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Nosocomial Infections among Patients with Intracranial Hemorrhage: A Retrospective Data Analysis of Predictors and Outcomes

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ABSTRACT

Objective: Intracranial hemorrhage is a critical medical emergency. Nosocomial infections may promote worse outcomes in these vulnerable patients. This study investigated microbial features, predictors, and clinical outcomes of nosocomial infections among patients with multiple subtypes of intracranial hemorrhage.

Patients and methods: We conducted a retrospective cohort study of patients that were hospitalized with intracranial hemorrhage between January 2015 and October 2018, and divided them into two groups based on the development of nosocomial infection. Within the cohort of patients with nosocomial infections, microbiology and resistance patterns were established across multiple sites of infection. Moreover, consequences of nosocomial infection such as mortality and length of hospital stay were determined.

Results: A total of 233 cases were identified that met our inclusion and exclusion criteria out of which were 94 cases of nosocomial infection (40.3%) versus 139 cases with no nosocomial infection (59.7%). The most common infections were pneumonia, urinary tract infections, and bacteremia. Resistance accounted for 70.2% of cultures. Multivariable analysis revealed significant association of nosocomial infections with hypertension (OR: 2.62, 95% CI: 1.11–6.16, $p = 0.027$), hospital LOS (OR: 1.08, 95% CI: 1.05–1.12, $p < 0.001$), levetiracetam (OR: 3.6, 95% CI: 1.41–0.922, $p = 0.007$), and GCS category (OR: 5.42, 95% CI: 1.67–17.55, $p = 0.005$ and OR: 7.63, 95% CI: 2.44–23.87, $p < 0.001$ for moderate and severe, respectively). Patients with nosocomial infections witnessed a significant increase in the length of hospital stay (23 versus 8 hospital days, $p < 0.001$). This finding was significant across most types of brain hemorrhage. Mortality was significantly associated with GCS category (OR: 10.1, 95% CI: 4–25.7, $p < 0.001$) and percutaneous endoscopic gastrostomy tube insertion (OR: 19.6, 95% CI: 4.1–91, $p < 0.001$).

Conclusions: Collectively, these findings suggest that nosocomial infections are common among patients with intracranial hemorrhage and can be predictable by considering certain risk factors. Future studies are warranted to evaluate the efficacy of implementing infection control strategies or protocols on these patients to achieve better therapeutic outcomes.

1. Introduction

Intracranial hemorrhage includes any pathological bleeding within the cranial vault [1]. It may involve the brain parenchyma itself (intracerebral hemorrhage [ICH]) which may further extend into brain ventricles (intraventricular hemorrhage [IVH]), or may occur within the meningeal spaces surrounding the brain, including epidural hematoma (EDH), subarachnoid hemorrhage (SAH), and subdural hematoma (SDH) [1,2].

Notably, ICH is the second most common type of all strokes (after ischemic stroke), and has accounted for more than 3.0 million deaths globally in 2010 [3,4]. Hypertension is the most common cause for ICH incidence [5–7]. It was associated with more than double the risk of ICH in one study [8]. The 30-day mortality rate was reported in one study as high as (35–52%) [9]. Despite that the incidence was decreasing in the past decade, mortality rates had remained unchanged [10]. This implies that while preventive measures were effective, the management itself remains suboptimal.

Most cases of SAH are caused following trauma. Eighty-five percent of non-traumatic cases are attributed to ruptured aneurysm [1].

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Outcomes following SAH have been improved significantly after the introduction of surgical modalities such as aneurysmal clipping and coiling [11]. Factors contributing to poor prognosis in SAH are increasing age, severe neurological grade; such as Glasgow Coma Scale (GCS), ICH or IVH, elevated systolic blood pressure (SBP) on admission, and previous history of hypertension, myocardial infarction, liver disease, or SAH. Other contributing factors to unfavorable outcomes during hospitalization are elevated temperature (> 38 °C), use of anticonvulsants, symptomatic vasospasm, and cerebral infarction [12]. Overall mortality rate in patients with SDH that required surgery was 40–60% [13–15]. Increased age and decreased GCS level are among the most important poor prognostic indicators [16,17]. While EDH is uncommon, it is a serious consequence of head trauma. EDH was reported in 1–4% of traumatic brain injury (TBI) cases [18].

Nosocomial infections (NI) are frequently encountered post admission of intracranial hemorrhage [19]. It was reported in 23–31% of patients with ICH and 15.8–37% among patients with SAH [20–23]. Furthermore, NIs incidence had increased from 18.7% to 24.1% across the time period from 2002 to 2011 in patients with ICH [20]. The most common types of NI were pneumonia, urinary tract infections (UTIs), bacteremia, and intracranial infections such as meningitis and ventriculitis [24,25]. Nosocomial pneumonia affects 1 in 5 patients with spontaneous ICH [26]. This might be linked to systemic immunodepression induced by acute brain injury, thereby increasing susceptibility to post-stroke infections [24]. Stroke impairs the immune system and can increase the susceptibility to infection [27]. Although inconsistent findings were reported in the literature, NIs can promote poor medical outcomes, higher mortality, increased length of hospital stay (LOS), and higher costs in patients with ICH and SAH [20,28,29]. IVH was the only significant contributor to NI among patients with ICH 25]. To our knowledge, NIs after SDH were not subjected to analysis of predictors and outcomes.

Despite the current advancements in the prompt diagnosis and management, prognosis of hemorrhagic strokes has remained poor. Regular updates and a better understanding of stroke epidemiology and incidence of hemorrhagic complications, such as NIs would be essential to provide the best evidence-based care. We hypothesized that there are still many undiscovered risk factors for NIs and that NIs predict poor outcomes, such as increased mortality rates and LOS among patients with intracranial hemorrhage who were admitted to a tertiary health care center in Jordan.

2. Patient and methods

2.1. Study design

This is a retrospective descriptive study conducted at King Abdullah University Hospital (KAUH), which is a tertiary teaching hospital located at the north of Jordan. The local institutional review board committee at Jordan University of Science and Technology and KAUH has approved this project.

2.2. Study population and case ascertainment

A cohort of patients that were admitted to KAUH between January 2015 to October 2018, with one or more types of intracranial hemorrhage (ICH, SAH, SDH or EDH) was included in this study. Medical and surgical indices were retrospectively screened for appropriate codes. The potential cases were reviewed for inclusion by the research team. Inclusion criteria include patients 18 years old or more at the time of diagnosis and who were admitted because of intracranial hemorrhage. Exclusion criteria include incomplete medical record and hemorrhagic transformation after ischemic stroke. Eligible patients were divided into two groups based on the presence of NI. Baseline demographics, comorbid conditions, medications received during hospitalization, invasive device use, GCS score, and operations were retrospectively reviewed. Both groups were also followed up and compared regarding outcomes including mortality and LOS.

2.3. Data collection

Data were collected by trained neurologists from electronic medical records. For every patient that met inclusion criteria, the following data were collected: age at admission, gender, type of intracranial hemorrhage (ICH, SAH, EDH or SDH), GCS at admission (mild [13–15], moderate [9–12], severe [8 or less]), severity score (for ICH and SAH only), proposed etiology of intracranial hemorrhage, comorbidities (diabetes, hypertension, ischemic heart disease (IHD), cancer, others), invasive device use (bladder catheterization, external or internal brain drainage, mechanical ventilator, percutaneous endoscopic gastrostomy [PEG]), medications during admission, craniotomy or craniectomy, clipping or coiling in aneurysmal SAH, tracheostomy, LOS (days), and mortality within 3 months of admission. For patients with NI, the following information was additionally obtained: site of infection, microorganism(s) identified in the culture, and mode of resistance if any. Microbiology and resistance patterns were established across multiple sites of infection.

2.4. Key measures

NI, as defined by the National Nosocomial Infection Surveillance System (NISS), is any infection noticed after 48 h of admission, up to 3 days after discharge, or up to 30 days after an operation, in a healthcare facility when someone was admitted for reasons other than the infection [30]. Multidrug-resistant (MDR) bacteria are defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug-resistant (XDR) is the non-susceptibility to at least one agent in all, but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories), while pandrug-resistance (PDR) is known as nonsusceptibility to all agents in all antimicrobial categories [31]. Severity scores were measured for ICH by ICH score (out of 6 grading scale) and SAH by Hunt and Hess grading system (Grade 1–5) as previously described [32–34]. ICH score is composed of six simple clinical and radiographic points; it has been designated to predict mortality after ICH. Hunt and Hess grade correlates with the severity of hemorrhage. External brain drainage includes placement of external ventricular, subdural, or epidural drains.

2.5. Statistical analysis

Categorical variables are described by count and percentage. Continuous variables are described using median and interquartile range (IQR). Univariate analyses were performed using Chi-square test ($\chi 2$ test) or Fisher's exact test (if one or more cells have expected count of less than 5) for categorical outcomes, and Mann-Whitney U test for continuous outcomes. Univariate binary logistic regression was initially used to identify potential continuous predictor variables associated with NI or mortality, such as age, LOS, and GCS score out of 15. Binary logistic or multiple linear regressions were implemented to assess predictors of NI, mortality, and hospital LOS as appropriate, adjusting for potential covariates. Kaplan Meier (KM) method was used to estimate cumulative survival as a function of time. Statistical significance was set at a two-sided p value less than 0.05. Statistical analyses were performed using SPSS (IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Cohort characteristics

A cohort of 233 adult patients was hospitalized with one or more type of intracranial hemorrhage and included in the final analysis

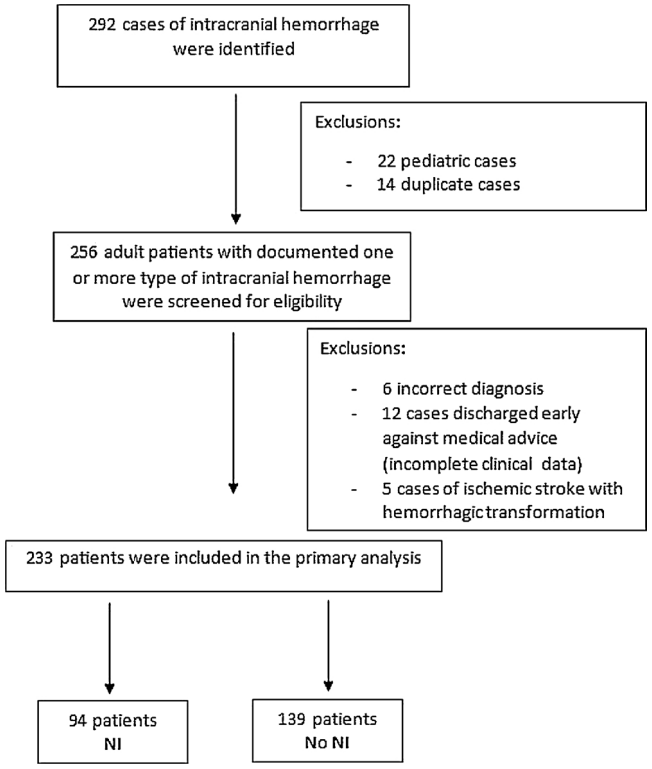

Fig. 1. Study flow chart. Abbreviations: NI, nosocomial infection.

(Fig. 1). Different types of intracranial hemorrhage were distributed among patients as depicted in Fig. 2. ICH made up the majority of cases (43.6%), followed by IVH, SDH, and SAH, respectively. Only one case of epidural hemorrhage was identified, the cause of which was iatrogenic. Table 1 lists demographics, comorbid conditions, and etiology for each class of intracranial hemorrhage. Male gender accounted for more than two-thirds of all admitted cases (67.8%). The median age at the time of admission was 60 years old (IQR, 46–71 years). The most prevalent comorbidities were hypertension (63.1%), diabetes (35.2%), and IHD (16.3%). More than third (37.8%) of patients were on chronic antiplatelet or anticoagulant therapy prior to the diagnosis of hemorrhage, of which aspirin was the most frequently prescribed (30.5%).

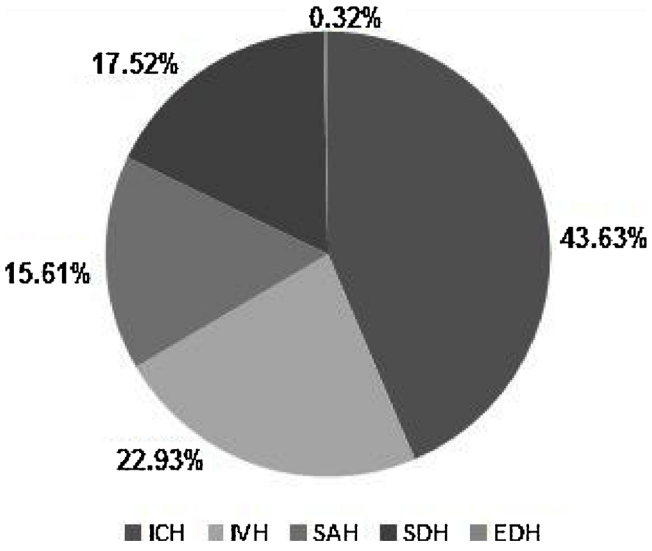

Fig. 2. Pie diagram showing the distribution of the classes of intracranial hemorrhage among patients. ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

Hypertensive crises were the leading cause of intracranial hemorrhage (39.9%), which was primarily frequent for ICH (67.2%) and IVH (60.3%). Aneurysmal rupture and trauma were common causes for SAH and SDH, respectively.

3.2. Nosocomial infections and antimicrobial resistance

Ninety-four cases (40.3%) of NI were recorded and distributed as follows: the highest percentage was for IVH (56.2%), followed by either ICH or SAH (46% each) as illustrated in Fig. 3. The most common infections were pneumonia (59.6%) and UTI (56.4%). They account for the commonest infections across each type of hemorrhage. The frequency and percentage of other types of infection, resistance patterns, and causative microorganisms are listed in Table 2. Resistance was documented in 66 patients (70.2%), of which 83.3% demonstrated MDR and 42.4% showed XDR bacteria. A total of 63.5% of urine cultures showed some type of resistance; sputum cultures showed 78.5%, while cultures of blood showed only 16.6% of generalized resistance. Extended-spectrum beta-lactamases producing bacteria (ESBL +ve) were found in 9 urine cultures (8 *E. coli* and 1 *Klebsiella pneumoniae*), 1 blood culture (*Klebsiella pneumoniae*), 1 sputum culture (*E. coli*), and 1 wound culture (*E. coli*). Methicillin-resistant *Staphylococcus aureus* (MRSA) was encountered in three specimens: sputum, blood, and wound cultures. Pneumonia was mainly caused by resistant strains of *Acinetobacter baumannii*. UTI was predominately caused by resistant *E.coli* and *Candida* species. The majority of septic cases were contributed by *Coagulase-Negative Staphylococci*. The use of levetiracetam was significantly associated with the development of resistance ($p = 0.038$), specifically MDR ($p = 0.043$). The most encountered bacteria among infections within subjects taking levetiracetam was *Acinetobacter baumannii*. The most frequently prescribed antibiotics for treating NIs among patients with intracranial hemorrhage were: vancomycin, meropenem, piperacillin-tazobactam, and levofloxacin.

3.3. Risk factors of nosocomial infections

Table 3 displays the association between demographic and clinical factors and the development of NI as determined by univariate and multivariable analyses. Significant positive associations between NI and the following were detected by univariate analysis: hypertension, hospital LOS, ICH, IVH, levetiracetam, prior antibiotic use, GCS category, Foley's catheter, mechanical ventilation, PEG tube, craniotomy or craniectomy, and external and internal brain drainage devices. In contrast, SDH was negatively associated with infection rates (odds ratio (OR): 0.404, 95% CI: 0.206–0.793, $p = 0.003$). Among these factors, the highest OR was for severe GCS category (OR: 5.38, 95% CI: 2.86–10.10) followed by Foley's catheter use (OR: 4.65, 95% CI: 2.27–9.52). Clipping and coiling of aneurysmal SAH did not increase the risk for NIs.

Subgroup analysis revealed that pneumonia was markedly associated with mechanical ventilation, tracheostomy, and PEG tube ($p < 0.001$). Bladder catheterization was the only significant association with UTI ($p < 0.001$). Bacteremia was markedly associated with the insertion of PEG tube, mechanical ventilator, and tracheostomy ($p < 0.001$) as well as Foley's catheter insertion and Craniotomy/Craniectomy ($p = 0.013$ and 0.034, respectively). Moreover, external and internal brain drainage devices were significantly associated with meningitis ($p = 0.013$ and 0.007, respectively). Levetiracetam was significantly associated with bacteremia and surgical site infection ($p = 0.003$ for both). Hypertension showed a significant increase in the incidence of UTI ($p = 0.001$).

For multivariable analysis, the dependent variable was NI status and independent variables were all factors that demonstrated statistical significance as aforementioned with univariate analysis. Hypertension (OR: 2.62, 95% CI: 1.11–6.16, $p = 0.027$), hospital LOS (OR: 1.08, 95% CI: 1.05–1.12, $p < 0.001$), levetiracetam (OR: 3.6, 95% CI: 1.41–0.922, $p = 0.007$), and GCS category (OR: 5.42, 95% CI:

Table 1
Baseline demographics, comorbid diseases, and etiology across classes of intracranial hemorrhage.

Characteristic	All cases (n = 233)	ICH (n = 137)	IVH (n = 73)	SAH (n = 50)	SDH (n = 56)
Age, (median, IQR)	60 (46-71)	60 (50-69)	61 (50-69)	48 (38-65)	64 (47-76)
Gender, n (%)[a]					
Male	158 (67.8%)	97 (70.8%)	49 (67.1%)	24 (48%)	40 (71.4%)
Female	75 (32.2%)	40 (29.2%)	24 (32.9%)	26 (52%)	16 (28.6%)
Comorbidities (%)[a]					
Hypertension	63.1	77.4	75.3	30	55.4
Diabetes	35.2	40.9	42.5	22	32.1
Cancer	2.6	2.2	1.4	6	0
IHD	16.3	17.5	24.7	6	25
Parkinson	1.7	2.2	1.4	0	1.8
Ischemic stroke	6.4	7.3	4.1	4	7.1
AF	3.4	3.6	5.5	0	8.9
HF	7	3.6	2.7	0	3.6
CKD	10	5.8	6.8	2	0
Valve Replacement	2.1	3.6	4.1	2	0
VTE	2.1	2.2	1.4	0	5.4
Hypothyroidism	1.7	2.2	0	2	0
Others	10.3	8.8	4.1	4	16.1
Antiplatelet or anticoagulant use (%)[a,b]	37.8	42.3	46.6	20	44.6
Warfarin	9.4	10.9	11	6	12.5
Aspirin	30.5	34.3	41.1	16	33.9
Clopidogrel	5.6	5.1	2.7	4	10.7
Dipyridamole	0.4	0	0	0	1.8
Etiology (%)					
Aneurysm	10.7	2.19	5.48	44	3.57
Trauma	9.4	2.19	1.37	10	26.79
Hypertensive crises	39.9	67.15	60.27	36	3.57
AVM	3	4.38	2.74	4	0
Warfarin toxicity	4.3	3.65	1.37	4	8.93
Unknown	29.2	17.52	26.03	2	50
Others	3.4	2.92	2.74	0	7.14

AF, atrial fibrillation; AVM, arteriovenous malformation; CKD, chronic kidney disease; HF, heart failure; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; VTE, venous thromboembolism.
[a] Percentage within type of hemorrhage.
[b] Patients may take more than one antiplatelet or anticoagulant.

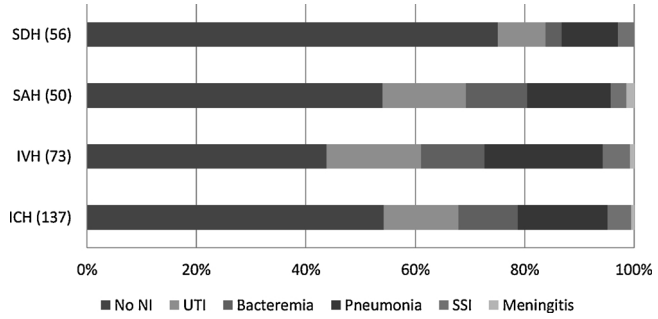

Fig. 3. Percentage of different types of nosocomial infections among each type of intracranial hemorrhage (frequency). ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; NI, nosocomial infection; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

1.67–17.55, p = 0.005 and OR: 7.63, 95% CI: 2.44–23.87, p < 0.001 for moderate and severe, respectively) were significant predictors of nosocomial infections after adjustment for other covariates (Table 3).

3.4. Complications of nosocomial infections

Development of NI in patients with intracranial hemorrhage resulted in a significant increase in the median hospital LOS versus those without infections as listed in Table 4 (23 vs. 8 days, p < 0.001). This finding remained significant even after adjustment for other covariates using multiple linear regression (p = 0.031, beta coefficient = 0.286). Fig. 4 depicts the LOS by infection status and type of intracranial hemorrhage. This finding remained significant when comparing the two groups by the category of intracranial hemorrhage, except for SAH (p = 0.2). Patients with infection showed higher all-cause mortality after 3 months of the admission as compared to patients without infection (45.2% versus 20.7%, p < 0.001), (Table 4). The relationship between NIs and cumulative survival within 3 months classified by the type of intracranial hemorrhage is depicted in Fig. 5. Among patients with IVH, NIs were negatively associated with survival (p < 0.001), while NIs in SDH were shown to increase survival (p = 0.008). Relationship between survival and NIs in ICH and SAH was marginally significant (p = 0.073 and 0.084, respectively).

3.5. Predictors of mortality

Unadjusted univariate analysis was performed to detect relationships between mortality and potential predictors (Table 5). NI, bacteremia, pneumonia, GCS category, IVH, SDH, resistance, PEG, and craniotomy/craniectomy were the only significant factors associated with 3 months mortality (Table 5). In the adjusted regression analysis, GCS, SDH, and PEG were the only significant predictors of mortality (p < 0.001, OR: 10.1 (4–25.7), 19.6 (4.1–91), respectively). Indications for PEG tube placement were dysphagia, decreased level of consciousness, and failed ex-tubation (81, 51, and 2 cases, respectively). Three complications of PEG tube had developed: 2 bleeding from the insertion site and 1 infection. Severity scores of ICH and SAH were assessed using ICH score and Hunt and Hess grade, respectively. Mortality at three months according to the score of hemorrhage are listed in Table 6. Overall, a significant association between severity scores of ICH or SAH and mortality was also observed.

4. Discussion

The global burden of hemorrhagic stroke is increasing worldwide in

Table 2
Sites of infection, causative microorganisms, and modes of resistance among patients with nosocomial infection.

Site of infection	Number of patients (%)	Resistance n (%)[a]	Number of positive cultures according to causative microorganisms[b]
UTI	52 (55.3)	Total: 33 (63.5) MDR: 25 (48.1) XDR: 6 (11.5) MDR & XDR: 2 (3.8)	*Escherichia coli* (3S, 13MDR, 1XDR) *Enterococcus species* (2S, 6MDR) *Acinetobacter baumannii* (1S, 6XDR) *Morganella morganii* (2S, 1MDR) *Pseudomonas aeruginosa* (3S, 1MDR) *Klebsiella pneumoniae* (1S, 9MDR, 1XDR) *Enterobacter cloacae* (1S) *Candida* (11 T)
Bacteremia	36 (38.3)	MDR: 6 (16.7)	*Enterococcus species* (1S) *Acinetobacter baumannii* (1MDR) *Proteus mirabilis* (1S) *Pseudomonas aeruginosa* (3S, 1MDR) *Staphylococcus aureus* (1S, 2MDR) *Coagulase-Negative Staphylococci* (19S) *Klebsiella pneumoniae* (2S, 2MDR) *Diphtheroid* (1S)
Pneumonia	56 (59.6)	Total: 44 (78.5) MDR: 21 (37.5) XDR: 12 (21.4) MDR & XDR: 11 (19.6)	*Escherichia coli* (1MDR) *Acinetobacter baumannii* (3S, 18MDR, 22XDR) *Proteus mirabilis (*2S) *Pseudomonas aeruginosa* (4S, 5MDR, 3XDR) *Staphylococcus aureus* (5S, 2MDR) *Klebsiella pneumoniae* (5S, 8MDR) *Enterobacter cloacae (*2S) *Candida* (2 T)
SSI	15 (16)	Total: 11 (73.3) MDR: 9 (60) XDR: 2 (13.3)	*Escherichia coli* (2MDR) *Acinetobacter baumannii* (2MDR, 1XDR) *Proteus mirabilis* (1S) *Pseudomonas aeruginosa* (2S) *Staphylococcus aureus* (1S, 1MDR) *Klebsiella pneumonia* (6MDR)
Meningitis	4 (4.3)	MDR: 1 (25)	*Acinetobacter baumanni* (1MDR) *Pseudomonas aeruginosa* (1S) *Staphylococcus aureus* (1S) *Coagulase-Negative Staphylococci* (1S) *Klebsiella pneumoniae* (1MDR)
Others	3 (3.2)	MDR: 2 (66.7)	*Escherichia coli* (1MDR[c]) *Acinetobacter baumannii (*1MDR[d]) *Staphylococcus aureus* (1S[e])

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MDR, multidrug resistant; S, susceptible; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; SSI, surgical site infection; T, total; UTI, urinary tract infection; XDR, extensively drug resistant.

[a] Percentage within site of infection.

[b] Patients may have more than one type of intracranial hemorrhage, more than one infection, and more than one culture for the same infection.

[c] Infected bedsore.

[d] Central line infection **e**: eye infection.

terms of deaths and disability [35]. Many efforts had been taken to prevent or correctly manage complications of intracranial hemorrhage. However, management is still suboptimal as many risk factors and outcomes are still not fully clarified. Previous studies have shown that NIs were common and led to poor outcomes among patients with ICH and SAH, such as increased hospital LOS, mortality rates, and cost of care [20,25,36,37]. However, these findings were inconsistent between studies. To our knowledge, risk factors for the development of NI in these patients were not studied except in few studies among patients with ICH [25]. Furthermore, the relationship between NIs and SDH was never investigated. Our study described NIs and evaluated various potential risk factors contributing to the development of NI in a cohort of patients with one or more types of intracranial hemorrhage. The study found that hypertension, levetiracetam, hospital LOS, and GCS category were significant contributors of NI. Moreover, the study also revealed that NI resulted in a significant increase in LOS but did not alter mortality after adjustment to covariates. This is the first study to characterize microbial features, predictors, and outcomes of NI in patients with various types of intracranial hemorrhage.

Assessment of infections' microbiological features, common sites, risk factors, and outcomes is essential for the implementation of appropriate management and preventive procedures. A total of 94 cases developed at least one type of NI (40.3%). Our study is the first to estimate the incidence of NIs among patients with intracranial hemorrhage in Jordan. Incidence of NIs among patients with ICH (46%) was a bit higher than previously reported estimates in the United States (23–31%) [20,21]. Similarly, NIs were higher in Jordan (46%) than in Canada (15.8%) and the Netherlands (37%) [22,23]. The study demonstrated that IVH carried the highest percentage of NI. Previous studies showed that IVH was a significant predictor for NI among patients with ICH [25]. Antimicrobial resistance poses a significant health issue as it leads to increased morbidity and mortality along with increased health costs [38]. Bacterial isolates; such as *Pseudomonas Aeruginosa*, *Methicillin Resistant Staphylococcus Aureus* (MRSA), *Vancomycin Resistant Enterococci* (VRE), and *Enterobacteriaceae* family (i.e, *Klebsiella pneumoniae*, *E. coli*, and *Proteus* species) are known as rapidly spreading and acquiring resistance [39]. We found that more than two thirds of bacteria demonstrated resistance which primarily presented as multidrug resistant. The most commonly resistant bacterial species encountered were: *Acinetobacter baumannii, Klebsiella pneumoniae*, and *Escherichia coli*. In our institution, infection control efforts concentrate on the promotion of hand washing practices, head of the bed elevation, and aseptic techniques of invasive device placements. Periodic surveillance cultures and close monitoring for the emergence of resistant strains of bacteria are crucial to implement effective measures for infection control and to guide future empiric antimicrobial choices.

Table 3
Univariate and multivariable analysis of risk factors for nosocomial infections in patients with intracranial hemorrhage.

Characteristic	NI (n = 94), no. %	No NI (n = 139), no. %	Univariate analysis, p value	Univariate analysis, OR (95% CI)	Multivariable analysis, p value	Multivariable analysis, OR (95% CI)
Age			0.532			
18–40	14 (14.9)	25 (18)	ref	–	–	–
41–65	48 (51.1)	67 (48.2)	0.521	1.28 (0.60–2.71)	–	–
> 65	32 (34)	47 (33.8)	0.725	1.15 (0.52–2.55)	–	–
Gender						
Female	31 (33.3)	44 (31.4)	ref	–	–	–
Male	62 (66.7)	96 (68.6)	0.761	0.92 (0.52–10.60)	–	–
Comorbidities						
Hypertension	69 (74.2)	78 (55.7)	0.004[a]	2.35 (1.33–4.16)	0.027[a]	2.62 (1.11–6.16)
Diabetes	36 (38.7)	46 (32.9)	0.36	1.26 (0.73–2.17)	–	–
Cancer	4 (4.3)	2 (1.4)	0.22	3.14 (0.55–16.97)	–	–
IHD	18 (19.4)	20 (14.3)	0.305	1.41 (0.70–2.83)	–	–
Parkinson	3 (3.2)	1 (0.7)	0.304	4.55 (0.47–44.42)	–	–
Ischemic stroke	9 (9.7)	6 (4.3)	0.101	2.34 (0.81–6.83)	–	–
AF	2 (2.2)	6 (4.3)	0.482	0.48 (0.10–2.44)	–	–
HF	4 (4.3)	3 (2.1)	0.441	2.02 (0.44–9.22)	–	–
CKD	4 (4.3)	6 (4.3)	1	0.99 (0.27–3.59)	–	–
Valve Replacement	3 (3.2)	2 (1.4)	0.391	2.26 (0.37–13.78)	–	–
VTE	1 (1.1)	3 (2.1)	1	0.49 (0.05–4.76)	–	–
Hypothyroidism	3 (3.2)	1 (0.7)	0.148	4.55 (0.47–44.42)	–	–
Others	11 (11.8)	13 (9.3)	0.532	1.29 (0.55–3.00)	–	–
Type of hemorrhage						
ICH	63 (67.7)	74 (52.9)	0.024[a]	1.79 (1.04–3.08)	0.568	0.75 (0.28–2.01)
IVH	41 (44.1)	32 (22.9)	0.001[a]	2.59 (1.47–4.56)	0.687	0.83 (0.33–2.1)
SAH	22 (23.7)	28 (20)	0.506	1.21 (0.64–2.28)	–	–
SDH	13 (14)	43 (30.7)	0.003[a]	0.40 (0.21–0.79)	0.362	0.553 (0.15–1.1)
Length of hospital stay (days) [median, IQR]	21 (10-49)	8 (4-12)	< 0.001[a]	1.08 (1.05–1.11)	< 0.001	1.08 (1.05–1.12)
Dexamethasone receipt	46 (48.9)	58 (41.7)	0.277	1.34 (0.79–2.27)	–	–
Antiepileptic use	68 (72.3)	88 (63.3)	0.151	1.52 (0.86–2.68)	–	–
Phenytoin	53 (56.4)	66 (47.5)	0.182	1.43 (0.85–2.42)	–	–
Levetiracetam	32 (34)	21 (15.1)	0.001[a]	2.9 (1.54–5.45)	0.007[a]	3.6 (1.41–9.22)
Valproic acid	5 (5.3)	10 (7.2)	0.567	0.73 (0.24–2.19)		
Prior antibiotic use	50 (53.2)	43 (30.9)	0.001[a]	2.54 (1.48–4.36)	0.429	1.51 (0.55–4.17)
Dysphagia	41 (43.6)	55 (39.5)	0.538	1.18 (0.7–2.01)	–	–
GCS						
Mild (3–8)	37 (39.4)	105 (75.5)	ref	–	–	–
Moderate (9–12)	15 (16)	11 (7.9)	0.002[a]	3.87 (1.63–9.18)	0.005[a]	5.42 (1.67–17.56)
Severe (13–15)	42 (44.7)	23 (16.5)	< 0.001[a]	5.38 (2.86–10.10)	< 0.001[a]	7.63 (2.44–23.87)
Prior anticoagulant or antiplatelet therapy	38 (40.4)	50 (36)	0.491	1.21 (0.71–2.07)	–	–
Invasive device use						
Mechanical ventilation	0 (0)	11 (11.7)	< 0.001[a]	NPC	0.998	NPC
Foley's catheter	83 (88.3)	86 (61.9)	< 0.001[a]	4.65 (2.27–9.52)	0.211	1.97 (0.68-5.66)
External brain drainage device	47 (50)	45 (32.4)	0.007[a]	2.089 (1.22–3.58)	0.691	0.79 (0.25–2.49)
Internal brain drainage device	8 (5.8)	15 (16)	0.01[a]	3.109 (1.261–7.665)	0.488	0.582 (0.13–2.69)
PEG	76 (80)	72 (52.2)	< 0.001[a]	3.57 (1.95–6.53)	0.753	0.84 (0.28–2.51)
Central line venous catheter	6 (6.4)	4 (2.9)	0.208	2.3 (0.63–8.39)	–	–
Craniectomy/craniotomy	23 (24.5)	13 (19.4)	0.002[a]	3.14 (1.5–6.58)	0.46	1.49 (0.52–4.28)
Tracheostomy	8 (8.4)	7 (5.1)	0.306	1.72 (0.6–4.92)	–	–

AF, atrial fibrillation; CKD, chronic kidney disease; HF, heart failure; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; IVH, intraventricular; NI, nosocomial infection; NPC, not possible to calculate, OR, odd ratio; PEG, percutaneous endoscopic gastrostomy; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; VTE, venous thromboembolism hemorrhage.
[a] Significant differences (p value < 0.05).

Table 4
Mortality at three months and length of stay (LOS) classified by infection status among patients with intracranial hemorrhage.

Outcome	NI (n = 94)	No NI (n = 139)	p value
3 months mortality[a]	42 (45.2%)	29 (20.7)	< 0.001
Length of stay (LOS)[b]	23 (11–50)	8 (4-12)	< 0.001

NI, nosocomial infections.
[a] Presented as count and percentage within the infection group.
[b] Presented as median and IQR (days).

Consistent with previous findings [24,25], the current study identified GCS category as a significant predictor of NIs. Patients who spend more days of hospital stay are more prone to healthcare associated infections [40,41]. Unexpectedly, age was not significantly associated with the emergence of NI although it is commonly reported in the literature as a general risk factor NI [42,43]. The observation that hypertension was markedly associated with increased risk of NI can be possibly mediated through an elevation in Renin-Angiotensin-Aldosterone system and thus increased inflammation [44]. This is prominently the case if hypertension was not treated, which is commonly encountered as a cause of brain hemorrhage. Increased inflammation may enhance microbial penetration into the cellular space [45]. Moreover, increased catecholamine levels is implicated to suppress immunity leading to the occurrence of infections [46]. In addition to hypertension, our study indicated that levetiracetam use is significantly associated with NIs when used as 500 mg twice P.O. to prevent seizures post brain insult. While it was reported previously that it can increase

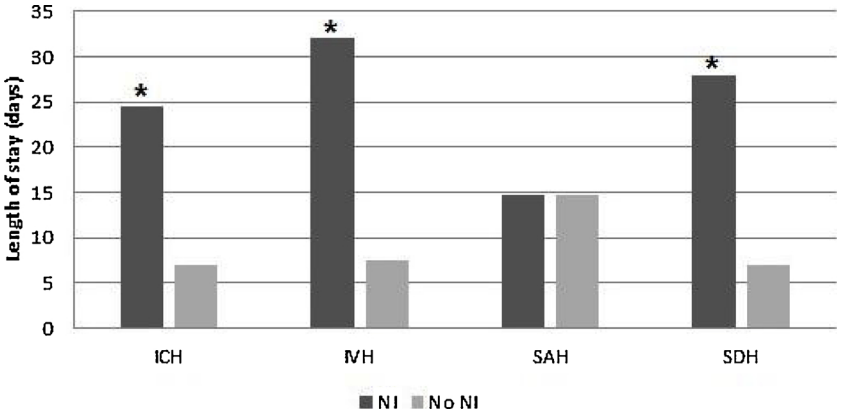

Fig. 4. Median of hospital length of stay (LOS) in days among patients with different classes of intracranial hemorrhage classified by infection status. * P value < 0.001 as compared to those who had no infection among the same type of hemorrhage using Mann-Whitney U test. Abbreviations: ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; NI, nosocomial infection; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

the rate of upper respiratory tract infections [47], our study is the first to elucidate levetiracetam as a risk factor for NIs. Studies reported infection incidence of 2.6–13.2% among patients using levetiracetam [48,49]. The dose was not shown to affect the incidence or severity of adverse events of levetiracetam including infection [50]. Abou-Khalil et al reported that patient receiving the lowest dose (1000 mg daily) had higher incidence of adverse effects [48]. It's still unclear how levetiracetam increases infection. One suggested mechanism is a decrease

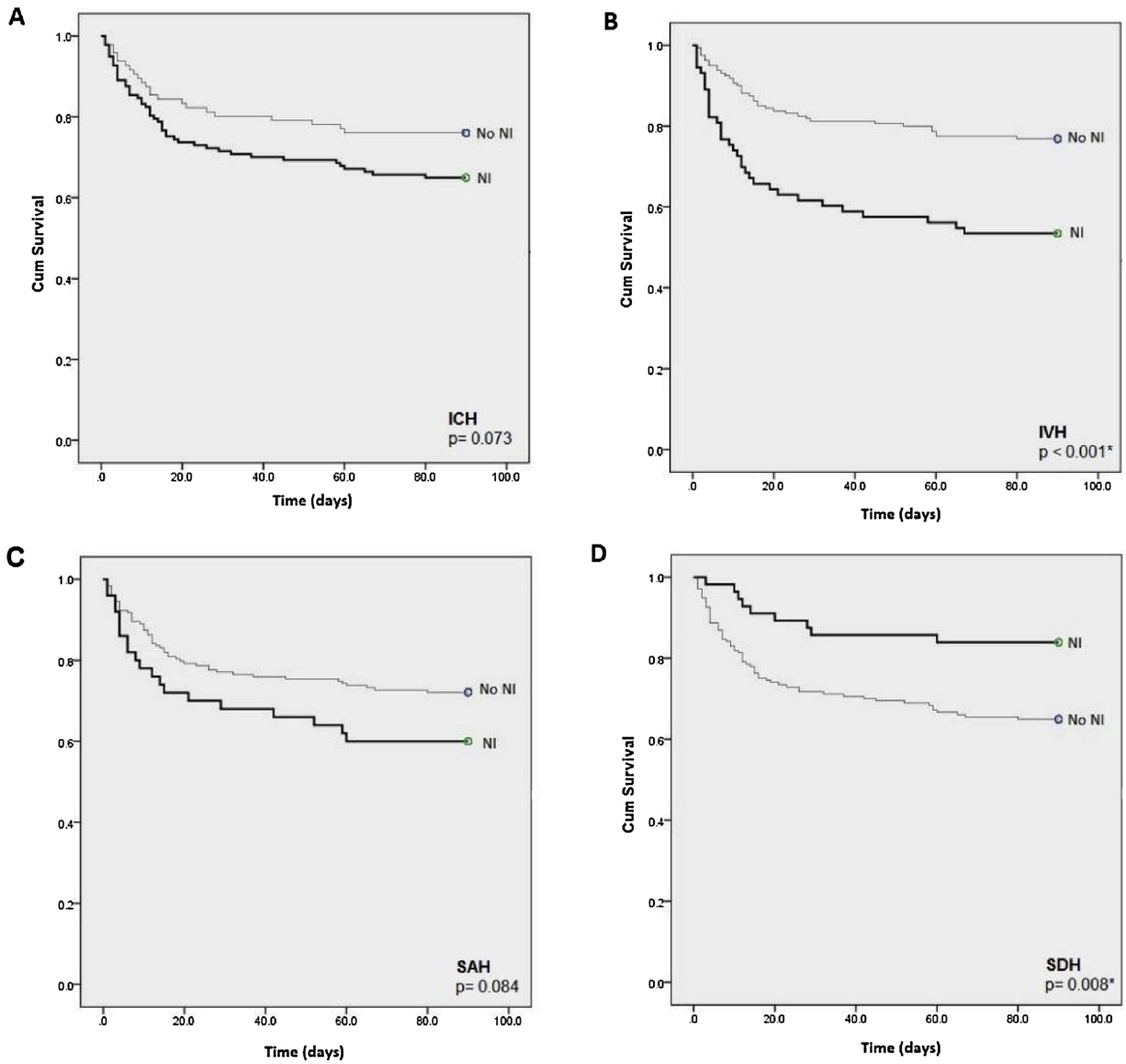

Fig. 5. Kaplan-Meier product estimates for cumulative survival within 3 months according to nosocomial infection in patients with (A) ICH, (B) IVH, (C) SAH, (D) SDH. *significant differences (p value < 0.05) Abbreviations: ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; NI, nosocomial infection; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

Table 5
Univariate and multivariable analysis of predictors of mortality among patients with intracranial hemorrhage.

Predictors	Univariate p value	Multivariable p value	Multivariable analysis, OR (95% CI)
Nosocomial infections	< 0.001[a]	0.08	3.36 (0.86–13.07)
Bacteremia	0.003[a]	0.549	0.72 (0.25–2.1)
Pneumonia	< 0.001[a]	0.51	0.65 (0.18–2.35)
GCS category	< 0.001[a]	< 0.001[a]	10.1 (4.0–25.7)
Mild	ref	ref	ref
Moderate	< 0.001[a]	0.01[a]	4.25 (1.39–12.95)
Severe	< 0.001[a]	< 0.001[a]	7.74 (3.03–19.8)
IVH	< 0.001[a]	0.38	0.67 (0.28–1.62)
SDH	0.008[a]	0.03[a]	0.31 (0.11–0.91)
Resistance	0.03[a]	0.122	2.64 (0.77–9.03)
PEG	< 0.001[a]	< 0.001[a]	25.1 (5.29–119.2)
Craniotomy/ craniectomy	0.018[a]	0.506	0.70 (0.25–2)

GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; OR, odds ratio; PEG, percutaneous endoscopic gastrostomy.
[a] Significant differences (p value < 0.05).

Table 6
Mortality at three months according to ICH and SAH scores.

Mortality[b] (n, % within SAH score)	SAH grade	Mortality[b] (n, % within ICH score)	ICH score[a]
–	–	2 (6.1)	0
4 (50)	1	7 (20.6)	1
1 (5.6)	2	11 (40.7)	2
3 (37.5)	3	17 (60.7)	3
7 (77.8)	4	10 (71.4)	4
5 (83.3)	5	1 (100)	5

ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.
[a] No cases with ICH score of 6 were identified. Only one case with ICH score of 5 was admitted.
[b] p < 0.001, Fisher's exact test.

in the number of white blood cells (WBCs), thereby increasing infection risk [51,52]. However, other placebo-controlled trials had shown no increase in the numbers of WBCs [53]. In our study sample, no of leukopenia or decrease in WBCs count was observed among patient who received levetiracetam. Together, this finding suggests that alternatives to levetiracetam might be considered with patients at increased risk of infection [54].

The findings of this study highlight the deleterious impact of NI on clinical outcomes after intracranial hemorrhage. The presence of NI significantly increased LOS, which was confirmed by the subgroup analysis by type of brain hemorrhage, except for SAH. This observation is consistent with previous findings among patients with ICH [20,25], and SAH [37]. The presence of NIs had increased risk of mortality at 3 months. However, this association was abolished when adjusting for other covariates. SDH showed significantly lower mortality rates compared to other types of hemorrhage. Mortality was significantly associated with GCS category, which is in agreement with previous findings [55]. Mechanisms by which infection leads to worse outcomes may include activation of pro-inflammatory cascade and lymphocytes thereby leading to secondary neuronal insult and thus worsening outcomes [21]. The association between PEG tube insertion and mortality is unclear because of limited evidence. Some studies investigated its use in certain subgroups of patients and found a survival advantage [56,57], while others recommend avoidance or delaying its use because of higher mortality rates [58,59]. We found that PEG insertion is significantly associated with mortality within 3 months despite the integration of its indications for use in the multivariable regression (dysphagia and level of consciousness). Previous studies have determined multiple predictors of PEG placement and its associated mortality among different patient population [60–62]. For example, GCS score, race, age and ICH volume were identified as predictors of PEG placement in ICH patients [60]. Others have shown that platelet count (< 100,000/μL), C-reactive protein (≥ 5 mg/dL), albumin (≤ 30 g/L), age, lower BMI, and diabetes were independent predictors of 30-day mortality with PEG placement 62–64]. These factors may explain in part the reasons for use of PEG and increased mortality observed in our study. Furthermore, mortality was associated with ICH score and Hunt and Hess grade in patients with ICH and SAH, respectively. These findings suggest that mortality should be predicted by considering such factors, and we recommend delaying the insertion of PEG tube among these predisposed patients.

Our study has several strong points. It is the first to examine NI in a general cohort of patients with intracranial hemorrhage and by the subclass. Infections were diagnosed as a part of daily medical assessment so findings can be generalizable. It is the first study to identify levetiracetam and hypertension as risk factors for hospital infection in patients admitted with intracranial hemorrhage. Data collection was performed by neurology senior residents who are familiar with data investigation from medical records. However, errors from underreporting of invasive device use may subject the study for possible errors. Moreover, the current study is retrospective and descriptive, thus causality cannot be established and some data were not available such as APACHE III (Acute Physiology and Chronic Health Evaluation II and III) and SOFA (Sepsis-related Organ Failure Assessment) scores. The study did not assess the development of other complications after intracranial hemorrhage which might affect the mortality rates.

5. Conclusions

Our study demonstrated that NIs are common in patients admitted with intracranial hemorrhage. Risk factors for the development of NI may include GCS category, bladder catheterization, prior antibiotic use, hypertension, and levetiracetam use. Infections were significantly associated with a longer hospital stay. Furthermore, mortality after intracranial hemorrhage can be predicted by GCS score and PEG tube insertion. Future experimental studies are warranted to investigate the mechanisms behind which, hypertension may increase susceptibility to NI. Studies that foster and evaluate the implementation of infection control protocols are highly desirable regionally and globally.

Disclosure statement

Authors declare that they have no financial/personal interest or belief that could affect the results of this study.

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