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ORIGINAL ARTICLE

Nosocomial Infections and Outcomes after Intracerebral Hemorrhage: A Population-Based Study

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Abstract

Background Infections after intracerebral hemorrhage (ICH) may be associated with worse outcomes. We aimed to evaluate the association between nosocomial infections (>48 h) and outcomes of ICH at a population level.

Methods We identified patients with ICH using ICD-9-CM codes in the 2002–2011 Nationwide Inpatient Sample. Demographics, comorbidities, surgical procedures, and hospital characteristics were compared between patients with and without concomitant nosocomial infections. Primary outcomes were in-hospital mortality and home discharge. Secondary outcome was permanent cerebrospinal shunt placement. Logistic regression analyses were used to analyze the association between infections and outcomes.

Results Among 509,516 ICH patients, infections occurred in 117,636 (23.1 %). Rates of infections gradually increased from 18.7 % in 2002–2003 to 24.1 % in 2010–2011. Pneumonia was the most common nosocomial infection (15.4 %) followed by urinary tract infection (UTI) (7.9 %). Patients with infections were older ($p < 0.001$), predominantly female (56.9 % vs. 47.9 %, $p < 0.001$), and more often black (15.0 % vs. 13.4 %, $p < 0.001$). Nosocomial infection was associated with longer hospital stay (11 vs. 5 days, $p < 0.001$) and a more than twofold higher cost of care ($p < 0.001$). In the adjusted regression analysis, patients with infection had higher odds of mortality [odds ratio (OR) 2.11, 95 % CI 2.08–2.14] and cerebrospinal shunt placement (OR 2.19, 95 % CI 2.06–2.33) and lower odds of home discharge (OR 0.49, 95 % CI 0.47–0.51). Similar results were observed in subgroup analyses of individual infections.

Conclusions In a nationally representative cohort of ICH patients, nosocomial infection was associated with worse outcomes and greater resource utilization.

Keywords Intracerebral hemorrhage · Infections · Pneumonia · Sepsis · Meningitis · Urinary tract infection · Clinical outcome · Nationwide inpatient sample

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Outcomes following intracerebral hemorrhage (ICH) have remained poor despite advancements in medical care [1]. While the focus has been on the initial insult from the hematoma volume and the subsequent secondary injury, nosocomial infections also contribute to poor outcomes [2]. While studies in heterogeneous cohorts of ischemic and hemorrhagic strokes have reported an incidence of about 30 % for nosocomial infections [2], results from cohorts of ICH range from 11 % to 31 % [3, 4]. Immunodepression,

mediated by catecholamines and steroids, is a potentially modifiable target in the pathogenesis of infections after stroke [5]. It is purported that changes in serum cortisol and catecholamine levels influence susceptibility to infection following a stroke [6]. This theory is further strengthened by animal data where steroid and adrenergic antagonists have been shown to decrease lymphocyte apoptosis and subsequently reduce rates of infection after brain injury [6]

Whether infections have an adverse impact on neurological outcomes after ICH remains an area of debate given conflicting results. For instance, a prospective multicenter study using the Virtual International Stroke Trials Archive concluded that infections were not associated with 90-day functional outcomes [3]. This study, however, was underpowered ($n = 201$) to detect an association. More recently, an analysis of patients enrolled in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) showed a significant association between post-ICH infections and poor functional outcome [4]. Prior studies on infections in ICH included patients with the diagnosis of any infection following hospital admission, including in the first 48 h. The definition of hospital-acquired or nosocomial infection, however, entails infections that occur only after the first 48 h following hospital admission [7]. We hence aimed to study the relationship between nosocomial infections and ICH outcomes at a nationally representative sample of ICH patients.

Methods

Study Design and Population

Discharge data were obtained from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP) from 2002 to 2011 [8]. The NIS represents a 20 % stratified random sample of all inpatient admissions to the non-federal US hospitals. The data provide information on patient demographics, hospital characteristics, primary and secondary diagnoses, inpatient procedures, comorbidities, and case-severity measures. All diagnoses and procedures are recorded using *International Classification of Diseases, Clinical Modification, 9th Revision* (*ICD-9-CM*) codes.

We first identified cases with a primary diagnosis of nontraumatic ICH using the ICD-9-CM code 431 [9]. Cases with age <18 years, traumatic brain injury, brain malignancy, and cerebral vascular malformations were excluded to restrict our study sample to those with primary ICH. This diagnosis code in the absence of codes for trauma has been shown to have excellent sensitivity and specificity for spontaneous ICH [10]. We also excluded patients with early death (<48 h) and those with initiation of palliative care (code V66.7). In a comparison of 100 consecutive ischemic stroke patients (March 2010–June 2012) at two university-affiliated teaching hospitals, the accuracy of the PC code V66.7 was found to have a sensitivity of 81 % and specificity of 97 % [11]. Moreover, the use of the palliative care code in ICH has been validated in prior studies using the NIS database [12]. Patients with early death were excluded since the definition of hospital-acquired/nosocomial infections uses a cutoff time of 48 h [7], and patients with palliative care were also excluded to minimize the effect of the self-fulfilling prophecy [13]. Nosocomial infections were identified using the following ICD-9-CM codes: 480.x-486.x for pneumonia; 590.x, 595.x, and 599.x for urinary tract infection (UTI); 995.91 and 995.92 for sepsis; and 320.x-322.x for meningitis.

Measurements

A cumulative clinical score was calculated for each patient using the Charlson comorbidity index [14, 15]. The index is a weighted score of 17 different comorbidities using *ICD-9-CM* codes and has been validated for outcome adjustment for administrative datasets on ischemic stroke and ICH [16, 17]. Resource utilization measures included inflation-adjusted cost of care and length of hospital stay. Cost of care was obtained using HCUP cost-to-charge ratios and total hospital charges and was adjusted for inflation to obtain US 2013 dollar values using yearly inflation rates published by the US Department of Labor-Bureau of Labor Statistics [18].

Outcome

The main outcomes of interest were inpatient mortality and home discharge. We chose to include two primary outcome measures (i.e., mortality and discharge disposition). Discharge disposition has been validated as a surrogate for functional outcome [19]. Secondary outcome was permanent cerebrospinal shunt placement.

Statistical Analysis

We used Pearson's χ^2 test to compare categorical variables. For continuous variables, the Mann–Whitney *U* test was used since the data were not normally distributed. Binary logistic regression was used to study the association between nosocomial infections and ICH outcomes. In the multivariable analyses, we adjusted for age, sex, race, hospital teaching status, ICH case volume, Charlson comorbidity index, hypertension, diabetes mellitus, hyperlipidemia, smoking, anticoagulant use, hydrocephalus, and mechanical ventilation. These variables were selected based on a statistical significance of p value <0.05 with the exposure in the bivariate analysis.

To account for the lack of ICH severity variables in the NIS database, we performed similar regression analyses in the following four subgroups selected a priori: high-volume centers, patients undergoing mechanical ventilation >96 h, ICH requiring ventriculostomy, and patients with Charlson comorbidity index scores >3. The rationale of this analysis was to select subgroups with presumed high ICH severity so that the independent effect of infections could be estimated. Sampling weights were applied as indicated by the NIS [20]. All analyses were two-tailed and were performed using STATA® version 14 (StataCorp LP, College Station, TX, USA) with statistical significance set at p value <0.05.

Results

A total of 619,166 nontraumatic ICH admissions were recorded from 2002 to 2011 of whom 109,650 were excluded due to early death (<48 h) or implementation of palliative care. Infections occurred in 117,636 patients (23.1 %). Pneumonia was the most common nosocomial infection (78,515 cases, 15.4 %), followed by UTI (40,018 cases, 7.9 %), sepsis (18,243 cases, 3.6 %), and meningitis (1558 cases, 0.3 %). It is important to note that the sum total of individual infections (138,334) exceeds the actual number of patients with nosocomial infections. This is because some patients had more than one infection during their hospital stay. Rates of post-ICH infections gradually increased from 18.7 % in 2002–2003 to 24.1 % in 2010–2011 (Fig. 1).

Patients with infections were older ($p < 0.001$), predominantly female (56.9 % vs. 47.9 %, $p < 0.001$), and more often black (15.0 % vs. 13.4 %, $p < 0.001$) (Table 1). Among hospital characteristics, urban hospital location, teaching status, and high ICH case volume were associated with higher rates of infection. Nosocomial infections were also more common in ICH patients with high Charlson comorbidity scores ($p < 0.001$) and diabetes mellitus ($p < 0.001$). Similarly, patients with nosocomial infection also had higher rates of hydrocephalus (13.4 vs. 5.0 %, $p < 0.001$) and mechanical ventilation (24.9 vs. 6.7 %, $p < 0.001$) compared to those without infections (Table 2). Nosocomial infections were associated with longer hospital stay (11 vs. 5 days, $p < 0.001$) and a more than twofold higher cost of care (<0.001).

In the logistic regression models adjusted for confounders (Table 3), the presence of any infection was associated with significantly higher odds of in-hospital mortality [odds ratio (OR) 2.11, 95 % CI 2.08–2.14] and CSF shunt placement (OR 2.19, 95 % CI 2.06–2.33) and lower odds of home discharge (OR 0.49, 95 % CI 0.47–0.51). Similar results were obtained in the subgroup analyses of high-volume centers, patients undergoing mechanical ventilation >96 h, ICH requiring ventriculostomy, and patients with Charlson comorbidity index scores > 3 (supplemental table I). We subsequently performed subgroup analyses studying the relationship between individual infections and ICH outcomes (Table 4). For this analysis, we considered only ICH patients with the specific infection in question and compared them with patients without any infection (i.e., patients with more than one infection were excluded from the analysis to avoid being confounded from other infections). Pneumonia, UTI, sepsis, and meningitis were associated with worse primary and secondary outcomes. We subsequently performed additional regression analyses to assess the relationship between neurosurgical procedures (ventriculostomy, craniectomy, craniotomy) and nosocomial infections (supplemental table II). In the adjusted multivariable analysis, all three neurosurgical procedures were independently associated with infections; however, only ventriculostomy and craniectomy were independently associated with meningitis.

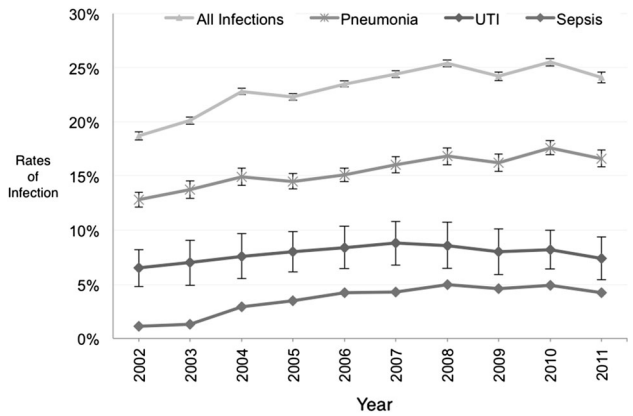

Fig. 1 Temporal trends in infection rates. *UTI* urinary tract infection

Discussion

In a large, heterogeneous, nationally representative cohort of ICH patients, nosocomial infections were associated with higher mortality and lower home discharge. Similar results were observed with individual infections. Patients with infections also had longer length of hospital stay and higher hospital costs. The rate of nosocomial infections after ICH appeared to have increased marginally over the last decade, which may reflect a reporting bias due to greater surveillance of reportable nosocomial infections over time.

The incidence of nosocomial infections in our study was 23 %, which is lower than previously reported rates.

Table 1 Demographics and hospital characteristics of patients with intracerebral hemorrhage with and without nosocomial infections

Characteristic	Any infection $n = 117,636$ (23.1 %)	No infection $n = 391,880$ (76.9 %)	p value
Age			<0.001
18–64 years	40,500 (34.4)	148,105 (37.8)	
65–79 years	39,634 (33.7)	132,141 (33.7)	
>80 years	37,502 (31.9)	111,634 (28.5)	
Sex			<0.001
Male	50,732 (43.1)	204,092 (52.1)	
Female	66,898 (56.9)	187,591 (47.9)	
Race			<0.001
Caucasian	58,383 (49.6)	199,882 (51.0)	
Black	17,663 (15.0)	52,510 (13.4)	
Hispanic	9531 (8.1)	30,442 (7.8)	
Asian	4547 (3.9)	14,483 (3.7)	
Other	3347 (2.8)	11,181 (2.9)	
Missing	24,165 (20.5)	83,381 (21.3)	
Hospital location			<0.001
Rural	6703 (5.7)	28,291 (7.3)	
Urban	109,926 (94.3)	361,004 (92.7)	
Hospital bed size			<0.001
Small	7794 (6.7)	28,444 (7.3)	
Medium	24,183 (20.7)	83,764 (21.5)	
Large	84,652 (72.6)	277,086 (71.2)	
Teaching status			<0.001
Non-teaching	43,726 (37.5)	166,491 (42.8)	
Teaching	72,904 (62.5)	222,804 (57.2)	
ICH case volume			
1–23 cases/year	24,664 (21.0)	94,403 (24.1)	<0.001
24–47 cases/year	27,803 (23.6)	101,435 (25.9)	
48–85 cases/year	31,272 (26.6)	100,309 (25.6)	
>85 cases/year	33,896 (28.8)	95,734 (24.4)	
Primary payer			<0.001
Medicare	74,911 (63.8)	235,238 (60.1)	
Medicaid	12,951 (11.0)	32,321 (8.3)	
Private	20,958 (17.8)	86,923 (22.2)	
Other	8657 (7.4)	36,738 (9.4)	

In a meta-analysis of 87 studies, the pooled rate was 30 % [2], which was later replicated in the ERICH study [4]. One possible explanation for the relatively lower incidence in our study could be due to the inclusion of patients treated at hospitals with low case volumes and nonteaching community hospitals. Screening for infections in these centers may have been less aggressive than the tertiary centers, leading to underdiagnosis. To explore this further, we performed a subgroup analysis of only the highest quartile of ICH case volume hospitals and found an incidence of 28 % for infections, congruent with other studies.

From a pathophysiological standpoint, infections are purported to be mediated by post-stroke immunodepression [5, 21]; however, anatomic location of lesions may also influence immunodepression, with lesions in the anterior middle cerebral artery territory cortex [22] and the insula [23] being associated with increased risk of infections after ischemic stroke. Lack of information on ICH characteristics in the NIS data precluded further exploration of the influence of anatomic location or hematoma volume. We also observed a significant association between nosocomial infection and higher hospital costs and also with length of hospital stay. Furthermore, neurosurgical procedures were

Table 2 Comorbidities, complications, and procedures performed on patients with intracerebral hemorrhage

Comorbidities	Any infection $n = 117,636$ (23.1 %)	No infection $n = 391,880$ (76.9 %)	p value
Modified Charlson comorbidity index			<0.001
0–1	79,249 (68.0)	276,205 (71.3)	
2	27,727 (23.8)	81,707 (21.1)	
≥3	9567 (8.2)	29,508 (7.6)	
Hypertension	87,470 (75.1)	300,389 (77.5)	<0.001
Diabetes mellitus	26,014 (22.3)	80,743 (20.8)	<0.001
Hyperlipidemia	23,253 (19.8)	99,900 (25.5)	<0.001
Smoking	8085 (6.9)	39,142 (10.0)	<0.001
Alcohol use	7261 (6.1)	22,604 (5.8)	0.756
Anticoagulant use	5417 (4.6)	23,862 (6.1)	<0.001
Complications			
Hydrocephalus	15,736 (13.4)	19,562 (5.0)	<0.001
Venous thromboembolism	4879 (4.1)	4942 (1.3)	<0.001
Procedures			
Craniotomy	1810 (1.5)	3124 (0.8)	<0.001
Craniectomy	309 (0.3)	767 (0.2)	0.450
Mechanical ventilation	29,293 (24.9)	26,090 (6.7)	<0.001
Tracheostomy	1939 (1.6)	911 (0.2)	<0.001
Gastrostomy	28,893 (24.6)	24,028 (6.1)	<0.001
Resource utilization measures			
Median length of stay (days, IQR)	11 (6–20)	5 (3–8)	<0.001
Median cost of care (USD, IQR)	23,721 (11,665–51,098)	10,340 (6203–18,603)	<0.001

IQR inter quartile range

Table 3 Logistic regression models showing the effect of nosocomial infections on binary intracerebral hemorrhage outcomes

Outcomes	Intracerebral hemorrhage patients			
	Any infection $n = 117,636$ (23.1 %)	No infection $n = 391,880$ (76.9 %)	Adjusted OR (95 % CI)	p value
In-hospital mortality	22,350 (19.0)	65,647 (16.8)	2.11 (2.08–2.14)	<0.001
Home discharge/self-care	12,321 (10.5)	110,146 (28.1)	0.49 (0.47–0.51)	<0.001
Permanent CSF shunt	2761 (2.3)	2100 (0.5)	2.19 (2.06–2.33)	<0.001

Models adjusted for age, sex, race, hospital teaching status, ICH case volume, Charlson comorbidity index, hypertension, diabetes mellitus, hyperlipidemia, smoking, anticoagulant use, seizures, hydrocephalus, craniectomy, and mechanical ventilation

p value < 0.05 was considered significant

CI confidence interval, *CSF* cerebrospinal fluid, *OR* odds ratio

also associated with infections. This may reflect ICH severity factors, which also increase risk for infection. Also noteworthy is the predominance of infection in black patients in our analysis, which has been highlighted in prior studies and attributed to low white blood cell counts and a subsequent higher risk of immunodepression [4].

The results of this study should be interpreted with caution due to inherent limitations of administrative databases, which meant that we lacked well-validated ICH severity measures such as the Glasgow Coma Scale score or ICH volume and location. Second, errors due to misclassification are also possible; however, the *ICD-9-CM* code 431 is validated to have high positive predictive value for diagnosing primary ICH from administrative datasets [9, 24]. Similarly, the accuracies of the codes for pneumonia, UTI, sepsis, and meningitis are also considered high and have been used in multiple studies from the NIS and other administrative datasets [25, 26]. Moreover, random

Table 4 Logistic regression models showing the effect of individual nosocomial infections on binary intracerebral hemorrhage outcomes

Outcomes	Pneumonia (reference: no infections)		UTI (reference: no infections)		Sepsis (reference: no infections)		Meningitis (reference: no infections)	
	Adjusted OR (95 % CI)	*p* value	Adjusted OR (95 % CI)	*p* value	Adjusted OR (95 % CI)	*p* value	Adjusted OR (95 % CI)	*p* value
In-hospital mortality	2.68 (2.58–2.77)	<0.001	1.42 (1.10–1.94)	0.030	2.93 (2.78–3.21)	<0.001	3.32 (2.87–3.98)	<0.001
Home discharge/self-care	0.53 (0.51–0.55)	<0.001	0.48 (0.46–0.49)	<0.001	0.41 (0.38–0.44)	<0.001	0.68 (0.56–0.83)	<0.001
Permanent CSF shunt	2.34 (2.16–2.53)	<0.001	2.48 (2.30–2.68)	<0.001	2.38 (2.16–2.64)	<0.001	2.57 (2.16–2.96)	<0.001

Models adjusted for age, sex, race, hospital teaching status, ICH case volume, Charlson comorbidity index, hypertension, diabetes mellitus, hyperlipidemia, smoking, anticoagulant use, seizures, hydrocephalus, craniectomy, and mechanical ventilation

p value < 0.05 was considered significant

CI confidence interval, *CSF* cerebrospinal fluid, *OR* odds ratio, *UTI* urinary tract infection

ICD-9-CM coding errors would bias the results toward the null and are, hence, unlikely to account for the measured differences in mortality rates found in this study. Third, data on the timing of complications (such as hydrocephalus) or procedures (such as mechanical ventilation) in relation to the diagnosis of nosocomial infections were not available. Additionally, the NIS data also do not allow for differentiation between initial and recurrent ICHs. Hence, patients with admissions for recurrent ICHs may also have been included. Given the random sampling of hospitals every year by the NIS and the low rate of ICH recurrence [27, 28], it appears less likely for the same patient to have been included more than once for a recurrent ICH admission. Finally, it is also important to note that statistical significance was often achieved despite small differences in proportions between the groups, due to the large sample size of the study.

Conclusion

Nosocomial infections after spontaneous ICH appear to be associated with higher mortality, lower rates of home discharge, and higher resource utilization measures. Strategies to reduce infection rates in these patients may eventually lead to reductions in the morbidity and mortality associated with ICH.

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