS.[21, 31, 32] Alternatively, IL-2 and interferon-γ have been found to be reduced following traumatic injury,[20] supporting our observations that higher IL-2 levels were associated with reduced mechanical ventilation duration and the absence of VAP.

This study has important clinical relevance. The reported results not only provide novel data related to the overall inflammatory response following THI, but also provide important correlations between various cytokine profiles and patient morbidity and mortality. As these data and others have demonstrated, severe traumatic head injury results in a varied neuroimmunologic response compared to traumatic injuries without severe head injury. Moreover, to our knowledge, this study represents the largest series to examine the relationship between admission serum cytokine levels and outcomes among THI patients. The identification of certain cytokine expression profiles such as those for IL-2, IL-4, IL-6 and TNF-α among both SHI and NHI patients may provide clinicians with an objective measure of subacute systemic inflammation for which to provide earlier directed therapy. Thus, our results remain hypothesis generating and provide a legitimate clinical context from which future, prospective studies may be derived to help direct targeted therapeutic intervention.

Certain aspects of this study deserve further discussion. Various clinical scoring systems (ISS score, GCS score, etc.) or objective clinical parameters (*i. e.*, intracranial pressure (ICP) measurements) are frequently used to identify patients with varying degrees of head injury. Accordingly, in the present series, the SHI group, defined by ISS score, identified patients with *severe* head injury with a median GCS score of 6, and distinguished this population from those trauma patients suffering either *mild to moderate* head injury, the non-severe head injury (NHI) cohort, which had a median GCS score of 9. Unfortunately, although of great interest, ICP measurements to correlate within these populations were available in a minority of patients even with SHI and were not routinely collected. With respect to the observed cyokine profiles, these results reflect differences in cytokine levels drawn over a period of 72 hours from the time of admission. While these results may not provide a completely accurate representation of the initial cytokine response following traumatic injuries, nearly half of all cytokine levels included in this analysis were collected on the first day of admission. Moreover, little variation existed in expressed cytokine levels over a 72 hour period (data not shown). The analysis of cytokine levels expressed within the CSF were not collected but serve as an area of future investigation. In addition, these data to do not exclude the effects of pre-hospital interventions prior to cytokine collection that may have impacted reported profiles. Finally, the effect of penetrating head injuries was not specifically addressed; however, the relative contribution of severe penetrating head injuries to the SHI group was very small as many of these patients were excluded from TIMD due to deaths within 24 hours of presentation.

This study has several identifiable limitations. The influence of selection bias should be considered as a potential factor in any retrospective study design. The issue of confounding in the reported results must also be considered due to the inclusion of a relatively heterogeneous trauma patient population within two separate institutions. Reported results represent short-term outcomes, and cytokine profiles do not represent variations that may occur beyond 72 hours (ie. 5-7 days). Longer follow-up may have helped to define further small differences between study groups. In addition, further mortality details related such as cause of death or deaths following multi-organ dysfunction/failure or breath death as well as the ability to correlate cytokine response and outcomes to more detailed blood product transfusion profiles may provide additional context from which to scrutinize the reported results.

CONCLUSIONS

Based upon the present results, the null hypothesis is rejected. The presence of severe traumatic head injury significantly alters systemic cytokine expression and exerts an immunomodulatory effect. Systemic cytokine expression profiles among traumatically injured patients vary depending upon nature of injury. These results suggest that the early recognition of characteristic cytokine profiles may allow for targeted intervention to reduce patient morbidity and mortality.

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Table 1
Trauma Population Characteristics for Those With and Without Severe Head Injuries

Variable	Severe head injury (n=335)	No severe head injury (n=687)	p Value
Patient age, y	35.0 [29.0]	43.0 [30.0]	<0.001
Sex, female	19.4%	30.7%	<0.001
Race/Ethnicity			0.56
White	84.2%	81.4%	
Black	10.4%	13.4%	
Hispanic	3.9%	4.5%	
Native American	0.3%	0.1%	
Other	0.3%	0.3%	
Comorbidities			
Coronary artery disease	10.4%	13.6%	0.19
Cerebrovascular disease	3.0%	2.8%	0.84
Chronic renal disease	0.9%	0.9%	>0.99
Corticosteroids	0.6%	1.3%	0.52
Liver disease	2.7%	3.4%	0.70
Malignancy	3.3%	1.5%	0.06
Peripheral vascular disease	1.2%	2.0%	0.45
Pulmonary disease	6.0%	11.4%	0.01
Autoimmune disorders	0.0%	1.9%	0.01
Diabetes mellitus	6.0%	7.9%	0.31
Interventions			
Mechanical ventilation	97.9%	90.4%	<0.001
Total ventilator days	7.0 [6.0]	7.5 [8.0]	0.01
Trachesotomy	12.7%	8.9%	0.07
Transfusions	62.7%	77.1%	<0.001
Penetrating trauma	6.3%	14.2%	<0.001
Scoring			
ISS	34.0 [13.0]	25.0 [17.0]	<0.001
Abdomen	0.0 [2.0]	2.0 [3.0]	<0.001
Chest	3.0 [4.0]	3.0 [2.0]	<0.001
Extremities	2.0 [3.0]	2.0 [3.0]	<0.001
Face	0.0 [2.0]	0.0 [1.0]	<0.001
Head or neck	5.0 [1.0]	0.0 [2.0]	<0.001
External	0.0 [1.0]	0.0 [1.0]	0.83
GCS (Admit)	6.0 [5.0]	9.0 [5.0]	<0.001

Table 2
Outcomes for Trauma Population With and Without Severe Head Injuries

Variable	Severe head injury (n=335)	No severe head injury (n=687)	p Value
Hospital mortality	13.4%	9.3%	0.04
ICU Infection	50.1%	46.7%	0.32
No. of ICU infections	1.0 [1.0]	0.0 [1.0]	0.60
Blood stream infection	24.2%	35.4%	0.06
Ventilator associated pneumonia	29.6%	25.9%	0.23
Urinary tract infection	15.2%	13.5%	0.72
Catheter-related infection	13.1%	10.7%	0.56
Wound infection	4.0%	8.4%	0.22
Abdominal infection	2.0%	5.1%	0.34
CNS/CSF infection	-	-	n/a
Hospital length of stay, d	18.0 [15.0]	17.0 [15.0]	0.62
ICU Length of stay, d	9.0 [8.0]	9.0 [9.0]	0.34

Table 3
Cytokine Profile For Trauma Population With and Without Severe Head Injuries

Variable	Severe head injury (n=335)	No severe head injury (n=687)	p Value
IL-1	2.7 [4.8]	2.7 [2.5]	0.02
IL-2	3.9 [11.6]	2.8 [9.9]	0.11
IL-4	37.7 [195.5]	38.0 [214.9]	0.90
IL-5	2.7 [1.6]	2.7 [3.1]	0.35
IL-6	126.2 [236.7]	171.9 [359.7]	<0.001
IL-8	23.9 [48.5]	35.0 [55.3]	<0.001
IL-10	54.3 [111.0]	48.2 [94.4]	0.09
IL-12	3.4 [10.2]	2.7 [5.3]	0.003
IFN	4.5 [13.1]	2.9 [7.4]	0.01
GMCSF	5.1 [9.0]	3.8 [6.3]	0.09
TNF-α	4.5 [8.5]	5.4 [7.6]	0.02

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Table 4

Cytokine Profiles For Trauma Patients With and Without Severe Head Injuries Stratified by In-Hospital Mortality

Cytokine	Severe head injury (n=335)			No severe head injury (n=687)		
	Survivor (n=687) (n=290)	Mortality (n=45)	p Value	Survivor (n=623)	Mortality (n=64)	p Value
IL-1	2.7 [4.4]	2.7 [5.1]	0.98	2.7 [2.5]	2.7 [3.6]	0.55
IL-2	4.2 [11.4]	3.1 [13.2]	0.83	2.8 [10.2]	2.7 [4.7]	0.50
IL-4	30.3 [152.8]	108 [439.2]	0.001	31.2 [190.4]	112.7 [393.3]	0.001
IL-5	2.7 [2.8]	2.7 [6.9]	0.33	2.7 [1.6]	2.7 [1.7]	0.71
IL-6	116.1 [227.4]	162.5 [307.5]	0.07	162.0 [335.8]	247.4 [827.6]	0.003
IL-8	22.3 [45.5]	28.7 [56.8]	0.11	33.9 [53.2]	55.9 [126.9]	0.003
IL-10	48.0 [91.5]	50.8 [139.4]	0.69	53.1 [110.3]	66.9 [112.2]	0.21
IL-12	3.4 [10.1]	3.2 [12.6]	0.85	2.7 [5.4]	2.7 [5.2]	0.70
IFN	4.5 [11.5]	4.1 [15.1]	0.85	3.0 [7.5]	2.7 [5.9]	0.84
GMCSF	5.1 [8.8]	4.9 [9.2]	0.84	3.6 [6.3]	4.9 [11.2]	0.20
TNF-α	4.5 [6.0]	4.8 [9.0]	0.38	5.2 [7.2]	7.5 [10.1]	0.01

Table 5

Cytokine Profiles for Trauma Patients With and Without Severe Head Injuries Stratified by Total Ventilator Days

Cytokines	Severe head injury (n=335)				No severe head injury (n=687)			
	≤ 3 Days (n=687) (n=35)	4-6 Days (n=93)	≥ 7 Days (n=133)	p Value	≤ 3 Days (n=74)	4-6 Days (n=127)	≥ 7 Days (n=251)	p Value
IL-1	2.7 [3.1]	2.7 [11.3]	3.0 [12.4]	0.63	2.7 [3.9]	2.7 [5.8]	2.7 [15.4]	0.36
IL-2	11.0 [16.9] *	6.3 [15.3]	5.6 [11.4]	0.12	7.1 [19.1]	4.5 [11.3]	4.3 [15.4]	0.22
IL-4	36.0 [235.8]	44.9 [161.7]	39.0 [241.4]	0.20	12.1 [104.4]	43.3 [188.6]	37.5 [191.2]	0.74
IL-5	2.7 [2.7]	2.7 [8.5]	2.7 [3.2]	0.20	2.7 [2.3]	2.7 [3.9]	2.7 [3.9]	0.80
IL-6	111.4 [185.8]	126.9 [219.8]	144.1 [251.1]	0.70	135.7 [357.4]	180.5 [283.0]	215.6 [517.6]	0.19
IL-8	16.9 [32.2]	19.8 [40.1]	19.1 [44.2]	0.16	24.7 [39.7]	27.3 [42.4] †	36.3 [62.2]	0.04
IL-10	51.9 [82.0]	52.6 [90.7]	46.3 [102.6]	0.82	54.4 [119.8]	44.2 [92.3] †	67.4 [114.6]	0.06
IL-12	2.7 [15.6]	5.6 [14.0]	5.3 [12.0]	0.76	3.2 [7.6]	2.7 [7.7]	3.7 [7.7]	0.55
IFN	6.4 [11.9]	7.6 [16.8]	6.0 [15.8]	0.49	5.4 [9.7]	4.7 [11.5]	5.4 [13.4]	0.62
GMCSF	7.3 [9.8]	5.4 [12.6]	6.1 [9.1]	0.95	6.5 [8.0]	5.1 [9.8]	5.9 [8.2]	0.86
TNF-α	4.6 [4.8]	5.0 [6.6]	4.7 [7.3]	0.67	5.3 [5.1] *	6.8 [6.4]	7.2 [10.1]	0.02

*Pairwise comparisons: ≤ 3 days vs. ≥ 7 days,

†4-6 days vs. ≥ 7 days

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Table 6

Cytokine Profiles for Trauma Patients With and Without Severe Head Injuries Stratified by Incidence of Ventilator Associated Pneumonia

Cytokine	Severe head injury (n=335)			No severe head injury (n=687)		
	VAP (n=687) (n=99)	No VAP (n=236)	p Value	VAP (n=178)	No VAP (n=509)	p Value
IL-1	2.7 [1.8]	2.7 [5.9]	0.06	2.7 [3.5]	2.7 [2.4]	0.73
IL-2	3.1 [11.9]	4.4 [11.6]	0.30	3.3 [15.2]	2.7 [8.9]	0.33
IL-4	90.5 [311.8]	29.6 [141.5]	0.16	39.2 [202.9]	34.5 [226.6]	0.78
IL-5	2.7 [2.6]	2.7 [4.0]	0.35	2.7 [2.6]	2.7 [1.5]	0.99
IL-6	149.0 [263.5]	111.8 [222.9]	0.11	199.4 [429.5]	166.4 [340.1]	0.22
IL-8	33.6 [55.5]	20.4 [43.2]	0.01	39.1 [59.0]	33.8 [53.2]	0.14
IL-10	60.5 [121.7]	40.0 [85.4]	0.02	60.3 [117.1]	52.9 [108.7]	0.15
IL-12	3.9 [10.6]	2.7 [8.7]	0.28	2.7 [5.0]	2.7 [5.4]	0.61
IFN	2.7 [6.5]	5.4 [14.2]	0.06	3.8 [8.6]	2.8 [7.1]	0.34
GMCSF	5.3 [9.1]	5.0 [8.2]	0.85	3.4 [6.0]	4.0 [6.6]	0.62
TNF-α	4.8 [6.2]	4.5 [6.2]	0.57	6.4 [9.8]	5.0 [6.9]	0.01

VAP, ventilator associated pneumonia.

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