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Hospital Acquired Pneumonia is an Independent Predictor of Poor Global Outcome in Severe Traumatic Brain Injury up to 5 Years after Discharge:

HAP Predicts Poor Outcomes 5 years post TBI

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Abstract

Objectives—Long-term outcomes following traumatic brain injury (TBI) correlate with initial head injury severity and other acute factors. Hospital-acquired pneumonia (HAP) is a common complication in TBI. Little information exists regarding the significance of infectious complications on long-term outcomes post-TBI. We sought to characterize risks associated with HAP on outcomes 5 years post-TBI.

Methods—Data from the merger of an institutional trauma registry and the TBI Model Systems outcome data. Individuals with severe head injuries (Abbreviated Injury Scale 4), who survived to rehabilitation were analyzed. Primary outcome was Glasgow Outcome Scaled-Extended (GOSE) at 1, 2, and 5 years. GOSE was dichotomized into LOW (GOSE<6) and HIGH (GOSE ≥ 6). Logistic regression was utilized to determine adjusted odds of LOW-GOSE associated with HAP after controlling for age, sex, head and overall injury severity, cranial surgery, Glasgow Coma Scale (GCS), ventilation days, and other important confounders. A general estimating equation (GEE) model was used to analyze all outcome observations simultaneously while controlling for within-patient correlation.

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RRK: Data collection, data interpretation, critical revision

AKW: Data collection, data interpretation, critical revision

JCP: Data interpretation, critical revision

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JLS: Study design, data analysis, data interpretation, writing, critical revision

Results—A total of 141 individuals met inclusion criteria, with a 30% incidence of HAP. Individuals with and without HAP had similar demographic profiles, presenting vitals, head injury severity, and prevalence of cranial surgery. Individuals with HAP had lower presenting GCS. Logistic regression demonstrated that HAP was independently associated with LOW-GOSE scores at follow-up (1year: OR=6.39, 95%CI: 1.76-23.14, p=0.005; 2-years: OR=7.30, 95%CI 1.87-27.89, p=0.004; 5-years: OR=6.89, 95%CI: 1.42-33.39, p=0.017). Stratifying by GCS 8 and early intubation, HAP remained a significant independent predictor of LOW-GOSE in all strata. In the GEE model, HAP continued to be an independent predictor of LOW-GOSE (OR: 4.59; 95%CI: 1.82-11.60' p=0.001).

Conclusion—HAP is independently associated with poor outcomes in severe-TBI extending 5 years post-injury. This suggests precautions should be taken to reduce the risk of HAP in individuals with severe-TBI.

Level III—Retrospective Study

Pneumonia

TBI

Background

Approximately 1.7 million people sustain a traumatic brain injury (TBI) annually in the United States, and over a quarter of a million are hospitalized. (1) Half of hospitalized patients will develop long-term disability, and there are currently over 5.3 million people in the US living with TBI-related disabilities. (2) Studies are common that investigate acute phase factors associated with TBI, like initial injury severity and hypotension requiring transfusion. (3, 4) Research evaluating categorical outcome differences between sex, race and socioeconomic status are also prevalent. (5, 6) Though the incidence of nosocomial infection in TBI patients has been reported to be as high as 41%, (7) little is known about the effects of nosocomial infection in the acute setting on health care resource utilization and long-term outcomes in patients with TBI. It is well-established that TBI can independently result in a significant inflammatory burden. (8, 9) Thus, it is possible the co-morbidity of infection could contribute to an excessive chronic inflammatory response after injury and effect long-term outcomes.

The Traumatic Brain Injury Model Systems (TBIMS) Program is a multicenter longitudinal prospective study that began in 1987 with funding from the National Institute on Disability and Rehabilitation Research (NIDRR). TBIMS investigators follow individuals with TBI who receive care at a TBIMS acute inpatient rehabilitation center. Data from study participants consented to be followed as a part of the TBI-MS National Database are collected at 1, 2, and 5 years after injury, and in subsequent 5 year intervals, until death. With over 13,000 participants, this extensive database contains numerous long-term outcome measures, but the it is limited in information on injury characteristics, early complications, and pre-hospital data. (10)

We sought to combine relevant trauma and TBIMS data to characterize the significance of nosocomial infection in the acute setting on long-term outcomes up to five years after injury

using a single institution trauma registry and TBIMS follow-up data. We hypothesized that hospital acquired pneumonia (HAP) would be independently associated with poor global outcomes.

Methods

Research procedures and analyses conducted for this study received local institutional review board approval.

Population

Prospectively collected data on subjects enrolled in TBIMS between 2003 and 2007 from a single site within the TBIMS were deterministically merged with data on these same subjects abstracted from the trauma registry at a quaternary referral, level 1 trauma center that has over 5,000 trauma admissions a year. The merger was accomplished through medical record numbers. Individuals with TBI met inclusion criteria if they had a head AIS 4, survived to acute care discharge, were admitted to rehabilitation treatment at a TBIMS rehabilitation center, and had follow up data from at least one 1, 2, or 5 years. Therefore, a patient may have 2-year follow-up, but not 1-year. Baseline differences between patients were examined in order to detect potential systematic bias from loss to follow-up. Using demographics and baseline injury characteristics, a propensity for LOW GOSE was generated with the earliest follow-up data for the entire cohort. This was compared at each time point between patients with and without follow-up data.

In addition, the trauma registry data includes demographic and acute care clinical data such as mechanism of injury, length of stay, procedures and operations, presenting Glasgow Coma Scale (GCS), and days of mechanical ventilation. The trauma registry also includes complication information enabling identification of HAP. Patients were defined as having HAP if they had both of the following criteria: (1) temperature $> 38^{\circ}\text{C}$ or leukocytosis, and (2) two radiographs with pneumonic infiltrate or culture demonstrating pathogen. The TBIMS rehabilitation center is affiliated with the Level I trauma center.

The primary outcome measure was Glasgow Outcome Scale-Extended (GOSE). The GOSE is an 8 point scale that ranks global functional outcome into one of eight categories from 1 being death, 2 being persistent vegetative state and 3 to 8 for different levels of recovery. Mortality dates were determined by the Social Security Death Index for all patients who expired during the study period. Patients who expired between follow-up time points were considered as having a GOSE of 1 at the next appropriate time point. For instance a patient who died 2.5 years after discharge would have a GOSE of 1 at 5 years. GOSE was dichotomized at its sample median into LOW (GOSE < 6) and HIGH (GOSE ≥ 6) groups.

Data Analysis

All data were summarized as mean $\pm$ SD, median [IQR, inter-quartile range], or percentage (%). Student-t or Mann-Whitney statistical tests were used to compare continuous variables, while Chi-Square or Fischer's Exact test was used for categorical variables. A p-value of 0.05 was considered statistically significant. Kaplan-Meier analysis was conducted to determine the temporal development of HAP in relation to days post-TBI. Univariable

analysis was conducted with analysis of variance (ANOVA). Multivariable logistic regression was conducted to control for potential confounders.

Univariable analysis was conducted to determine baseline differences between those with and without HAP. All factors in the univariable analysis with p-value ≤ 0.2 , as well as important predictors previously described, were included in a multivariable logistic regression to determine the adjusted odds of a LOW GOSE score associated with HAP. Collinear diagnostics were employed to exclude predictors that captured redundant information about the outcome.

The final multivariable model controlled for age, sex, race, initial GCS, head AIS (4 vs. 5), Injury Severity Score (ISS) of other body regions, decompressive craniotomy, presence of severe chest injury (AIS > 3), and days of mechanical ventilation. Early intubation, defined as completed either in the pre-hospital setting or in the trauma bay, was collinear with initial GCS and was therefore excluded from the multivariable model. The cohort size at 2 and 5 years was small relative to the number of predictors. To mitigate this, backward step-wise regressions using all of the predictors from the multivariable model were conducted. Models were tested for goodness-of-fit with the Hosmer and Lemeshow test and the c-statistic was evaluated. The cohort was further stratified by GCS and early intubation status in order to determine the adjusted odds of LOW GOSE associated with HAP for each of the sub-populations. A survivor's analysis, excluding mortalities during the follow-up time period, was also conducted. Interaction effects on GOSE were investigated. Finally, we created a generalized estimating equation (GEE) model to simultaneously investigate all time points while controlling for within-patient correlation of repeated measures.

Results

The study cohort consisted of 141 patients in the trauma registry with a head-AIS ≥ 4 who were admitted to the TBIMS rehabilitation facility between 2003 and 2007 and who had follow-up data. The average age was 43.8 (SD=19.8), and 75.8% were men (N=104). There was a 30% incidence of HAP (N=42). The Kaplan-Meier analysis shows that the median time to pneumonia was 6 days. (Supplemental Digital Content 1)

When comparing group characteristics based on the presence or absence of HAP, groups had similar head AIS, systolic blood pressure, episodes of hypotension, similar prevalence of decompressive craniotomy and co-infections, and similar follow-up data. (Table 1) The HAP group had a higher percentage of men, was younger, and required more days of mechanical ventilation (MV). Though the groups had similar head AIS, the HAP group had a slightly higher Injury Severity Score (ISS); notably the HAP group had more severe injuries to the thorax. The HAP group also had a lower Glasgow Coma Scale (GCS) and was more likely to be intubated on scene or in the trauma bay. The HAP group also had longer inpatient rehabilitation length of stay (LOS).

There were 113 individuals with year-1 data, 81 with year-2 data, and 54 with year-5 data. Differences among individuals with and without follow-up data at each time point are shown in Table 2. There were no trends suggesting a systematic bias in patients lost to follow up.

The propensity to have low GOSE between analyzed patients and those lost to follow-up was not significantly different at any time point. (Table 2)

At 1, 2, and 5 years, subjects with HAP had lower GOSE. There were 11 mortalities after acute care discharge, 5% (N=2) from the HAP group and 9% (N=9) from the non-HAP group ($p = 0.381$). (Table 3) After adjusting for potential confounders of age, sex, race, head injury severity, injury severity to other parts of the body, severe injury to the thorax, decompressive craniotomy, initial GCS, and days of mechanical ventilation, HAP was independently associated with an approximately 7-fold increase in odds of low GOSE at 1, 2 and 5 years after injury (1 year adjusted OR = 6.39, 95%CI: 1.76 – 23.14, $p = 0.005$; 2 years adjusted OR = 7.30, 95%CI: 1.87 – 27.89, $p = 0.004$; 5 years adjusted OR = 6.89, 95%CI: 1.42 – 33.39, $p = 0.017$). (Figure 1) Due to smaller sample size, the models at 2 and 5 years were conducted in a backward step-wise fashion using the predictors from the full multivariable. Goodness-of-fit was adequate, measured by Hosmer and Lemeshow test, for the models at all time points (1 year: $p = 0.516$; 2 years $p = 0.541$; 5 years $p = 0.211$). C-statistics for the models were significant at all time points (1 year: $c = 0.791$, 95%CI: 0.673 – 0.848, $p < 0.001$; 2 years: $c = 0.765$; 95%CI: 0.658 – 0.871, $p < 0.001$; 5 years: $c = 0.761$, 95%CI: 0.633 – 0.889, $p = 0.001$). Among all covariates, HAP was the only predictor significant at all follow-up times. (Table 4) A survivor only analysis using backward step-wise regression, excluding the patients that died after the initial acute hospitalization period, had similar results (2 year adjusted OR = 7.23; 95%CI: 1.87 – 27.89; 5 year adjusted OR = 11.22; 95%CI: 1.89 – 66.52, $p = 0.008$).

Though the HAP and non-HAP groups differed significantly in terms of early intubation status, there was no interaction effect between early intubation and HAP on outcome ($p = 0.171$). Furthermore, when the cohort was stratified by early intubation status, HAP remained a significant predictor of poor outcome in both strata in a backwards step-wise model including the same covariates (early intubation stratum adjusted OR = 3.39, 95%CI: 1.16 – 9.91, $p = 0.025$; non-intubated stratum adjusted OR = 72.46, 95%CI: 5.20 – 1010.01, $p = 0.001$). Finally, when the cohort was stratified by GCS ≤ 8 versus GCS > 8 , HAP was independently associated with low GOSE in both groups (GCS ≤ 8 adjusted OR = 4.61, 95%CI: 1.58 – 13.42, $p = 0.005$; GCS > 8 adjusted OR = 38.99; 95%CI: 2.69 – 566.18, $p = 0.007$). (Figure 2)

Finally, given that no patterns of systematic bias are observed between patients with and without follow-up at different time points, we assume that the loss to follow-up was at random and constructed a generalized estimation equation (GEE) model. Among its uses, GEE modeling is used for repeated measures with loss to follow-up in order to account for within-patient correlations. This means that GEE modeling examines observations from all follow-up time points simultaneously while controlling for within-patient correlation. Placing all of the covariates from the full logistic model into the GEE model, patients with HAP had a 4.5-fold increased risk of poor global outcome (OR: 4.59; 95%CI: 1.82 – 11.60; $p = 0.001$).

Discussion

There has been significant success in determining acute factors that are predictive of short-term outcomes in TBI, like initial injury severity, hypotension, and more recently biomarkers of inflammation. (3, 4) Likewise, there is increasing research investigating demographic differences that predict long-term functional and cognitive outcomes in TBI such as sex, race, violence as a cause of TBI, and socioeconomic status. (5, 6, 11-14) The length of follow-up for studies evaluating TBI are often associated with the covariates of interest. Discharge to 1 year of follow-up post-injury is usually the longest period of follow-up when studies are evaluating pre-hospital and acute care variables in adult TBI populations. (15, 16) Several long-term studies exist, some following individuals with TBI for many years, but these studies rarely investigate factors in the acute setting. (17, 18) The incidence of nosocomial infection in TBI patients has been reported to be as high as 41%, (7) and specifically the incidence of HAP in the TBI population is consistently estimated at 30% or greater. (19, 20) Despite a moderate amount of research investigating in-hospital mortality and other short-term outcomes, (20-26) little is known about the effect of HAP on long-term outcomes after TBI.

This study demonstrated that HAP is independently associated with poor global outcomes at 1, 2, and 5 years post injury in patients with severe TBI. To our knowledge, this is the longest longitudinal study investigating HAP in the adult TBI population completed to date. The results of this study suggest that HAP is a significant contributor to poor long-term global outcomes. The survivor's analysis implies that a HAP-specific mortality effect is not a large contributory factor to the model, but rather that HAP has a substantial effect on recovery among survivors.

The majority of studies investigating in-hospital mortality and functional outcomes at hospital discharge have found no significant differences between TBI patients that do and do not contract HAP. (20-23, 26) Therefore, the goal of reducing the incidence of HAP in severe TBI patients has been to decrease ICU length of stay, hospital days, and reduce healthcare costs. However, the findings that HAP is common and contributes to poor long-term outcomes, suggests a need for reassessing measures for rigorous infection control in patients with severe TBI.

This study has several important implications. First, the analysis draws attention to the screening and surveillance for hospital acquired pneumonia and nosocomial infections in general. The most recent Guidelines for the Management of Severe Traumatic Brain Injury were published in 2007 (27-31) appropriately recommend against prophylactic use of antimicrobials. There may be a role in selected TBI cohorts for altered surveillance or different thresholds for screening for these types of infections to reduce the incidence of complications that result from them. Secondly, controversial issues of practice aimed at reducing nosocomial infection like the timing of tracheostomy, trans-pyloric feeding, stress ulcer prophylaxis, and early extubation take on a new importance. (32, 33) Most studies have concluded that early vs. late tracheostomy in the setting of severe TBI does not change mortality, however, there is converging evidence showing that early tracheostomy decreases ventilation days (34) and evidence-based protocols for early extubation can decrease

incidence of pneumonia. (32, 33) We cannot comment widely, however, on the mechanism that may underlie the long-term effect of HAP. It could be due to increased inflammation penetrating a compromised blood-brain barrier. Or it may be associated with chronic inflammation that lasts long after initial injury. (8)

A third implication involves the economic consequences and morbidity burden of complicating TBI with HAP. These include longer rehabilitation stays, higher resource utilization, and longer durations of mechanical ventilation and other specialized care in the acute setting. Although not the focus of this study, more work is needed to understand how HAP impacts cognitive, affective, functional, participation, and health quality outcomes. HAP influences on GOSE, particularly among survivors, suggest that HAP may have long-term consequences on multiple systems, including neurological systems after TBI.

Finally, this study raises important questions about what physiological mechanisms that may underlie the effects of HAP on long-term outcomes. The lung infiltrates associated with HAP could lead to cerebral hypoxia, causing additional secondary insult to an injured brain. Inflammation is fundamental to the complex processes associated with secondary TBI. It is now well-established that TBI results in a considerable inflammatory response that includes both peripheral and central production of pro-inflammatory cytokines, chemokines, and cell-adhesion molecules. (35, 36) The inflammatory response is necessary to clear cellular debris in the CNS after injury and for reparative functions. (37) Although some inflammation is necessary after injury, prolonged, chronic inflammation could be deleterious (8, 38, 39) and HAP may contribute to a prolonged and pathological inflammation response that influences TBI recovery. (40)

This study is not without limitation. The cohort studied is of a relatively small sample size, with little diversity in terms of racial background and other characteristics, which may limit the power of accounting for confounders. The incidence of HAP in our cohort was 30%. This is similar to a previous study but is smaller than others. Despite this, some cases of HAP may have been missed. Also, there is the potential that HAP is associated with more severe brain injuries. We mitigated this possibility by controlling for GCS, head AIS, stratifying the cohort, and by using the GEE model which was able to analyze all follow-up observations simultaneously while controlling for within-patient correlation. Based on the results from the stratified analyses, we are confident that these variables do not modify the relationship between HAP and outcome. Despite these limitations, this study shows that after adjusting for differences among individuals with and without HAP, as well as adjusting for differences among stratified groups, HAP is independently associated with poor global outcome at 1, 2, and 5 years after injury in severe TBI. Finally, patients that had 2 and 5 year follow-up may be subject to selection bias. Though selection bias could not be definitively ruled out, we feel it is unlikely given there were no patterns of systematic bias and no difference in propensity scores between patients analyzed and those lost to follow-up at any time point. Future studies will necessitate larger, more heterogeneous populations to validate the findings.

Conclusions

Hospital acquired pneumonia is independently associated with poor global outcomes in severe TBI up to 5 years after injury. Efforts should be taken to minimize the chance of pneumonia in patients with severe TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Logistic model demonstrating independent association of HAP and poor neurological outcomes in patients with severe TBI at 1, 2, and 5 years after controlling for age, sex, race, GCS, ISS, head (AIS 4 vs. 5), decompressive craniotomy, and number of ventilation days. Years 2 and 5 were conducted in a backwards stepwise fashion.

Figure 2.

Logistic model showing adjusted odds of HAP and poor global outcomes in patients with severe TBI stratified based on initial GCS and early intubation. The GCS stratification is adjusted for age, sex, race, ISS, head (AIS 4 vs. 5), decompressive craniotomy, and number of ventilation days. The early intubation stratification is adjusted for all of the cofactors listed above as well as initial GCS.

Table 1
Comparison of demographics and injury characteristics among individuals with and without HAP

	No HAP (N = 99)	HAP (N = 42)	p
Male, %	69	86	0.036
Age, mean (SD)	47.2 (20.6)	35.8 (15.0)	0.002
White, %	95	86	0.08
Transferred from OSH, %	61	67	0.497
Systolic BP, mean (SD)	146 (32)	140 (34)	0.320
Hypotension at scene or ED, %	2	5	0.582
Blood EtOH, mean (SD)*	0.071 (0.098)	0.092 (0.110)	0.285
Intubation at scene or in ED, %	41	76	< 0.001
GCS Admit, median (IQR)	7 (3-15)	3 (3-5.25)	< 0.001
ISS, median (IQR)	26 (20-34)	30 (26-38)	0.001
Head AIS, median (IQR)	5 (4-5)	5 (4-5)	0.099
Face Injury ISS, median (IQR)	1 (0-2)	1 (0-2)	0.253
Thorax ISS, median (IQR)	0 (0-2)	1.5 (0-3)	0.001
Extremity ISS, median (IQR)	1 (0-4)	2 (0-5)	0.270
Penetrating Injury, %	1	5	0.892
Decompressive Cranial Surgery, %	41	36	0.527
Vent Days, mean (SD)	3.7 (5.1)	13.7 (6.6)	< 0.001
Days of rehabilitation, mean (SD)	19.2 (12.1)	30.8 (30.8)	< 0.001
Urinary tract infection, %	9	10	0.935
Septicemia	4	12	0.126
*N=129			

OSH: Outside Hospital; GCS: Glasgow Coma Scale; AIS: Abbreviated Injury Scale; ISS: Injury Severity Scale; ED: Emergency Department; SD: Standard Deviation; IQR: Inter-quartile Range

Table 2

Baseline characteristics among patients with and without follow-up data at 1, 2 and 5 years.

	Year 1			Year 2			Year 5		
	Analyzed	Lost to Follow-up	p	Analyzed	Lost to Follow-up	p	Analyzed	Lost to Follow-up	p
Number	113	28	-	81	60	-	54	87	-
Male, %	73	75	0.868	75	72	0.627	65	79	0.057
Age, mean (SD)	44 (20)	44 (19)	0.934	38 (18)	51 (21)	< 0.001	50 (22)	40 (18)	0.003
White, %	87	89	0.716	89	85	0.494	85	89	0.566
Systolic BP, mean (SD)	145 (34)	141 (28)	0.473	140 (30)	151 (36)	0.06	146 (35)	143 (32)	0.703
Intubation at scene or in ED, %	54	42	0.292	54	48	0.482	44	56	0.17
GCS Admit, median (IQR)	3 (4–14)	3 (3 – 15)	0.624	3 (3 – 12)	7 (3 – 15)	0.265	7 (3 – 15)	3 (3 – 13)	0.288
Head AIS, median (IQR)	5 (4–5)	4 (4 – 5)	0.253	5 (4 – 5)	5 (4 – 5)	0.369	5 (4 – 5)	5 (4 – 5)	0.929
ISS, median (IQR)	29 (25–34)	26 (19–36)	0.94	29 (24–36)	27 (23–34)	0.427	26 (20–34)	30 (25–35)	0.033
Decompressive Craniotomy, %	39	39	0.973	39	38	0.888	43	37	0.492
Vent Days, mean (SD)	7.3 (7.4)	4.2 (5.9)	0.052	7.4 (6.9)	5.6 (7.6)	0.023	5.4 (7.1)	7.5 (7.3)	0.05
Pneumonia, %	32	21	0.28	35	23	0.149	24	33	0.243
Propensity for LOW GOSE, mean (SD)	0.476 (0.217)	0.418 (0.205)	0.097	0.477 (0.228)	0.482 (0.201)	0.878	0.473 (0.205)	0.482 (0.224)	0.799

OSH: Outside Hospital; GCS: Glasgow Coma Scale; AIS: Abbreviated Injury Scale; ISS: Injury Severity Scale; ED: Emergency Department; SD: Standard Deviation; IQR: Inter-quartile Range

Table 3
Unadjusted GOSE and mortality of patients with and without HAP

	No HAP (N = 99)	HAP (N = 42)	p
GOSE 1 yr, median (IQR)	6 (4-7.5)	4 (3.25-5.75)	< 0.001
GOSE 2 yr, median (IQR)	7 (5-8)	5 (3-7)	0.015
GOSE 5 yr, median (IQR)	7 (4-8)	5 (3-6)	0.017
Mortality	9 (9)	2 (5)	0.381

Table 4
Adjusted predictors of LOW GOSE at 1, 2, and 5 years. Years 2 and 5 are predictors of backward step-wise regressions using the predictors from the model at year 1

Year 1			
Predictor	Coefficient	95%CI	p
HAP	6.39	1.76 – 23.14	0.005
Age	1.04	1.01 – 1.07	0.012
Year 2			
HAP	7.30	1.87 – 27.89	0.004
Head AIS = 5 (vs. 4)	4.14	1.14 – 15.07	0.031
Severe Thorax Injury	14.02	1.13 – 147.36	0.028
ISS excluding Head	1.137	1.03 – 1.26	0.015
Decompressive Craniotomy	4.04	1.22 – 13.43	0.033
Year 5			
HAP	6.89	1.42 -33.39	0.017
Glasgow Coma Scale	1.20	1.05 – 1.15	0.008