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Substance P Mediates Reduced Pneumonia Rates After Traumatic Brain Injury

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Abstract

Objectives—Traumatic brain injury results in significant morbidity and mortality and is associated with infectious complications, particularly pneumonia. However, whether traumatic brain injury directly impacts the host response to pneumonia is unknown. The objective of this study was to determine the nature of the relationship between traumatic brain injury and the prevalence of pneumonia in trauma patients and investigate the mechanism of this relationship using a murine model of traumatic brain injury with pneumonia.

Design—Data from the National Trauma Data Bank and a murine model of traumatic brain injury with postinjury pneumonia.

Setting—Academic medical centers in Cincinnati, OH, and Boston, MA.

Patients/Subjects—Trauma patients in the National Trauma Data Bank with a hospital length of stay greater than 2 days, age of at least 18 years at admission, and a blunt mechanism of injury. Subjects were female ICR mice 8–10 weeks old.

Interventions—Administration of a substance P receptor antagonist in mice.

Measurements and Main Results—Pneumonia rates were measured in trauma patients before and after risk adjustment using propensity scoring. In addition, survival and pulmonary inflammation were measured in mice undergoing traumatic brain injury with or without pneumonia. After risk adjustment, we found that traumatic brain injury patients had significantly lower rates of pneumonia compared to blunt trauma patients without traumatic brain injury. A murine model of traumatic brain injury reproduced these clinical findings with mice subjected to traumatic brain injury demonstrating increased bacterial clearance and survival after induction of

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pneumonia. To determine the mechanisms responsible for this improvement, the substance P receptor was blocked in mice after traumatic brain injury. This treatment abrogated the traumatic brain injury–associated increases in bacterial clearance and survival.

Conclusions—The data demonstrate that patients with traumatic brain injury have lower rates of pneumonia compared to non–head-injured trauma patients and suggest that the mechanism of this effect occurs through traumatic brain injury–induced release of substance P, which improves innate immunity to decrease pneumonia.

Keywords

infection; innate immunity; leukocytes; lung inflammation; neuropeptide; vagus nerve

Traumatic brain injury (TBI) is a major cause of death and disability in both civilian and military populations. Although early mortality is primarily attributed to nonsurvivable head injury, delayed deaths following head injury are often secondary to nonneurologic organ dysfunction resulting from infectious and inflammatory processes (1–4). Pneumonia is the most common infectious complication associated with TBI, occurring in 20–60% of head-injured patients, rates that are generally believed to be increased compared to non–head-injured patients (5–7). Associated risk factors for the development of pneumonia after TBI include postinjury immunosuppression and prolonged mechanical ventilation (8, 9).

Immunosuppression after TBI has been demonstrated predominantly as a decline in the adaptive immune system. CD4 and CD8 cells are decreased after TBI for a prolonged period of time (9–11). However, both adaptive and innate immunity play important roles in controlling infection. Neutrophils and macrophages of the innate immune system are vital for appropriate bacterial clearance (12, 13). Neutrophil activation is regulated by multiple factors, including substance P, a tachykinin neuro-peptide released from afferent nerve endings that modulates the functions of immune cells, blood vessels, smooth muscles, and glands (14). Due to the extensive pulmonary innervation of the bronchial epithelium, substance P released in the lung can induce neutrophil recruitment to the lung and improve innate immunity (14, 15). In addition, substance P is known to be released following TBI and makes substantial contributions to neurogenic inflammation (16).

In the present study, we sought to determine the relationship between TBI and pulmonary infection. Our initial hypothesis was that head-injured trauma patients may not have a higher prevalence of and risk factors for the development of pneumonia when compared to appropriately matched blunt trauma patients without TBI. Our second hypothesis was that a murine model of TBI with postinjury immunomodulation via substance P on the pulmonary and systemic inflammatory responses to bacterial challenge following head injury would support our novel clinical findings.

MATERIALS AND METHODS

National Trauma Data Bank

The National Trauma Data Bank 7.2 (NTDB; American College of Surgeons) was queried to investigate the clinical association between TBI and pneumonia (17). The NTDB is the

largest aggregated trauma database, containing records of trauma patients voluntarily reported by trauma centers across the United States. The dataset was interrogated using source codes provided by the NTDB (17). The analysis for this study included the most recently available data, reporting hospital admissions for the year 2010. Our study included patients with a hospital length of stay greater than 2 days, an age greater than 18 years at admission, and a blunt mechanism of injury.

Data were analyzed for patients with and without an associated TBI. The primary outcome of interest was the in-hospital rate of pneumonia development determined by the reporting trauma facilities. Head-injured patients were identified as those individuals with at least one *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9 CM) code of 800–959. These individuals were further grouped, using the Glasgow Coma Score at hospital admission, into mild (13–15), moderate (9–12), and severe (< 9) TBI categories. A comparison group consisted of blunt traumatic injury patients whose diagnosis codes did not include a head or neck injury. Pneumonia was defined using either an ICD-9 diagnosis or a complication code defined by NTDB.

Demographics, baseline vital signs, injury severity score (ISS), hospital and ICU length of stay, and requirement for mechanical ventilation were summarized descriptively and analyzed statistically using SAS Version 9.3 (SAS Institute, Cary, NC). Because of the significant differences observed in the demographic and vital signs data (Table 1), and the potential impact of these differences on the prevalence of pneumonia, propensity scoring was used to more precisely match each TBI cohort to the blunt trauma cohort. Propensity scores were generated using the following variables: age, age², ISS, pulse, respiratory rate, systemic blood pressure, systemic blood pressure², race, gender, whether or not the injury was intentional, injury type, and the interactions of ISS with age and respiratory rate. Logistic regression was then used to estimate each individual's probability of having a particular category of TBI (18, 19). These predicted probabilities are the propensity scores. Matching was then accomplished using One to Many MTCH, a SAS macro (20). In all matched data, patients with chest injuries were excluded due to the synergistic factors contributing to the development of pneumonia. Chest injuries were defined by Barrell matrix ICD-9 codes (21).

Murine Models of Mild TBI and Pneumonia

Female ICR mice (Harlan-Sprague Dawley, Indianapolis, IN) were used for all experiments. All mice were 8–10 weeks old, weighed 24–30 g, and were acclimated for at least 3 days in a temperature- and humidity-controlled room with a 12-hour light/ dark cycle. Food and water were provided ad libitum throughout the studies. All experiments were approved by the Institutional Animal Care and Use Committees of Boston University.

Under isofluorane anesthesia, mice were placed in a prone position on a plexiglass bed with their head resting on a foam pad under a weight drop impact device. To induce the moderate TBI, a 170-g steel rod within a guide tube was released from a height of 5.2 cm to impact a point in the midline of the skull, halfway between the interauricular and interorbital lines, producing approximately 5 kg/cm² of impact force. Rebound impact was prevented and the mouse was immediately removed from the device and given an intraperitoneal (i.p.)

injection of 0.05 mg/kg buprenorphine in 1 mL of normal saline. Mice were placed supine on a warming bed and returned their cages after righting themselves to sternal recumbence. Sham mice underwent similar sedation and analgesia without TBI.

Pneumonia was induced 48 hours post-TBI by anesthetizing mice with isoflurane and administering 1×10^7 CFU of *Pseudomonas aeruginosa* (ATCC strain Boston 41501) in 50 μ L of Hank's balanced salt solution (HBSS) via hypopharyngeal administration (22). Control groups received only the vehicle. Mice were allowed to recover and were monitored for up to 7 days. To examine the role of substance P, mice received intra-peritoneal injections of the neurokinin-1 receptor antagonist CJ-12255 (Pfizer, New York, NY) or normal saline every 12 hours for five doses starting immediately after TBI. Pulmonary bacterial loads were determined by bronchoalveolar lavage (BAL) and lung homogenates obtained 4 hours after inoculation.

Serum and Tissue Analysis

Serum samples were obtained by cardiac puncture at the time of killing under ketamine/xylazine anesthesia. To determine whether this increased bacterial clearance was due to local cell recruitment, we analyzed the cellular content of the BAL fluid. BAL was performed with 5 mL of warm HBSS in 1 mL aliquots. One hundred microliters of the first aliquot was retained for bacterial count. The supernatant from the remainder of the first aliquot was used for cytokine analysis. The cell pellets of all aliquots were combined and counted using a Beckman-Coulter particle counter (Coulter Electronics, Denver, MA). Differential quantitation of cells was performed by counting 300 cells on cytopsin slides stained with Diff-Quick (Baxter, Detroit, MI). After lavage, the lungs were sterilely transferred to 3 mL of Hanks Balanced Salt Solution and homogenized. Bacterial counts in BAL fluids and lung homogenates were determined after samples were plated in triplicate on sheep blood agar plates. Cytokines and chemokines (interferon- γ , interleukin [IL]-1 α , IL-6, IL-10, keratinocyte-derived chemokine [KC], macrophage inflammatory protein-2 [MIP-2]) were measured by sandwich enzyme-linked immunosorbent assay using matched antibody pairs (R & D Systems, Minneapolis, MN) (23).

Statistical Analyses

In the NTDB data, predicted probabilities of group membership (propensity scores) were employed, in conjunction with a SAS 1:1 matching macro, to create matched comparison groups. The groups were then compared using chi-square test, *t* tests, and rank-sum tests to gauge whether any residual differences remained. For animal studies, survival data were compared with a Kaplan-Meier analysis. Comparisons of two groups were performed using a Student *t* test, and multiple group data were compared by analysis of variance with subsequent Bonferroni test.

RESULTS

Unadjusted NTDB Data Show Increased Pneumonia Rates in TBI Patients

The NTDB for the year of 2010 included a total population of 722,836 patients. After applying our inclusion criteria, 339,433 patients met criteria for further analysis. From this

cohort, 56,528 patients were found to have an ICD-9 code for TBI and 208,993 met criteria as blunt trauma patients without head or neck injuries. Demographic data for the analyzed cohorts are shown in Table 1. Statistically significant differences were found in all demographic variables analyzed except for systolic blood pressure. This indicates that these patients were quite dissimilar, particularly regarding ISSs. The TBI patients were divided into mild, moderate, and severe TBI to evaluate rates of pneumonia. The prevalence of pneumonia in patients with blunt trauma without TBI (control), mild, moderate, and severe TBI groups is shown in Figure 1. Patients with mild TBI had a similar prevalence of pneumonia as blunt trauma controls, whereas patients with moderate or severe TBI had a higher prevalence of pneumonia than the blunt trauma control patients. These data are similar to previous reports of increased prevalence of pneumonia in TBI versus non-TBI trauma patients (5–7).

Because mechanical ventilation is a primary risk factor for acquiring pneumonia, we evaluated the number of patients in each group requiring mechanical ventilation and the relationship of duration of time on the ventilator with the prevalence of pneumonia. Whereas 10.5% of the entire blunt trauma cohort required mechanical ventilation, 25.2% of all TBI patients required mechanical ventilation. The mechanical ventilation needs of head-injured patients increased with severity; 12.1% of mild, 48.2% of moderate, and 85.3% of severe TBI patients required mechanical ventilation. Pneumonia rates were directly proportional to the duration of mechanical ventilation (**Supplemental Table 1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/A981>).

Risk-Adjusted NTDB Data Demonstrate Lower Pneumonia Rates in TBI Patients

Patients requiring mechanical ventilation were divided into mild, moderate, and severe TBI groups and then matched using propensity scoring. Demographic and vital signs data for these groups are shown in Table 2. Although there were no differences in ISS or admission vital signs, other variables including number of days on mechanical ventilation reached statistical significance. Analysis of pneumonia prevalence rates in matched cohorts of mechanically ventilated patients demonstrated that those patients with TBI had significantly lower rates of pneumonia than their blunt trauma controls (Fig. 2A). Pneumonia rates in each cohort of TBI patients were reduced by approximately 25% compared to their matched controls.

Similar results were found when nonventilated patients were matched using propensity scoring. There were no differences in ISS or respiratory rate at admission, but due to the robust sample sizes, all other variables reached statistical significance (Table 2). Patients with mild TBI had a significantly lower prevalence of pneumonia than blunt trauma controls (Fig. 2B) (1.3% vs 0.8%, TBI vs control, $p < 0.0001$).

Mild TBI Confers a Survival Advantage in Mice With Pneumonia

To explore the biological mechanisms by which TBI alters the susceptibility to pneumonia, we employed a murine model of mild TBI followed 2 days later with intrapulmonary infection with *P. aeruginosa*. The model was developed to reproduce the common clinical scenario of a trauma patient developing nosocomial pneumonia. TBI mice demonstrated a

reduced mortality rate following the induction of postinjury pneumonia. All of the TBI mice survived the 1×10^7 CFU of *Pseudomonas* pulmonary challenge while 40% of sham animals died by 7 days (Fig. 3A). To assess whether this effect would be present with a greater infectious challenge, a second experiment was performed using 5×10^7 CFU of *P. aeruginosa* (Fig. 3A). Eighty percent of mice with TBI survived, whereas only 20% of sham animals survived. These data demonstrate that TBI promotes protection against pneumonia-induced mortality in this model system.

Mild TBI Increases Pulmonary Bacterial Clearance

To investigate the potential mechanisms of the survival advantage conferred in TBI mice with pneumonia, we assessed pulmonary bacterial clearance and leukocyte recruitment. TBI mice had significant reductions in bacterial counts in both the BAL fluid and lung homogenates (Fig. 3B). In addition, TBI mice had significantly increased cell recruitment to the lungs 4 hours after the induction of pneumonia (Fig. 3C). Differential counts of representative cytopspins prepared from the BAL fluid showed significant increases in both neutrophils and macrophages (Fig. 3C). Interestingly, the increased cell recruitment was not associated with elevated local or systemic pro-inflammatory cytokine and chemokine production. TBI mice had significantly lower levels of the cytokine IL-6 and the CXC chemokine MIP-2 in BAL fluids and serum 4 hours after infection (Fig. 3D). Serum, but not BAL, levels of KC were also significantly decreased in animals post-TBI (Fig. 3D). This differs from burn and blunt trauma models which are accompanied by increased proinflammatory cytokines with increased macrophages and neutrophils after bacterial loads (24, 25).

Antagonism of the Substance P Receptor Abrogates the Survival Benefit of Mild TBI to Lethal Pneumonia

Because the observed changes in proinflammatory cytokines do not explain the increased neutrophil recruitment and increased bacterial clearance observed in TBI mice, we examined the role of substance P, a neuropeptide known to protect against lung injury induced by polymicrobial sepsis (26, 27). Mice underwent sham injury or TBI and were treated immediately after injury with the substance P receptor antagonist CJ-12555. Two days after TBI mice received an intrapulmonary infection with 5×10^7 CFU of *P. aeruginosa*. Only 20% of infected sham injured mice, treated with saline or CJ-12555, survived (Fig. 4A). Similar to Figure 1, 80% of infected TBI mice treated with saline survived. By contrast, there was a four-fold increase in mortality with substance P receptor inhibition, with only 20% of infected TBI mice treated with CJ-12555 surviving. This suggests that blockade of substance P abrogated the survival benefit conferred by TBI. We next examined the mechanism of how substance P receptor blockade decreased survival by measuring pulmonary leukocyte recruitment and bacterial clearance. Treatment with CJ-12555 reversed TBI-induced increases in pulmonary leukocyte recruitment (Fig. 4B). These effects were accompanied by significant increases in pulmonary bacterial counts (Fig. 4C). These data suggest that TBI induces the release of substance P in the lung that promotes increased leukocyte recruitment and bacterial clearance.

DISCUSSION

To the best of our knowledge, the current study is the first to use propensity score matching as a method of risk adjustment to evaluate the probability of developing postinjury pneumonia in TBI patients. Previous studies have shown high rates of pneumonia, as high as 60%, in trauma populations with brain injury (5, 6, 9, 28–30). However, these studies focus only on severe TBI patients who require prolonged courses of mechanical ventilation. Our study is unique in that we evaluated TBI patients along the entire spectrum of mild, moderate, or severe injury.

In our study, patients were comparatively matched for injury severity, length of hospital stay, age, race, vital signs at the time of admission, and mechanical ventilator days. Prior studies have compared a subset of severe TBI patients to nontrauma patients or the general population of trauma patients (31, 32). This limits the validity of these studies due to the differences in mechanism of injury, severity of injury, and time mechanically ventilated. The groups in our study included only trauma patients with or without head injury induced by a blunt mechanism. Blunt trauma was chosen because it is the most common mechanism of TBI and is known to cause a robust inflammatory response (33–36).

By using the NTDB, the study results are powered by a large population of trauma patients from multiple institutions using standardized trauma registry data points (37). The use of a national database has inherent limitations, including the inability to capture all desired data points and control for all possible patient variables. Pneumonia is not a clearly defined diagnosis, but is most often coded as a complication. The criteria to establish and record the diagnosis of pneumonia may vary from one institution to another, using variable definitions by radiographic, BAL, or clinical score findings. However, the present dataset is strengthened by its robust numbers and the use of propensity scoring to appropriately match trauma patient populations.

To further support our clinical findings with a potential physiologic mechanism, we examined an animal model of head injury with subsequent pneumonia to determine the causes of reduced infectious risk. To date, there have not been any comprehensive studies of bacterial pneumonia after TBI in animal models. Our studies demonstrate an increased resistance to *P. aeruginosa* pneumonia following TBI. This enhanced resistance occurred through increased neutrophil recruitment to the airways resulting in more effective bacterial clearance and improved survival. Neutrophil responses to bacteria in the lungs largely determine the outcome of infection as insufficient neutrophil recruitment can lead to an inability to clear the infection (38). Studies performed after burn and blunt trauma have shown enhanced resistance to bacterial infection after injury due to increased neutrophil recruitment and bacterial clearance but are accompanied by concurrent increases in pro-inflammatory cytokines due to increased toll-like receptor signaling in macrophages and neutrophils (24, 25). Interestingly, proinflammatory cytokine levels following post-TBI bacterial inoculation were significantly decreased in this study. Because our results suggest increased neutrophil recruitment with concomitant reduced proinflammatory response, the observed resistance to infection may be due to a different mechanism specific to TBI.

Pulmonary inflammation after TBI has been attributed in both the clinical and basic science literature to neurogenic pulmonary edema (NPE). Multiple mechanisms have been implicated in the pathophysiology of post-TBI NPE including catecholamine storm, hydrostatic pressure increase, leukotriene B₄, and importantly, substance P (39–41). Substance P is an important mediator of vasodilation, vascular permeability, and neutrophil priming and migration in the lung (1, 15). It is released from afferent vagal sensory neurons after noxious stimulus or distant injury (40, 42, 43). Our brain injury model may cause a substance P release that, while not sufficient to cause secondary injury, could serve to prime and recruit neutrophils in response to bacterial inoculation via the neurokinin (NK)-1 receptor (44). Blockade of the NK-1 receptor abolished the enhanced neutrophil recruitment, resulting in decreased bacterial clearance and decreased survival in treated TBI mice.

Increased vagus nerve signaling after TBI has been shown to initiate a systemic anti-inflammatory response (45, 46). Although our study demonstrates improved neutrophil recruitment and bacterial killing, the vagal anti-inflammatory pathway could account for the decreased levels of proinflammatory cytokines despite the presence of more inflammatory cells in the lung. The afferent and efferent pathways of the vagus nerve reduce the inflammatory process in stroke and brain injury models (47–50). Efferent stimulation of the vagus nerve results in a drastic anti-inflammatory process (49, 50). This could serve to moderate the immune response resulting in less collateral damage in the lung parenchyma and improved survival.

Taken together, our findings may help direct clinical algorithms in brain-injured patients to reduce posttraumatic infectious complications and related morbidity. Because the current analysis encompasses the overall pneumonia rate of the patients in the NTDB and a single timepoint of BAL and serum contents in the murine model, additional work is needed to further define the kinetics of the post-TBI immunological phenotype following injury (51). Early intervention to enhance immune resistance and modulate immune suppression after head injury could improve the systemic response to TBI in order to minimize infection risk and its impact on neurological outcome (8, 52). In addition, further investigation is needed to determine the impact of substance P signaling in the blunt trauma population as a potential posttraumatic immunomodulator.

CONCLUSIONS

The present study demonstrates, using propensity score matching for patient risk adjustment, that TBI reduces the susceptibility to pneumonia in blunt injured patients. These findings were confirmed and validated in a murine model of TBI with pneumonia. The mechanism of the reduced rate of pneumonia appears to be mediated by the release of substance P in response to TBI.

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Figure 1.

Prevalence of pneumonia from the National Trauma Database for 2010 for blunt traumatic injuries without traumatic brain injury (TBI) ($n = 209,056$), mild TBI ($n = 42,802$), moderate TBI ($n = 3,163$), and severe TBI ($n = 8,285$). * $p < 0.05$ compared to blunt trauma.

Figure 2.

Propensity scoring was used to match patients in the control group (blunt trauma without traumatic brain injury [TBI]) to TBI groups. The rate of pneumonia for each matched group was then calculated. **A**, Propensity scoring and matching of patients requiring mechanical ventilation. Mild TBI versus control, $n = 2,311/\text{group}$; moderate TBI versus control, $n = 694/\text{group}$; severe TBI versus control, $n = 2,524/\text{group}$. $*p < 0.05$ compared to control group. **B**, Propensity scoring and matching of patients not requiring mechanical ventilation. Mild TBI versus control, $n = 21,431/\text{group}$. $*p < 0.05$ compared to control group.

Figure 3.

Mice with traumatic brain injury (TBI) are more resistant to pulmonary infection. **A**, TBI abrogates pneumonia-induced mortality. Two days after sham or TBI, mice received intratracheal instillation of 1×10^7 CFU or 5×10^7 CFU of *Pseudomonas aeruginosa*. $n = 10$ in each group. **B**, TBI increases bacterial clearance in lung. Four hours after intratracheal administration of 1×10^7 CFU of *P. aeruginosa*, bronchoalveolar lavage (BAL) fluids and whole-lung homogenates were analyzed for bacterial counts. $n = 5$ in each group. $*p < 0.05$ compared to sham. **C**, TBI increases cell recruitment to the lung. Four hours after intratracheal administration of 1×10^7 CFU of *P. aeruginosa*, BAL fluids were analyzed for cell counts measured by Beckman-Coulter particle counter and differential count from representative cytopspins. $n = 8$ in each group. $*p < 0.05$ compared to sham. **D**, TBI reduces cytokine and chemokine expression after pulmonary infection. Four hours after intratracheal administration of 1×10^7 CFU of *P. aeruginosa*, BAL fluids and serum from sham and TBI-injured mice were assessed by enzyme-linked immunosorbent assay. $n = 10$ in each group. $*p < 0.05$ compared to sham. IL = interleukin, KC = keratinocyte-derived chemokine, MIP = macrophage inflammatory protein.

Figure 4.

Blockade of the neurokinin-1 receptor abrogates the antibacterial and survival benefits of traumatic brain injury (TBI). **A**, Blockade of the neurokinin-1 receptor worsens survival after TBI. Sham and TBI mice treated with either vehicle or neurokinin-1 receptor antagonist CJ-12255 were followed for survival after intratracheal administration of 5×10^7 CFU of *Pseudomonas aeruginosa*. $n = 10$ in each group. **B**, Blockade of the neurokinin-1 receptor reverses TBI-mediated effects on pulmonary cell recruitment. Leukocyte counts were determined in bronchoalveolar lavage (BAL) fluids from sham and TBI mice treated with vehicle or the neurokinin-1 receptor antagonist, CJ-12255, 4 hr after intratracheal instillation of 1×10^7 CFU of *P. aeruginosa*. $n = 10$ in each group $*p < 0.05$ compared with all other groups. **C**, Blockade of the neurokinin-1 receptor in TBI-injured mice reduces bacterial clearance. Bacterial counts were determined in BAL fluids from sham and TBI mice treated with vehicle or the neurokinin-1 receptor antagonist, CJ-12255, 4 hr after intratracheal instillation of 1×10^7 CFU of *P. aeruginosa*. $n = 10$ in each group $*p < 0.05$ compared with all other groups.

Table 1

Demographics of All Blunt Traumatic Injuries and Traumatic Brain Injuries in the National Trauma Database for 2010, Excluding Patients in the Hospital for Less Than 2 Days and Less Than 18 Yr Old

Variable	Blunt Trauma Without TBI <i>n</i> = 208,993	Blunt Trauma With TBI <i>n</i> = 56,528
Age, yr	56.2 ± 21.1	52.5 ± 21.3 ^a
Sex, % male	56.0	64.5 ^a
Injury severity score	9.8 ± 7.2	16.6 ± 9.8 ^a
Heart rate, beats/min	86.5 ± 19.0	89.9 ± 20.9 ^a
Systolic blood pressure, mm Hg	140.8 ± 27.0	140.7 ± 28.3
Temperature, °C	36.4 ± 2.0	36.4 ± 1.8 ^a
Time in ICU, d	0 (0–2)	2 (0–4) ^a
Hospital length of stay, d	5 (4–8)	6 (4–10) ^a

TBI = traumatic brain injury.

^a *p* < 0.05 compared to blunt trauma without traumatic brain injury group.

Data for sex are expressed as %. Data for age, injury severity score, heart rate, systolic blood pressure, and temperature are expressed as mean ± sem. Data for time in ICU and hospital length of stay are expressed as median (interquartile range).

Table 2

Demographics for Patient Groups Matched With Propensity Scoring

Variable	Control	Mild TBI	Control	Moderate TBI	Control	Severe TBI
Patients requiring mechanical ventilation						
Sample size, <i>n</i>	2,311	2,311	694	694	2,524	2,524
Age, yr	56.1 ± 20.3	57.0 ± 20.6	49.6 ± 19.8	50.3 ± 20.3	45.0 ± 19.4	45.4 ± 19.6
Sex, % male	72.48	69.67 ^a	71.76	70.03	75.40	74.37
ISS	17.9 ± 8.3	17.6 ± 8.4	17.9 ± 8.5	17.6 ± 8.9	18.2 ± 9.3	18.2 ± 9.3
Heart rate, beats/min	89.9 ± 23.3	90.0 ± 21.6	92.9 ± 24.9	93.8 ± 24.0	96.0 ± 24.8	95.4 ± 24.2
Respiratory rate, beats/min	19.4 ± 6.4	19.2 ± 4.5	18.4 ± 7.5	18.7 ± 6.3	12.5 ± 8.8	12.2 ± 9.3
Systolic blood pressure, mm Hg	143.7 ± 29.5	144.5 ± 29.4	142.0 ± 30.3	146.9 ± 33.4	143.4 ± 32.2	143.8 ± 31.4
Temperature, °C	36.3 ± 1.5	36.3 ± 2.1	36.2 ± 1.6	36.1 ± 2.8	36.1 ± 2.6	36.1 ± 2.7
Time on ventilator, d	3 (2–9)	3 (1–8) ^a	4 (2–10)	3 (1–8) ^a	3 (1–9)	3 (2–8) ^a
Time in ICU, d	6 (3–12)	6 (3–12)	6 (3–12)	5 (3–11)	5 (3–12)	5 (3–11)
Hospital length of stay, d	11 (6–20)	11 (6–20)	11 (6–20)	10 (5–19) ^a	11 (6–20)	10 (5–18) ^a
Patients not requiring mechanical ventilation						
Sample size, <i>n</i>	21,431	21,431				
Age, yr	53.8 ± 21.7	56.0 ± 21.8 ^a				
Sex, % male	62.27	58.93 ^a				
ISS	12.6 ± 6.8	12.6 ± 6.7				
Heart rate, beats/min	86.5 ± 18.3	86.1 ± 18.2 ^a				
Respiratory rate, beats/min	18.5 ± 4.2	18.5 ± 3.8				
Systolic blood pressure, mm Hg	142.4 ± 26.5	143.3 ± 26.4 ^a				
Temperature, °C	36.4 ± 1.7	36.5 ± 1.8 ^a				
Time in ICU, d	0 (0–2)	0 (0–2) ^a				
Hospital length of stay, d	4 (5–8)	4 (3–7) ^a				

TBI = traumatic brain injury, ISS = injury severity score.

^a *p* < 0.05 compared to respective control group.

Data for age, ISS, heart rate, respiratory rate, systolic blood pressure, and temperature are expressed as mean $\pm$ sem. Data for sex are expressed as %. Data for time on ventilator, time in ICU, and hospital length of stay are expressed as median (interquartile range).