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Characteristics of Stroke Associated Pneumonia by Stroke Subtypes: Incidence, Time Course, Potential Risk and Microbiological Pathogen

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Abstract

Objective: To compare incidence, time course, potential risk and microbiological pathogens of SAP by stroke subtypes.

Methods: This study is based on a cohort (in-hospital Medical Complication after Acute Stroke, iMCAS), which consecutively enrolled patients with Acute Ischemic Stroke (AIS), Intracerebral Hemorrhage (ICH) and Subarachnoid Hemorrhage (SAH) admitted to stroke unit of Beijing Tiantan hospital From January 2014 to December 2016. In-hospital SAP was diagnosed based on the criteria for hospital-acquired pneumonia of Center for Disease Control and Prevention.

Results: A total number of 1771 patients (1129 of AIS, 314 of ICH and 329 of SAH) were enrolled in the iMCAS. The mean age was 57.1±12.9 and 27.5% were female. The median length of stay was 14 days (Interquartile Range [IQR], 11-16). In-hospital SAP after AIS, SAH and ICH was 86 (7.6%), 55 (16.8%) and 59 (18.8%), respectively. The median time from onset to diagnosis of SAP after AIS, SAH and ICH were 4 days (IQR:2-7), 5 days (IQR:3-7) and 3 days (IQR: 2-5), respectively. After adjusting for potential confounders, patients with ICH (OR=2.050; 95% CI=1.241-3.388; P=0.005) and SAH (OR=4.903; 95% CI=2.788-8.623; P<0.001) had significantly higher risk of SAP than those with AIS. Microbiological assessment was established in nearly half patients by sputum culture and three quarters was identified with Gram-negative bacteria. Overall, 57.7% patients with positive sputum culture had multi-drug resistant pathogen. The distribution of causative bacteria was not significant different by subtypes.

Conclusion: Patients with hemorrhagic stroke (ICH and SAH) have significantly higher risk of in-hospital SAP than patients with AIS. Further studies on molecular mechanisms are warranted.

Introduction

Stroke Associated Pneumonia (SAP) is a common medical complication after stroke [1] and has significant impact on stroke outcomes [2-4]. Evidence showed that SAP not only increase the length of hospital stay and medical cost [5,6], but also is an important risk factor of mortality and morbidity after stroke [7,8].

Although its contribution to worse stroke outcomes, time course and spectrum of culpable organisms for SAP remains poorly understood [9,10], especially for patients without mechanical ventilation and in stroke unit settings. As a result, optimal time window and strategies for SAP prophylaxis are not well established [11,12]. In addition, SAP is the most common medical complication

after Acute Ischemic Stroke (AIS) [1,4,13,14], Intracerebral Hemorrhage (ICH) [4,13,15-18] and Subarachnoid Hemorrhage (SAH) [16,19,20]; however, its clinical characteristics might be different for different stroke subtypes. Previous studies indicated that the incidence of SAP was higher among patients with ICH than those with AIS [13]. There is lack of study to make a systematic face-to-face comparison on potential risk of developing in-hospital SAP by different stroke subtypes (AIS, ICH, and SAH). Clarifying the potential risk of SAP by stroke subtypes will be an important step towards making individualized SAP prophylaxis strategies and improving stroke outcomes [21].

In the present study, we sought to 1) clarifying incidence and time course of SAP during acute hospitalization by stroke subtypes (AIS, ICH and SAH); 2) comparing potential risk of developing in-hospital SAP by stroke subtypes; and 3) identifying spectrum and multi-drug resistance of microbiological pathogens of SAP by stroke subtypes.

Methods

Study population

This study is based on a cohort (in-hospital medical complication after acute stroke, iMCAS) [22], which is a prospective registry of consecutive stroke patients admitted to stroke unit of Tiantan hospital (Supplementary Figure 1). To be eligible for the iMCAS, subjects had to meet the following criteria: (1) age 18 years or older; (2) hospitalized with a primary diagnosis of AIS, ICH or SAH according to the World Health Organization (WHO) criteria [23]; (3) stroke confirmed by head Computerized Tomography (CT) and/or brain Magnetic Resonance Imaging (MRI); (4) time from stroke onset to hospital admission was less than 7 days; (5) written informed consent from patients or their legal representatives. The iMCAS was approved by the ethics committee of Tiantan hospital.

Diagnosis of SAP

The SAP was diagnosed by treating physician according to the criteria for hospital-acquired pneumonia of Center for Disease Control and Prevention [24,25], on a basis of clinical and laboratory indices of respiratory tract infection (fever, cough, auscultatory respiratory crackles, new purulent sputum, or positive sputum culture) and supported by typical chest X-ray findings. Only hospitalacquired pneumonia was documented and pneumonia occurred before stroke was not considered.

Microbiologic assessment of SAP

For patients with SAP, sputum sample was collected and sputum culture was performed to establish microbiological diagnosis. Sputum sample were taken when symptoms of infectious events appeared and before the use of antibiotics. Pathogen identification and susceptibility testing were performed by standard methods [26]. Microbiological diagnosis was defined by the presence of at least one potentially pathogenic microorganism in sputum samples according to criteria made by Clinical and Laboratory Standards Institute. Multi-Drug-Resistant pathogens (MDR) pathogens were defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [27].

Date collection

A standard case report form was established to collect relevant data. For the present study, the following variables was analyzed: (1) demographics; (2) stroke risk factors: hypertension (history of hypertension or anti-hypertensive medication use), diabetes mellitus (history of diabetes mellitus or anti-diabetic medication use), dyslipidemia (history of dyslipidemia or lipid-lowering medication use), atrial fibrillation (history of atrial fibrillation or documentation of atrial fibrillation on admission), coronary heart disease, history of stroke/TIA, and current smoking; (3) preexisting comorbidities: congestive heart failure, valvular heart disease, Chronic Obstructive Pulmonary Disease (COPD), peripheral artery disease, hepatic cirrhosis, peptic ulcer, renal failure, arthritis and cancer; (4) index vascular event (AIS, ICH and SAH); (5) pre-stroke dependence (modified Rankin Scale [mRS] score≥3); (6) admission stroke severity based on the National Institutes of Health Stroke Scale (NIHSS) score; (7) admission Hunt-Hess scale score and World Federation of Neurologic Surgeons (WFNS) scale score (for SAH); (8) dysphagia at admission (evaluated with 3oz Water Swallow Test); (9) systolic (SBP) and Diastolic Blood Pressure (DBP); (10) Body Mass Index (BMI) (Kg/m^2); (11) admission blood tests: White Blood Cell (WBC) count ($10^9/L$), Red Blood Cell (RBC) count ($10^{12}/L$), Hemoglobin (HGB)(g/L), Platelet count ($10^9/L$), Triglyceride (TG) (mmol/L), cholesterol (TC)(mmol/L), High Density Lipoprotein (HDL) (mmol/L), Low Density Lipoprotein (LDL) (mmol/L), Glucose (mmol/L) and Creatine (mmol/L); (12) time from stroke onset to hospital admission (days); (13) Length of hospital Stay (LOS) (days); and (14) sputum culture and antibiotics susceptibility.

Statistical analysis

Continuous variables were summarized with mean and Standard Deviation (SD) or median and Interquartile Range (IQR). Categorical variables were summarized as proportions. In univariate analysis, Chi-square test or Fisher test was used to compare categorical variables and T test was employed to compare continuous variables. In multivariate analysis, Logistic regression was performed to assess association between stroke subtypes (AIS, ICH and SAH) and occurrence of SAP and adjusted for demographics, stroke risk factors, preexisting comorbidities, pre-stroke dependence(mRS>3), admission NIHSS score, dysphagia, BMI, admission blood pressure, blood tests, and length of hospital stay. All tests were 2-tailed and statistical significance was determined at α level of 0.05. Statistical analysis was performed using SPSS 20.

Results

Patient characteristics

A total number of 1771 patients (1129 of AIS, 314 of ICH and 329 of SAH) were enrolled in the iMCAS. The mean age was 57.1±12.9 and 27.5% were female. The median LOS was 14 days (IQR, 11-16) (Table 1). The median admission NIHSS score of patients with AIS, ICH and SAH was 4 (IQR: 2-8), 4 (IQR:1-10), and 0 (IQR:0-0), respectively. For patients with SAH, the median HuntHess scale score and WFNS scale score at admission was 2 (IQR:1-2) and 1 (IQR:1-1). It was more common for patients with SAP to be with older age, present history of atrial fibrillation, non-current smokers, index vascular event of ICH and SAH, admission NIHSS score, dysphagia at admission, admission SBP, higher level of admission WBC count, TG, TC, LDL, HDL, glucose, time from onset to admission and longer hospital stay. Comparison of patients' baseline characteristics by stroke subtypes was listed in Supplementary Table 1.

	All (N=1771)	Without SAP (N=1571)	With SAP (N=200)	P value
Demographics				
Age, mean ± SD	57.1±12.9	56.5±12.8	62.4±12.7	<0.001
Gender (female), n (%)	487 (27.5)	427 (27.2)	60 (30.0)	0.4
Stroke risk factor, n (%)				
Hypertension	1147 (64.8)	1004 (63.9)	143 (72.0)	0.03
Diabetes mellitus	411 (23.2)	361 (23.0)	50 (25.0)	0.52
Dyslipidemia	270 (15.2)	245(15.6)	25 (12.5)	0.25
Atrial fibrillation	82 (4.6)	65 (4.1)	17 (8.5)	0.01
Coronary artery disease	197 (11.1)	170 (10.8)	27 (13.5)	0.26
History of stroke/TIA	343 (19.4)	306 (19.5)	37 (18.5)	0.89
Current smoking	866 (48.9)	788 (50.2)	38 (19.0)	0.01
Comorbidities, n (%)				
Congestive heart failure	9 (0.5)	9 (0.6)	0 (0.0)	0.34
Valvular heart disease	13 (0.7)	10 (0.6)	3 (1.5)	0.17
COPD	41 (2.3)	33 (2.1)	8 (4.0)	0.04
Peripheral artery disease	8 (0.5)	7 (0.4)	1 (0.5)	0.62
Hepatic cirrhosis	24 (1.4)	21 (1.3)	3 (1.5)	0.52
Peptic ulcer	30 (1.7)	30 (1.9)	0 (0.0)	0.04
Renal failure	10 (0.6)	7 (0.4)	3 (1.5)	0.06
Arthritis	21 (1.2)	18 (1.1)	3 (1.5)	0.66
Cancer	21 (1.2)	17 (1.1)	4 (2.0)	0.26
Index vascular event n (%)				<0.001
Acute ischemic stroke	1129 (63.7)	1043 (66.3)	86 (43.0)	
Intracerebral hemorrhage	314 (17.7)	255 (16.2)	59 (29.5)	
Subarachnoid hemorrhage	328 (18.5)	273 (17.4)	55 (27.5)	

Pre-stroke dependence(mRS≥3), n (%)	26 (1.5)	22 (1.4)	4 (2.0)	0.14
Admission NIHSS score, median(IQR)	3 (1-8)	3 (1-6)	10 (2-16)	＜0.001
Dysphagia at admission, n (%)	150 (8.5)	122 (7.8)	28 (14.0)	0.003
Admission SBP (mm Hg), median(IQR)	151 (136-167)	150 (136-166)	158 (141-172)	＜0.01
Admission DBP (mm Hg), median(IQR)	89 (80-99)	89 (80-99)	88 (79-98)	0.68
BMI(Kg/㎡), median(IQR)	25.2 (21.0-29.4)	25.2 (21-29.4)	25.2 (21-29.4)	0.29
Admission blood test				
WBC, (10^9 /L), median (IQR)	8.06 (6.45-10.1)	7.81 (6.35-9.56)	10.99 (8.8-13.74)	＜0.001
RBC, (10^{12} /L), median (IQR)	4.63 (4.30-4.97)	4.63 (4.31-4.96)	4.61 (4.2-5.02)	0.86
HGB, (mmol/L), median (IQR)	143 (132-153)	143 (132-153)	141 (131-141)	0.81
Platelet, (109 /L), median (IQR)	212 (178-247)	213 (179-247)	204 (172-253)	0.42
TG, (mmol/L), median(IQR)	1.31 (0.98-1.78)	1.32 (0.99-1.8)	1.19 (0.94-1.67)	＜0.01
TC, (mmol/L), median(IQR)	4.28 (3.62-5.06)	4.23 (3.59-5)	4.75 (3.89-5.38)	＜0.001
LDL (mmol/L), median(IQR)	2.66 (2.06-3.34)	2.64 (2.04-3.3)	3.00 (2.23-3.59)	＜0.01
HDL (mmol/L), median(IQR)	1.06 (0.90-1.28)	1.05 (0.89-1.25)	1.21 (0.96-1.47)	＜0.001
Glucose (mmol/L), median(IQR)	5.08 (4.41-6.46)	4.98 (4.37-6.18)	6.20 (5.10-8.04)	＜0.001
Creatine (mmol/L), median(IQR)	61.8 (51.6-72.1)	61.9 (51.9-71.7)	61.6 (48.9-77.5)	0.64
LOS (days), median(IQR)	14 (11-16)	14 (11-16)	18 (13-25)	＜0.01

SAP: Stroke Associated Pneumonia; **SD:** Standard Deviation; **IQR:** Interquartile Range; **TIA:** Transient Ischemic Attack; **COPD**: Chronic Obstructive Pulmonary Disease; **mRS:** modified Rankin Scale; **NIHSS:** National Institutes of Health Stroke Scale; **SBP:** Systolic Blood Pressure; **DBP:** Diastolic Blood Pressure; **BMI:** Body Mass Index; **WBC:** White Blood Cell; **RBC:** Red Blood Cell; **HGB:** Hemoglobin; **TG:** Triglyceride; **TC:** Total Cholesterol; **LDL:** Low Density Lipoprotein; **HDL:** High Density Lipoprotein; **LOS:** Length of Hospital Stay.

Table 1: Baseline characteristics (N=1771).

Proportion of SAP by stroke subtypes

A total number of 200 (11.3%) patients developed SAP during hospitalization. In-hospital SAP after AIS, SAH and ICH was 86 (7.6%), 55 (16.8%) and 59 (18.8%), respectively. In-hospital SAP was significantly higher among patients with ICH (18.8% vs. 7.6%, P<0.001) and SAH (16.8% vs. 7.6%, P<0.001) than those patients with AIS (Figure 1A).

Time course of SAP by stroke subtypes

Time course from onset to diagnosis of SAP stratified by stroke subtypes is shown in figure 1B. The median times from onset to diagnosis of SAP after ICH, AIS and SAH were 3 days (IQR: 2-5), 4 days (IQR:2-7) and 5 days (IQR:3-7), respectively (Figure 1B). The median time from onset to diagnosis of SAP after ICH was significantly shorter than that after SAH (P=0.02). Although there is a trend that the median time from onset to diagnosis of SAP after ICH was shorter in comparison with that after AIS, it was not significantly different (P=0.18).

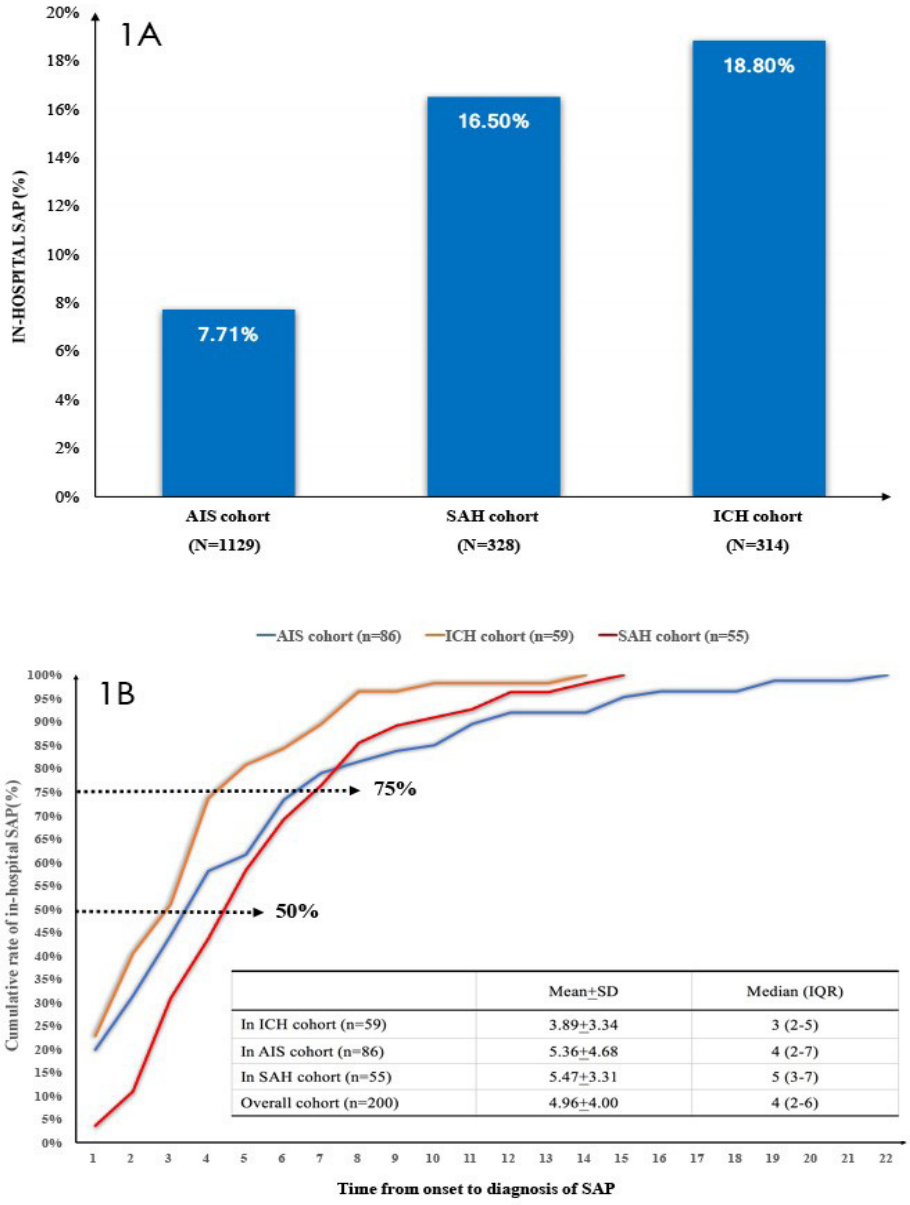

Figure 1: Incidence and time course of in-hospital SAP by stroke subtypes.

1A: Indicated that in-hospital SAP was significantly higher among patients with ICH (18.8% vs. 7.7%, P<0.001) and SAH (16.5% vs. 7.7%, P<0.001) than those patients with AIS.

1B: Showed that three quarters of in-hospital SAP occurred within the first week after onset. In addition, there was a trend that in-hospital SAP developed earlier among patients with ICH than those with AIS and SAH. (**SAP:** Stroke Associated Pneumonia; **AIS:** Acute Ischemic Stroke; **ICH:** Intracerebral Hemorrhage; **SAH:** Subarachnoid Hemorrhage; **SD:** Standard Deviation; **IQR:** Interquartile Range)

Association between SAP and stroke subtypes

Association between stroke subtypes and occurrence of in-hospital SAP is shown in Table 2. In univariate analysis, patients with ICH and SAH had significantly higher risk of in-hospital SAP than those patients with AIS. After adjusting for all potential confounders, patients with ICH (OR=2.050; 95% CI=1.241-3.388; P=0.005) and SAH (OR=4.903; 95% CI=2.788-8.623; P<0.001) had significantly higher risk of in-hospital SAP than those patients with AIS (Table 2).

	Category	OR	95% CI	P
Unadjusted model	ICH vs. AIS	2.806	1.961-4.016	<0.001
	SAH vs. AIS	2.443	1.698-3.515	<0.001
Adjusted models				
Model 1	ICH vs. AIS	3.495	2.406-5.076	<0.001
	SAH vs. AIS	3.418	2.303-5.072	<0.001
Model 2	ICH vs. AIS	3.648	2.480-5.367	<0.001
	SAH vs. AIS	3.750	2.483-5.664	<0.001
Model 3	ICH vs. AIS	3.757	2.531-5.575	<0.001
	SAH vs. AIS	4.034	2.650-6.141	<0.001
Model 4	ICH vs. AIS	2.449	1.443-4.152	0.001
	SAH vs. AIS	4.999	2.616-9.552	<0.001
Model 5	ICH vs. AIS	2.050	1.241-3.388	0.005
	SAH vs. AIS	4.903	2.788-8.623	<0.001

Model 1: Adjusted for demographics (age and gender);

Model 2: Adjusted for demographics and stroke risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, history of stroke/TIA, and current smoking);

Model 3: Adjusted for demographics, stroke risk factors, comorbidities (congestive heart failure, valvular heart disease, chronic obstructive pulmonary disease, peripheral artery disease, hepatic cirrhosis, peptic ulcer or previous GIB, renal failure, arthritis, dementia, and cancer) and pre-stroke dependence (mRS≥3);

Model 4: Adjusted for demographics, stroke risk factors, comorbidities, pre-stroke dependence, admission NIHSS score, and admission blood tests (WBC, HGB, Platelet, TG, TC, LDL, HDL, Glucose, and Creatine);

Model 5: Adjusted for adjusted for demographics, stroke risk factors, comorbidities, pre-stroke dependence, admission NIHSS score, dysphagia, BMI, admission blood pressure, blood tests and length of hospital stay; Abbreviation: AIS, Acute Ischemic Stroke; ICH, Intracerebral Hemorrhage; SAH, subarachnoid hemorrhage; OR, Odd Ratio; C.I., Confidence Interval.

Table 2: Association between stroke subtypes and occurrence of in-hospital SAP.

Microbiologic assessment

Among patients with in-hospital SAP (n=200), 115 patients (57.5%) underwent sputum culture. Overall, microbiological diagnosis was positive in 52 patients (45.2%). Among them, 38 patients (73.1%) were identified with Gram-negative bacteria and 14 (26.9%) with Gram-positive bacteria.

The top two most common Gram-negative bacteria were *Klebsiella pneumoniae* (n=22, 42.3%) and *Pseudomonas aeruginosa* (n=5, 9.6%), respectively. The most frequent Gram-positive bacteria was *Staphylococcus aureus* (n=12, 23.1%). The distribution of causative bacteria was not significant different among stroke subtypes (P=0.45) (Table 3).

	All (N=115)	AIS (N=56)	ICH (N=30)	SAH (N=29)	P value
Microbiological assessment					0.45
Negative cases, n (%)	63 (54.8)	32 (57.1)	18 (60.0)	13 (44.8)	
Positive cases, n (%)	52 (45.2)	24 (42.9)	12 (40.0)	16 (55.2)	
Gram-negative, n (%)					
Klebsiella pneumoniae	22/52 (42.3)	9/24 (37.5)	7/12 (58.3)	6/16 (37.5)	0.44
Pseudomonas aeruginosa	5/52 (9.6)	3/24 (12.5)	1/12 (8.3)	1/16 (6.3)	0.79
Acinetobacter baumannii	2/52 (3.8)	2/24 (8.4)	0/12 (0.0)	0/16 (0.0)	0.16
Serratia marcescens	2/52 (3.8)	1/24 (4.2)	0/12 (0.0)	1/16 (6.3)	0.69
Serratia plymuthica	1/52 (1.9)	0/24 (0.0)	0/12 (0.0)	1/16 (6.3)	0.32
Enterobacter agglomerans	1/52 (1.9)	1/24 (4.2)	0/12 (0.0)	0/16 (0.0)	0.55
Enterobacter cloacae	1/52 (1.9)	0/24 (0.0)	1/12 (8.3)	0/16 (0.0)	0.18
Burkholderia cepacia	1/52 (1.9)	1/24 (4.2)	0/12 (0.0)	0/16 (0.0)	0.55
Enterobacter aerogenes	1/52 (1.9)	1/24 (4.2)	0/12 (0.0)	0/16 (0.0)	0.55
Aeroenterobacter baumannii acetate	1/52 (1.9)	1/24 (4.2)	0/12 (0.0)	0/16 (0.0)	0.55
Gram-positive, n (%)					
Staphylococcus aureus	12/52 (23.1)	3/24 (12.5)	3/12 (25.0)	6/16 (37.5)	0.18
MRSA	3/52 (5.8)	0/24 (0.0)	1/12 (8.3)	2/16 (12.5)	0.23
MSSA	9/52 (17.3)	3/24 (12.5)	2/12 (16.7)	4/16 (25.0)	0.59
Streptococcus pneumoniae	2/52 (3.8)	1/24 (4.2)	0/12 (0.0)	1/16 (6.3)	0.69
Haemolytic staph	1/52 (1.9)	1/24 (4.2)	0/12 (0.0)	0/16 (0.0)	0.55

AIS: Acute Ischemic Stroke; **ICH:** Intracerebral Hemorrhage; **SAH:** Subarachnoid Hemorrhage; **MRSA:** Methicillin-Resistant Staphylococcus Aureus; **MSSA:** Methicillin-Sensitive Staphylococcus Aureus.

Table 3: Microbiological diagnosis of sputum culture by stroke subtypes.

Multi-drug resistant of microbiological pathogens

The proportion of multi-drug resistant of causative pathogens was shown in table 4. Overall, 57.7% patients with positive sputum culture had multi-drug resistant pathogen. The MDR for Gramnegative bacteria and Gram-positive bacteria was 56.8% and 60%, respectively. The MDR for specific microbiological pathogens was shown in Table 4.

Pathogen	Overall (N=52)	Multi-drug resistant
Sputum culture positive cases, n (%)	52 (100.0)	30/52 (57.7)
Gram-negative, n (%)	37 (71.2)	21/37 (56.8)
Klebsiella pneumoniae	22 (42.3)	8/22 (36.4)
Pseudomonas aeruginosa	5 (9.6)	4/5 (80.0)
Acinetobacter baumannii	2 (3.8)	1/2 (50.0)
Serratia marcescens	2 (3.8)	2/2 (100.0)
Serratia plymuthica	1 (1.9)	1/1 (100.0)
Enterobacter agglomerans	1 (1.9)	1/1 (100.0)
Enterobacter cloacae	1 (1.9)	1/1 (100.0)
Burkholderia cepacia	1 (1.9)	1/1 (100.0)
Enterobacter aerogenes	1 (1.9)	1/1 (100.0)
Aeroenterobacter baumannii acetate	1 (1.9)	1/1 (100.0)
Gram-positive, n (%)	15 (28.8)	9/15 (60.0)
Staphylococcus aureus	12 (23.1)	8/12 (66.7)
MRSA	3/52 (5.8)	3/3 (100.0)
MSSA	9/52 (17.3)	5/9 (55.6)
Streptococcus pneumoniae	2 (3.8)	0/2 (0.0)
Haemolytic staph	1 (1.9)	1/1 (100.0)

MRSA: Methicillin-Resistant Staphylococcus Aureus; **MSSA:** Methicillin-Sensitive Staphylococcus Aureus.

Table 4: The multi-drug resistance of microbiological pathogens.

Discussion

In the study, we aimed to compare clinical characteristics of in-hospital SAP by stroke subtypes (AIS, ICH and SAH). It was found that three quarters of SAP occurred within the first week after stroke onset. Patients with hemorrhagic stroke (ICH and SAH) had significantly higher risk of inhospital SAP than those with AIS. Microbiological diagnosis was established in nearly half patients by sputum culture and three quarters was identified with Gram-negative bacteria. More than half patients with positive sputum culture had multi-drug resistant pathogen.

Time course of stroke associated pneumonia remains poorly understood despite its contribution to poor stroke outcomes. As a result, optimal time window for SAP prophylaxis is uncertain. In the study, we found that the median time from stroke onset to SAP after ICH, AIS and SAH was 3, 4 and 5 days, respectively. Three quarters of SAP occurred within the first week after stroke onset. In addition, there was a trend that in-hospital SAP was earlier among patients with ICH than those with SAH and AIS. It would be helpful to take these kinds of information into account when making individualized SAP prophylaxis strategies in daily clinical practice.

Clarifying the potential risk of SAP by stroke subtypes will be an important step towards determining the most appropriate prophylaxis strategies. To the best of our knowledge, we are the first to make a systematic face-to-face comparison on potential risk of in-hospital SAP by three most common stroke subtypes. After adjusting for potential confounders, it was shown that

patients with ICH had a 2-fold and SAH 4.9-fold greater risk of in-hospital SAP than patients with AIS. These data point out the need for more aggressive SAP prophylaxis among patients with hemorrhagic stroke (ICH and SAH) in comparison with AIS. It is more significant for ICH management due to that treatment for ICH remains strictly supportive with not many evidence-based interventions currently available [16,18].

It is unclear about potential pathophysiological mechanisms underlying the phenomenon that hemorrhagic stroke (ICH and SAH) has higher risk of in-hospital SAP than AIS. One might argue that it might be due to more severe neurological deficit for patients with hemorrhagic stroke. In the study, we systematically adjusted for potential confounders including demographics, stroke risk factors, coexisting comorbidities, admission NIHSS score, dysphagia, admission blood tests and length of stay when investigating association between stroke subtypes and occurrence of in-hospital SAP (Table 2). Meanwhile, it is interesting that patients with SAH had the lowest level of focal neurological deficit measured with NIHSS score and proportion of dysphagia at admission (Supplementary table 1), however, they had the highest risk of in-hospital SAP in comparison with patients with AIS (Table 2). Together these data indicated that besides traditional risk factors of developing SAP after stroke, such as abnormal mental status, reduction of bulbar reflexes and dysphagia, there might be some other predisposing factors. Recent studies have indicated that stroke could disturb the normally well-balanced interplay between nervous system and immune system and induce a profound and long-lasting immunodepression (Stroke-induced immunodepression syndrome, SIDS) [28,29]. SIDS is characterized by a down-regulation of systemic cellular immune responses, i.e. rapid decrease in peripheral lymphocyte subpopulations and functional deactivation of monocytes [30,31]. In addition, studies showed that some cytokines and chemokines, such as IL-6, IL-1, Tumor necrosis factor-alpha and monocyte chemotactic protein-1 play important role in the development of SIDS [32-34]. The molecular mechanisms responsible for SIDS after stroke are largely elusive and just being uncovered. An improved understanding of intricacies of immune activation following stroke is essential to develop new treatment strategies for improving the outcomes of stroke patients.

Stroke associated pneumonia is a common medical complication after stroke. However, the spectrum of culpable organisms in non-ventilated patients and stroke unit setting are not well characterized. Timely identification of the contributory pathogens is vital in determining the proper use of antibiotics. In according with previous studies [9,35,36], organisms implicated from our study suggest a predominance of pathogens associated with hospital-acquired pneumonia, such as *Klebsiella pneumoniae* (42.3%), *Staphylococcus aureus* (23.1%), and *Pseudomonas aeruginosa* (9.6%). In addition, more than half patients (57.7%) with positive sputum culture had a multi-drug resistant pathogens. Our study systematically provided relevant information on microbiological pathogenesis by stroke subtypes, as can be useful for empirical treatment adequacy and for future RCT studying new antibiotics.

Although mounting evidence has shown that SAP was an independent risk factors for worse outcome after stroke, recently two large multi-center randomized controlled trials failed to show efficacy of prophylactic antibiotics after acute stroke [11,12]. In addition, previous studies indicated significant proportion of negative sputum cultures in stroke patients not receiving ventilation (31%–83%) [35,37,38]. These enlighten us that in-hospital SAP might not exclusively caused by bacteria, at least at certain stage [39]. For example, aspiration was one of the most common risk factor for pneumonia after stroke (called aspiration pneumonia). Aspiration pneumonia can be classified as: aspiration (chemical) pneumonitis, primary bacterial aspiration pneumonia and secondary bacterial infection of chemical pneumonitis [40]. Antibiotics are indicated for primary bacterial aspiration pneumonia and secondary bacterial infection of aspiration (chemical) pneumonitis, but not for uncomplicated chemical pneumonitis. Thus, deeply understanding the pathophysiological mechanisms underlying SAP would be useful to identify targets and to design relevant trials for improving stroke outcomes.

Our study has limitations despite having some meaningful findings. First, like all observational studies, we cannot rule out the possibility that additional variable (unmeasured confounders) might have some impact on potential risk of in-hospital SAP after stroke, such as bio-markers of strokeinduced immunodepression. Second, our study included only hospitalized patients and those patients died in emergency room or treated in outpatient clinics were not included. Third, for establishing microbiological diagnosis, this study mainly relay on sputum culture. Previous study showed that invasive methods, such as endotracheal aspirate, bronchial aspirate and bronchoalveolar lavage, could improve the likelihood of microbiological pathogens identification[10]. Finally, this study focused on risk of SAP during acute hospitalization after stroke. It is important for further studies to clarify the potential risk of SAP in subacute and chronic phase by stroke subtypes.

Conclusion

In summary, three quarters of SAP occurred within the first week after stroke onset. Patients with hemorrhagic stroke (ICH and SAH) had significantly higher risk of in-hospital SAP than those with AIS. Microbiological assessment suggests a predominance of pathogens associated with hospitalacquired pneumonia. Further studies to clarify potential pathophysiological mechanisms on different risk of SAP by stroke subtypes are warranted.

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Disclosure

All Authors reports no disclosures.

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