Original Article

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Pneumonia after Hemorrhagic Stroke: Incidence, Risk Factors, and Outcomes

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Objective: Pneumonia is one of the most common medical complications after stroke, with an estimated incidence ranging from 5% to 26%. Pneumonia increases the risk of death by approximately 3 times that of patients who do not contract pneumonia, and it has the highest attributable mortality of all medical complications after stroke. Clinical studies have identified the risk factors for pneumonia in patients with ischemic stroke. We undertook this study to retrospectively evaluate the incidence, risk factors, and outcomes of hospital-acquired bacterial pneumonia in a group of patients with hemorrhagic stroke.

Methods: This was a retrospective review of consecutive adult patients admitted to the neurosurgical intensive care unit (ICU) in our hospital because of hemorrhagic stroke between January 2008 and December 2010.

Results: During the study period, 466 patients were admitted to the ICU. Multivariable Cox regression analysis showed that Glasgow Coma Scale (GCS) score (hazard ratio [HR] 0.94; 95% confidence interval [CI] 0.89 – 0.99), nasogastric tube (NG tube) insertion (HR 7.61; 95% CI 2.26 – 25.59), and the length of ICU stay (HR 1.05; 95% CI 1.04 – 1.07) were significantly associated with the development of pneumonia.

Conclusions: Our study identified 3 risk factors for pneumonia in hemorrhagic stroke patients; GCS score (cutoff point, 12; sensitivity 76.5%; specificity 55.8%), NG tube insertion, and the length of ICU stay (cutoff point, 10 days; sensitivity 84.3%; specificity 90.1%). These risk factors constitute the basis of a simple screening tool used to evaluate the risk of pneumonia.

Key words: pneumonia, hemorrhagic stroke, risk factors, incidence, outcomes

Introduction

Pneumonia is one of the most common medical complications after stroke, with an estimated incidence ranging from 5% to 26%.[1-9] Pneumonia increases the risk of death to approximately 3 times that of patients who do not contract pneumonia,[3,10] and it has the highest attributable mortality of all medical complications after stroke.[11] Such infections are also associated with longer hospital stays and a greater likelihood of discharge to a nursing home, as compared with patients

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who do not contract pneumonia.[7,12-13] Previous studies have identified a diverse set of factors that can be evaluated early in the course of stroke and that may predispose an individual to pneumonia. These include greater severity of neurologic impairment,[3,7,13-15] older age,[3,13] and diabetes mellitus.[3] Most studies of pneumonia after stroke have examined pneumonia after ischemic stroke. We undertook this study to retrospectively evaluate the incidence, risk factors, and outcomes of pneumonia in a group of patients with hemorrhagic stroke who were admitted to a neurosurgical intensive care unit (ICU).

Patients and Methods

Patient population

The study was performed at a major stroke center in Kaohsiung, Taiwan. We performed a retrospective review of consecutive adult patients admitted to the Neurosurgical ICU in E-Da Hospital because of hemorrhagic stroke between January 2008 and December 2010. The study was approved by the Institutional Review Board (EMRP-099-095). The 1100-bed hospital has a 16-bed Neurosurgical ICU, and there are 12 neurosurgeons in the department, all of whom are certified in neurosurgical critical care. We included patients with first or recurrent hemorrhagic stroke and we excluded patients with concurrent infection, tumoral bleeding, autoimmune diseases, and those who were immunocompromised. The diagnosis of stroke was based on clinical features, supported by brain computed tomography or magnetic resonance imaging scanning. Critical care management was provided by a 24-hour, in-house neurosurgical critical care team.

Fever management

We performed sputum cultures, sputum routine tests, blood cultures, and urine routine tests for patients with fever. All infection cases were evaluated and controlled by the infection control unit.

Diagnosis of pneumonia

The diagnosis of pneumonia required 3 or more of the following characteristics: pulmonary infiltrates in chest radiography, fever (> 38.0˚C), dyspnea, abnormal respiratory examination, and white blood cell count (WBC) > 12,000 cells/mL.[16]

Risk factors for pneumonia

We evaluated the following as potential risk factors for pneumonia: gender, age, etiology of hemorrhagic stroke, Glasgow Coma Scale (GCS) score, acute physiology and chronic health evaluation II (APACH II),[17] the National Institutes of Health Stroke Scale (NIHSS), hemiplegia or hemiparesis (muscle power ≤ Gr 3), nasogastric tube (NG tube) insertion, ventilator use, chronic obstructive pulmonary disease, chronic systemic diseases (including diabetes mellitus), hypertension, previous stroke, active cancer, and duration of ICU stay.

Outcome analysis of patients with pneumonia

We evaluated the following as potential survival risk factors for patients with pneumonia: gender, age, etiology of hemorrhagic stroke, GCS score, APACH II, NIHSS, hemiplegia or hemiparesis (muscle power ≤ Gr 3), NG tube insertion, ventilator use, chronic obstructive pulmonary disease, chronic systemic diseases (including diabetes mellitus), hypertension, previous stroke, active cancer, and duration of ICU stay.

Statistical analysis

Categorical data are presented as a number (percentage) and continuous data are presented as the mean ± standard deviation. We compared continuous variables between groups (e.g., with and without pneumonia)

using independent sample t-tests. We used chi-square tests or Fisher's exact tests, as appropriate, to compare categorical variables between groups.

Survival from the time of ICU admission to occurrence of pneumonia or last follow-up was estimated using the Kaplan-Meier method. We used univariate (unadjusted) and multivariable Cox proportional hazard models to identify factors predictive of survival. Results of Cox regressions are presented as hazard ratios (HR) with their corresponding 95% confidence intervals and *p*-values. To build the Cox regression models, we first conducted a series of univariate analyses to identify potential predictive factors. Next, the significant variables in univariate analysis were treated as covariates in multivariable analysis. Those variables that were significant covariates (p-value < 0.05) in multivariable analysis were then considered to be independently predictive factors for development of pneumonia.

All tests and models were 2-tailed and the significance level was set at $p < 0.05$. Statistical analyses were carried out using SPSS for Windows (SPSS 15.0, SPSS Inc., Chicago, IL).

Results

Baseline characteristics associated with pneumonia of study participants

During the study period, 466 patients who met the study inclusion criteria were admitted to the ICU, and 102 (21.88%) of these developed pneumonia. Pneumonia developed 7.25 ± 6.41 days after admission. Univariate analysis demonstrated that development of pneumonia was associated with age, etiology, GCS score, APACH II score, NIHSS, NG tube insertion, ventilator use, chronic obstructive pulmonary disease, and the duration of ICU stay (Table 1).

Among the 102 patients who developed pneumonia by the end of follow-up, the median survival time was 37 days. The cumulative probability of event-free survival among patients with pneumonia was 75%, 69%, 56%, 49%, and 49% after 10, 20, 30, 40, and 50 days following admission, respectively (Fig. 1).

Factors that significantly associated with pneumonia

Multivariate analysis indicated that, after adjusting for other covariates, GCS score (HR 0.94; 95% confidence interval [CI] 0.89 – 0.99), NG tube insertion (HR 7.61; 95% CI 2.26 – 25.59), and the duration of ICU stay (HR 1.05; 95% CI 1.04 – 1.07) were significantly associated with an increased risk of pneumonia (Table 2 & Fig. 2).

Baseline characteristics associated with mortality among pneumonia participants

In order to find the clinically optimal cutoff points for predicting pneumonia from the GCS score and duration of ICU stay, we performed receiver operating characteristic (ROC) analysis. According to the Youden index, the cutoff GCS score was 10 with a sensitivity of 84.3% and a specificity of 90.1%. The duration of ICU stay cutoff was 12 days with a sensitivity of 76.5% and a specificity of 55.8% (Table 3 & Fig. 3). Of the 102 patients with pneumonia, 8 died of severe hemorrhagic stroke and severe brain swelling, 5 died of pneumonia, and 4 died of cardiogenic shock. Univariate analysis revealed that APACH II, and hemiplegia/hemiparesis were associated with mortality in these patients (Table 4).

The most common bacterial pathogens

Table 5 shows the 16 pathogens isolated from pneumonia patients. The most common gram-positive organism was Staphylococcus aureus (13 patients, oxacillin-sensitive; 5 patients, oxacillin-resistant), and the most common gram-negative organisms were Pseudomonas aeruginosa (32 patients), Haemophilus influenzae (17 patients), and Klebsiella pneumoniae (17 patients).

Table 1. Baseline epidemiological, clinical, and biochemical characteristics associated with pneumonia of study participants.

Variables	Total (N = 466)	Non-pneumonia (n = 364)	Pneumonia (n = 102)	*p* value
Gender, male, %	282 (60.5)	215 (59.1)	67 (65.7)	0.227
Age, year	61.74 ± 14.38	60.94 ± 14.32	64.59 ± 14.34	0.024
Etiology, %				0.015
Aneurysm	108 (23.2)	74 (20.3)	34 (33.3)	
Hypertension associated	308 (66.1)	247 (67.9)	61 (59.8)	
Unknown etiology or arteriovenous malformation	50 (10.7)	43 (11.8)	7 (6.9)	
GCS score	10.07 ± 4.68	10.62 ± 4.71	8.08 ± 4.03	< 0.001
APACH II	18.29 ± 8.98	17.35 ± 9.27	21.64 ± 6.93	< 0.001
NIHSS	16.70 ± 12.73	15.28 ± 12.71	21.78 ± 11.49	< 0.001
Hemiparesis/hemiplegia, %	192 (41.2)	147 (40.4)	45 (44.1)	0.498
Nasogastric tube, %	307 (65.9)	208 (57.1)	99 (97.1)	< 0.001
Ventilator, %	265 (56.9)	176 (48.4)	89 (87.3)	< 0.001
Diabetes mellitus, %	108 (23.2)	83 (22.8)	25 (24.5)	0.718
Hypertension, %	374 (80.3)	286 (78.6)	88 (86.3)	0.084
COPD, %	10 (2.1)	5 (1.4)	5 (4.9)	0.045†
Renal disease, %	58 (12.4)	46 (12.6)	12 (11.8)	0.813
Malignancy, %	45 (9.7)	37 (10.2)	8 (7.8)	0.483
Previous stroke, %	55 (11.8)	46 (12.6)	9 (8.8)	0.291
Mortality, %	133 (28.5)	116 (31.9)	17 (16.7)	0.003
ICU days	8.26 ± 9.77	4.74 ± 4.71	20.80 ± 12.51	< 0.001

Categorical variables were presented as number (percentage) and continuous variables were presented as mean ± standard deviation.
† indicates using Fisher's Exact test.
APACH II: Acute Physiology and Chronic Health Evaluation II; COPD: Chronic Obstructive Pulmonary Disease; GCS: Glasgow Coma Scale; ICU: intensive care unit; NIHSS: National Institutes of Health Stroke Scale.

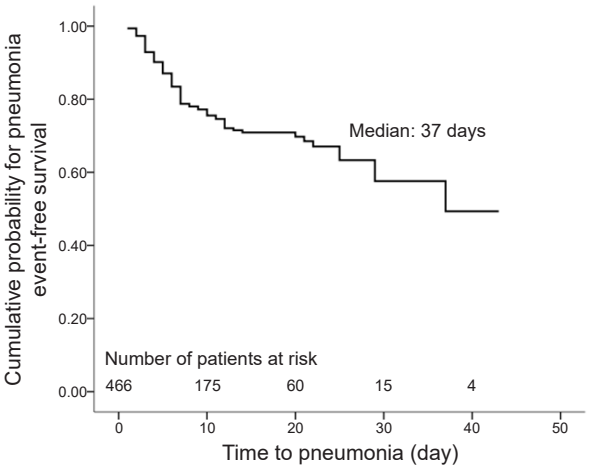

Fig. 1 Kaplan-Meier curve of event-free survival among patients with hemorrhagic stroke complicated by pneumonia.

Discussion

The mortality and neurological outcome of patients with stroke are crucially influenced by the occurrence of infection.[5] Pneumonia is the most frequent complication in patients with stroke and confers a risk of 30-day mortality that is 3 times higher than that of patients who do not contract pneumonia.[10,18-20] In this study, we explored a comprehensive range of features associated with the development of pneumonia in patients after hemorrhagic stroke. We included demographic, clinical, and neurologi-

Table 2. Clinical characteristics for predicting survival of pneumonia.

Predictors	Univariate analysis			Multivariable analysis I		
	HR	95% CI of HR	*p*	HR	95% CI of HR	*p*
Gender (male)	1.31	0.87 – 1.98	0.194			
Age (per year)	1.01	1.00 – 1.03	0.057			
Location						
Aneurysm	1.53	1.01 – 2.33	0.046			
Hypertension associated	Ref.	-	-			
Unknown etiology or Arteriovenous malformation	0.76	0.35 – 1.67	0.499			
GCS score	0.85	0.81 – 0.89	< 0.001	0.94	0.89 – 0.99	0.017
APACH II	1.08	1.06 – 1.10	< 0.001			
NIHSS score	1.06	1.04 – 1.08	< 0.001			
Hemiparesis/ hemiplegia (yes)	0.86	0.58 – 1.27	0.437			
Nasogastric tube (yes)	20.37	6.45 – 64.32	< 0.001	7.61	2.26 – 25.59	0.001
Ventilator (yes)	6.51	3.63 – 11.67	< 0.001			
Diabetes mellitus (yes)	1.07	0.68 – 1.68	0.762			
Hypertension (yes)	1.41	0.80 – 2.48	0.230			
COPD (yes)	2.32	0.94 – 5.70	0.067			
Renal disease (yes)	1.14	0.62 – 2.09	0.665			
Malignancy (yes)	0.94	0.46 – 1.94	0.875			
Previous stroke (yes)	0.81	0.41 – 1.61	0.547			
ICU days	1.07	1.06 – 1.08	< 0.001	1.05	1.04 – 1.07	< 0.001

N = 466.

APACH II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; GCS: Glasgow Coma Scale; HR: hazard ratio; ICU: intensive care unit; NIHSS: National Institutes of Health Stroke Scale.

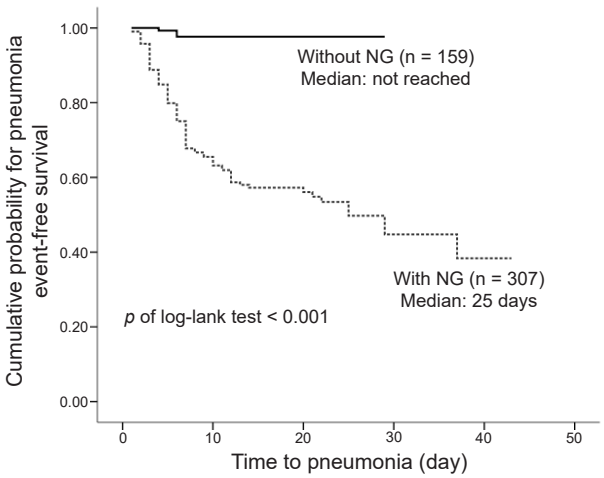

Fig. 2 Kaplan-Meier curve of pneumonia stratified by nasogastric tube insertion.

cal factors as well as the impact of stroke on motor and swallowing functions. Our findings confirm the multifactorial nature of pneumonia in patients after hemorrhagic stroke and they indicate that a few relatively simple clinical characteristics may provide the most robust predictors of pneumonia. Univariate analysis indicated that age, etiology, GCS score, APACH II score, NIHSS, NG tube insertion, ventilator use, chronic obstructive pulmonary disease, and the duration of stay in the ICU were associated with increased risk of developing pneumonia. Multivariable Cox regression analysis showed that the main risk factors were

Table 3. Youden index of the duration of ICU stay and GCS score predicting pneumonia in hemorrhagic stroke patients.

Variable/cutoff	Sensitivity (%)	Specificity (%)
ICU stay (days)		
7	93.1	80.2
8	88.2	84.9
9	86.3	87.6
10*	84.3	90.1
GCS		
10	67.6	63.5
11	71.6	59.6
12*	76.5	55.8

* indicates the cutoff point was judged according to Youden index.
GCS: Glasgow Coma Scale; ICU: intensive care unit.

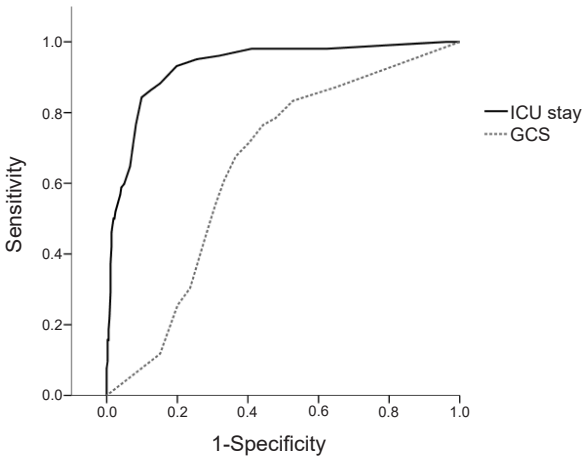

Fig. 3 ROC curve analysis of ICU stay and GCS in predicting pneumonia. Area under the ROC and 95% CI was 0.931 (0.903 – 0.959) and 0.649 (0.594 – 0.704) for ICU stay and GCS respectively.

Table 4. Baseline epidemiological, clinical, and biochemical characteristics associated with mortality among pneumonia participants.

Variables	Total (N = 102)	Survivors (n = 85)	Death (n = 17)	*p* value
Gender, male, %	67 (65.7)	59 (69.4)	8 (47.1)	0.076
Age, year	64.59 ± 14.34	65.35 ± 14.49	60.76 ± 13.31	0.230
Location, %				0.077
Aneurysm	34 (33.3)	25 (29.4)	9 (52.9)	
Hypertension associated	61 (59.8)	55 (64.7)	6 (35.3)	
Unknown etiology or arteriovenous malformation	7 (6.9)	5 (5.9)	2 (11.8)	
GCS score	8.08 ± 4.03	8.29 ± 4.02	7.00 ± 4.05	0.229
APACH II	21.64 ± 6.93	20.80 ± 6.79	25.82 ± 6.23	0.006
NIHSS	21.78 ± 11.49	21.31 ± 11.59	24.18 ± 10.97	0.349
Hemiparesis/hemiplegia, %	45 (44.1)	42 (49.4)	3 (17.6)	0.016
Nasogastric tube, %	99 (97.1)	82 (96.5)	17 (100.0)	1.000†
Ventilator, %	89 (87.3)	72 (84.7)	17 (100.0)	0.118†
Diabetes mellitus, %	25 (24.5)	22 (25.9)	3 (17.6)	0.554†
Hypertension, %	88 (86.3)	73 (85.9)	15 (88.2)	1.000†
COPD, %	5 (4.9)	5 (5.9)	0 (0.0)	0.587†
Renal disease, %	12 (11.8)	9 (10.6)	3 (17.6)	0.417†
Malignancy, %	8 (7.8)	8 (9.4)	0 (0.0)	0.346†
Previous stroke, %	9 (8.8)	6 (7.1)	3 (17.6)	0.170†
ICU days	20.80 ± 12.51	21.71 ± 12.61	16.29 ± 11.28	0.104

Categorical variables were presented as number (percentage) and continuous variables were presented as mean ± standard deviation.
† indicates using Fisher's Exact test.
APACH II: Acute Physiology and Chronic Health Evaluation II; COPD: Chronic Obstructive Pulmonary Disease; GCS: Glasgow Coma Scale; ICU: intensive care unit; NIHSS: National Institutes of Health Stroke Scale.

Table 5. Bacterial pathogens isolated from the sputum of patients with hemorrhagic stroke complicated by pneumonia.

Organism	Number
Gram-positive organisms	
Staphylococcus aureus (OSSA)	13
Staphylococcus aureus (ORSA)	5
Streptococcus pneumoniae	4
Gram-negative organisms	
Pseudomonas aeruginosa	32
Haemophilus influenzae	17
Klebsiella pneumoniae	17
Stenotrophomonas maltophilia	12
Acinetobacter baumannii	9
Escherichia coli	9
Enterobacter aerogenes	3
Enterobacter cloacae.	3
Branhamella catarrhalis	3
Serratia marcescens	3
Burkholderia cepacia	2
Acinetobacter calcoaceticus	1
Proteus miraabilis	1

GCS score, NG tube insertion, and the duration of stay in the ICU.

Several studies have demonstrated a correlation between the severity of stroke and the incidence of infections.[2-4,9,10,20] Among the patients we studied, those with low GCS scores were at high risk for developing pneumonia. Other studies of pneumonia after stroke indicate that patients with larger strokes are at higher risk for pneumonia compared with those with smaller strokes, and stroke severity is the factor that has the strongest association with post stroke pneumonia.[9,21] The patients in our study experienced at least 3 types of hemorrhagic stroke, namely, aneurysmal subarachnoid hemorrhage, hypertension-associated hemorrhagic stroke, and hemorrhagic stroke of unknown etiology. We therefore used GCS score, APACH II, and NIHSS as measures of stroke severity to evaluate the association between stroke severity and risk of pneumonia. ROC analysis indicated that GCS scores below 12 were predictive of pneumonia (sensitivity 76.5%; specificity 55.8%).

Patients with severe strokes remained in ICU for a longer period of time than those with less severe strokes. ROC analysis indicated that ICU stays longer than 10 days were predictive of pneumonia (sensitivity, 84.3%; specificity, 90.1%).

Table 2 suggests that the etiology of stroke is associated with the frequency of pneumonia. Patients with aneurysmal hemorrhage were more likely to develop pneumonia compared with those with hypertensive hemorrhage (odds ratio [OR] = 1.53, p = 0.046). This may be because aneurysmal hemorrhage causes diffuse brain injury, and more neurological complications are found in these patients.

Previous studies have suggested that dysphagia may be more strongly associated with pneumonia.[4,22] Our results indicate that dysphagia is a necessary, but insufficient, sole condition for the development of pneumonia. However, we found NG tube usage to be an important risk factor for the development of pneumonia. We inserted NG tubes in patients who choked on food and water. The NG tubes may alter the oral flora and interfere with oral care. Patients with NG tubes also had impaired gag reflexes and cough functions. NG tube usage constituted a possible mechanism for the development of pneumonia.

The most common pneumonia pathogens identified in our study were *Pseudomonas aeruginosa, Haemophilus influenzae, Staphylococcus aureus* (oxacillin-susceptible), and *Klebsiella pneumoniae*. We suggest that when pneumonia is suspected in hemorrhagic stroke patients, antibiotics should be administered that target these pathogens first. This information about the common pathogens isolated from patients with pneumonia may help physicians select antibiotics to treat pneumonia before cultures can be identified.

Of the 102 patients with pneumonia, 8 died of severe hemorrhagic stroke and severe brain swelling, 5 died of pneumonia, and 4

died of cardiogenic shock. Univariate analysis revealed that APACH II, and hemiplegia/hemiparesis were associated with mortality in these patients. Analysis of mortality cases indicated that 9 (53%) died of infection and heart disease, which might explain why APACH II is associated with mortality.

Conclusions

Our study identified 3 risk factors for pneumonia in hemorrhagic stroke patients: GCS score, NG tube insertion, and the duration of ICU stay. A simple screening tool based on these factors can be used to evaluate a stroke patient's risk of pneumonia. This screening tool can be readily used in clinical practice by nursing and medical staff to identify patients likely to develop pneumonia after severe head injury. Patients with aneurysmal hemorrhage were more likely to develop pneumonia, as compared to those with hypertensive hemorrhage (OR = 1.53, $p = 0.046$).

Author Contributions

Study Design, Yu-Duan Tsai; Data Collection, Jui-Sheng Chen; Statistical Analysis, Shao-Ang Chu; Data Interpretation, Cien-Leong Chye; Manuscript Preparation, Hao-Kuang Wang; Literature Search, Kang Lu. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of E-Da Hospital (EMRP-100-115).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The study data was from the patients bank of Department of Neurosurgery, E-Da Hospital.

Conflicts of Interest

The authors declare no conflict of interest.

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