STROKE ASSOCIATED PNEUMONIA (SAP) AMONG ACUTE ISCHAEMIC STROKE PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA: ASSOCIATED FACTORS AND CLINICAL OUTCOMES

DR SHARIFAH NURSAMIHAH

BINTI SYED ABD RAHMAN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE)

UNIVERSITI SAINS MALAYSIA

2021

ACKNOWLEDGMENT

Bismillahirrahmanirrahim.

In the name of ALLAH, the most compassionate and the most merciful. Salutations be upon His messenger Muhammad (peace be upon him), his family and his companions. With the help and success granted by ALLAH, I have finished and completed this dissertation. I would like to express my sincere gratitude and appreciation to the following individuals who have contributed and supported me in many ways in conducting this study:

1. This work would not have been possible without the support and encouragement from my supervisor, Dr. Sanihah Abdul Halim. I am forever grateful for her expertise, kindness, and patience in making this research possible.
2. I would like to thank Dr Kueh Yee Cheng from Unit of Biostatistics and Research Methodology USM for the analytical advice.
3. I would like to express my gratitude to my family especially my husband, children, parents and siblings for the utmost support and for standing firm beside me for this study.
4. I would like to acknowledge all my colleagues and lecturers in the Department of Internal Medicine who constantly provided support and help in completing this research project.

Sharifah Nursamihah Binti Syed Abd Rahman

TABLE OF CONTENTS

ACKNOWLEDGEMENT ……... ii

TABLE OF CONTENTS…….. iii

LIST OF TABLES AND FIGURES ……..... iv

LIST OF ABBREVIATIONS……... v

ABSTRAK ……... viii

ABSTRACT…….. x

CHAPTER 1: INTRODUCTION……. 1

CHAPTER 2: OBJECTIVES OF STUDY …….. 2

CHAPTER 3: MANUSCRIPT……. 3

ABSTRACT……. 4

INTRODUCTION…… 6

METHODOLOGY..... 8

RESULTS……. 11

DISCUSSION……15

CONCLUSION, LIMITATIONS AND RECOMMENDATIONS…….. 21

REFERENCES……..... 23

TABLES AND FIGURES …… 30

CHAPTER 4: APPENDICES ……

Appendix 1: Study Protocol …….. 43

Appendix 2: Proforma checklist……... 86

Appendix 3: Approval Letter from Secretariat ……. 90

Appendix 4: Outcome Based Budgeting (OBB) ……... 92

Appendix 5: Raw Data/CD …… 95

LIST OF TABLES AND FIGURES

1. Descriptive analysis of baseline patient's characteristics

    Table 1.1: Baseline demography and comorbidities

    Table 1.2: Baseline stroke subtypes

    Table 1.3: Baseline clinical presentations

    Table 1.4: Baseline severity score

    Table 1.5: Baseline investigations

    Table 1.6: Baseline treatment

2. Factors associated with SAP

    Table 2.1: Association of sociodemographic and co-morbidities with SAP using SLR test

    Table 2.1: Association of stroke subtypes and SAP using SLR test

    Table 2.3: Association of clinical presentations and SAP using SLR test

    Table 2.4: Association of severity score and SAP using SLR test

    Table 2.5: Association of treatment prescribed and SAP using SLR test

    Table 2.6: Factors associated with SAP using MLR

3. Clinical outcomes

    Table 3: Association of SAP and adverse clinical outcomes

LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
AF	Atrial fibrillation
AHA	American Heart Association
BP	Blood pressure
CAD	Coronary artery disease
CDC	Centre for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CXR	Chest X-ray
ECG	Electrocardiogram
FEES	Fibreoptic endoscopic examination of swallowing
FEV_1/FVC	Forced expiratory volume in one second/ forced vital capacity
GCS	Glasgow Coma Scale
HAP	Hospital acquired pneumonia
HbA1c	Haemoglobin A1c
HDL-C	High Density Lipoprotein -Cholesterol
HUKM	Hospital Universiti Kebangsaan Malaysia
ICD	International classification of disease

INR	International normalised ratio
IOHC	Intensified oral hygiene care
LDL-C	Low Density Lipoprotein-Cholesterol
LVEF	Left ventricular ejection fraction
MCA	Middle cerebral artery
mmHg	Millimetre of mercury
MRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke scale
O_2	Oxygen
OHC	Oral hygiene care
OR	Odd ratio
$P_{a,CO2}$	Arterial carbon dioxide tension
$P_{a,O2}$	Arterial oxygen tension
PCA	Posterior cerebral artery
PISCES	Pneumonia in Stroke Consensus Group
RR	Relative risk
SAP	Stroke associated pneumonia
SD	Standard deviation
SpO2	Oxygen saturation
SPSS	Statistical Package for the Social Sciences

TC	Total cholesterol
TG	Triglyceride
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
UMNL	Upper motor neuron lesion
USM	Universiti Sains Malaysia
WCC	White cell count
WHO	World Health Organisation

ABSTRAK

Latar belakang: Jangkitan paru-paru dikalangan pesakit serangan angin ahmar memberi kesan buruk yang menyebabkan peningkatan kos hospital. Terdapat pelbagai faktor yang menyebabkan pesakit serangan angin ahmar menghidapi jangkitan paru-paru. Walaubagaimanapun, data berkenaan ini masih sedikit. Oleh itu, kami menjalankan kajian ini untuk menentukan bilangan pesakit yang menghidapi jangkitan paru-paru di kalangan pesakit serangan angin ahmar dan menentukan faktor-faktor penyebabnya serta mengkaji kesan buruknya, di mana hasil kajian ini dapat membantu kami untuk menguruskan pesakit seperti ini dengan lebih baik di masa akan datang.

Kaedah: Kajian keratan rentas dengan mengkaji rekod-rekod pesakit serangan angin ahmar yang dimasukkan ke Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan dari tempoh Januari 2016 sehingga Disember 2020. Kaedah persampelan sistematik digunakan untuk memilih pesakit. Data pesakit berkaitan dengan demografik, penyakit-penyakit yang dihidapi, gejala dan tanda-tanda yang di alami, rawatan dan kesan-kesan yang berkaitan dengan jangkitan paru-paru di kalangan pesakit serangan angin ahmar dikutip dan di analisa menggunakan kaedah kekerapan, regresi logistik sederhana dan regresi logistik berganda.

Keputusan: 446 orang pesakit serangan angin ahmar telah terpilih dalam kajian ini. Didapati 22.9% (n=102) menghidapi jangkitan paru-paru berkaitan dengan serangan angin ahmar. Faktor-faktor yang dikenal pasti berkait rapat dengan jangkitan paru-paru dikalangan pesakit serangan angin ahmar adalah pesakit yang mempunyai penyakit arteri koronari (OR 2.27, 95% CI (1.12,4.68), p = 0.024), bacaan paras gula yang tinggi semasa tiba di hospital (OR

1.152, 95% CI (1.081,1.23), p<0.001), penggunaan tiub makan (OR 4.04, 95% CI (1.91,8.56), p<0.001) dan skor A^2DS^2 yang tinggi (OR 1.58, 95% CI (1.35,1.85), p<0.001). Dari segi kesan-kesannya, jangkitan paru-paru di kalangan pesakit serangan angin ahmar berkait rapat dengan kerosakan fungsi organ (jangkitan yang teruk, kerosakan fungsi buah pinggang, kerosakan fungsi hati, kegagalan pernafasan, intubasi, trakeostomi), jangkitan paru-paru berulang, lebih lama ditahan di hospital, skor MRS yang tinggi semasa pulang ke rumah dan kematian, p<0.25.

Kesimpulan: Faktor-faktor yang dikenal pasti berkait rapat dengan jangkitan paru-paru dikalangan pesakit serangan angin ahmar adalah pesakit yang mempunyai penyakit arteri koronari, bacaan paras gula yang tinggi semasa tiba di hospital, penggunaan tiub makan dan skor A^2DS^2 yang tinggi. Jangkitan paru-paru dikalangan pesakit serangan angin ahmar berkait rapat dengan kesan buruk iaitu kerosakan fungsi organ, jangkitan paru-paru berulang, lebih lama ditahan di hospital, skor MRS yang tinggi semasa pulang ke rumah dan kematian. Oleh itu, pencegahan kepada faktor penyumbang harus di jalankan untuk mengurangkan risiko jangkitan paru-paru dikalangan pesakit serangan angin ahmar.

ABSTRACT

Background: Stroke-associated pneumonia (SAP) is associated with adverse clinical outcomes which increase the cost of hospitalisation. There are various factors that contribute to SAP among acute ischaemic stroke patients. However, data on SAP in our population are scarce. Hence, a study to determine the proportion and associated factors of SAP and its clinical outcomes is conducted and it is hoped that the findings of this study could guide future management of patient.

Method: A cross-sectional study among acute ischaemic stroke patients who were admitted to Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan between January 2016 until December 2020, were studied. Systematic sampling method were used to select the patient. Variables collected were demograhics, comorbidities, clinical presentations, treatment of SAP and clinical outcomes. These variables were then analysed using descriptive, simple and multiple logistic regression for any significant associations.

Results: 446 subjects with acute ischaemic stroke were selected in this study. Proportion of SAP is 22.9% (n=102). Significant independent associated factors for SAP are coronary artery disease (CAD) (OR 2.27, 95% CI (1.12,4.68), p = 0.024), high random blood glucose on admission (OR 1.152, 95% CI (1.081,1.23), p<0.001), nasogastric tube feeding (OR 4.04, 95% CI (1.91,8.56), p<0.001) and high A^2DS^2 score (OR 1.58, 95% CI (1.35,1.85), p<0.001). For the clinical outcomes, SAP has significant association with all outcomes that were studied; organ impairments (e.g. septic shock, acute kidney injury (AKI), liver dysfunction, respiratory failure, tracheal intubation, need of trachesotomy), recurrent hospital acquired

infection (HAP), prolonged hospital stays, higher Modified Rankin Scale (MRS) score on discharge and inpatient mortality, $p< 0.05$.

Conclusion: The significant independent associated factors for developing SAP are CAD, high random blood glucose on admission, nasogastric tube feeding and high A^2DS^2 score. SAP is significantly associated with adverse outcomes which are organ impairments, recurrent HAP, prolonged hospital stays, poor MRS score on discharge and inpatient mortality. Thus, preventive measure of these significant associated factors needs to be done to reduce incidence of SAP.

Keyword: *Stroke associated pneumonia, acute ischaemic stroke*

CHAPTER 1: INTRODUCTION

Stroke is one of the major causes of morbidity and mortality in both developed and developing countries. According to Department of Statistic Malaysia, stroke is the third leading cause of death in Malaysia in year 2019 which account 8%, after ischaemic heart disease (15%) and pneumonia (12.2%). Globally in year 2016, there were 5.5 million (95% uncertainly intervals 5.3 – 5.7) deaths and 116.4 million (111.4 – 121.4) disability-adjusted life-years (DALYs) due to stroke [1]. In Malaysia, 75% of DALYs were due to non-communicable diseases with the main three heavy contributors were ischaemic heart disease, stroke and diabetes mellitus [2].

One of the complications of acute ischaemic stroke is infection, mainly pneumonia and urinary tract infection. Post stroke pneumonia can be subcategorised into stroke associated pneumonia and hospital acquired pneumonia. Pneumonia in Stroke Consensus (PISCES) Group defined stroke associated pneumonia (SAP) as pneumonia which occurred within first week of acute stroke [3]. Pneumonia which occurred after first week of stroke is defined as hospital acquired pneumonia [3]. Based on previous study, there are diverse factors contributed to stroke associated pneumonia such as patient's age, comorbidities and clinical presentation on admission. Stroke associated pneumonia is associated with adverse clinical outcomes which increase the cost of hospitalisation. In view of stroke associated pneumonia is preventable, a local study is conducted to determine the proportion, its associated factors and clinical outcomes. Hence, preventive measures for stroke associated pneumonia could be planned in the future to reduce the cost of hospitalisation.

CHAPTER 2: OBJECTIVES OF STUDY

General objective:

To study the prevalence, associated factors and clinical outcomes of stroke associated pneumonia among acute ischemic stroke patients in Hospital USM.

Specific objectives:

1. To determine the prevalence of stroke associated pneumonia among acute ischaemic stroke patient in Hospital USM.
2. To determine the associated factors for developing stroke associated pneumonia in acute ischaemic stroke patient in Hospital USM.
3. To determine the association of stroke associated pneumonia and poor clinical outcomes among acute ischaemic stroke patient in Hospital USM.

CHAPTER 3: MANUSCRIPT

JOURNAL: Malaysian Journal of Medical Sciences

TITLE: Stroke Associated Pneumonia (SAP) among acute ischemic stroke patients in Hospital Universiti Sains Malaysia-: Associated factors and clinical outcomes.

Author: SHARIFAH Nursamihah

Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, MALAYSIA.

Corresponding Author : SANIHAH Abdul Halim

Department of Internal Medicine,

School of Medical Sciences, Universiti Sains Malaysia,

16150 Kubang Kerian, Kota Bharu, Kelantan, MALAYSIA.

Email : sanihahabdhalim@gmail.com; Tel: +609-7676590 Fax: +6097673949

Disclosure of finding: none of the author receive any financial support for this study.

ABSTRACT

Background: Stroke-associated pneumonia (SAP) is associated with adverse clinical outcomes which increase the cost of hospitalisation. There are various factors that contribute to SAP among acute ischaemic stroke patients. However, data on SAP in our population are scarce. Hence, a study to determine the proportion and associated factors of SAP and its clinical outcomes is conducted and it is hoped that the findings of this study could guide future management of patient.

Method: A cross-sectional study among acute ischaemic stroke patients who were admitted to Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan between January 2016 until December 2020, were studied. Systematic sampling method were used to select the patient. Variables collected were demograhics, comorbidities, clinical presentations, treatment of SAP and clinical outcomes. These variables were then analysed using descriptive, simple and multiple logistic regression for any significant associations.

Results: 446 subjects with acute ischaemic stroke were selected in this study. Proportion of SAP is 22.9% (n=102). Significant independent associated factors for SAP are coronary artery disease (CAD) (OR 2.27, 95% CI (1.12,4.68), p = 0.024), high random blood glucose on admission (OR 1.152, 95% CI (1.081,1.23), p<0.001), nasogastric tube feeding (OR 4.04, 95% CI (1.91,8.56), p<0.001) and high A^2DS^2 score (OR 1.58, 95% CI (1.35,1.85), p<0.001). For the clinical outcomes, SAP has significant association with all outcomes that were studied; organ impairments (e.g. septic shock, acute kidney injury (AKI), liver dysfunction, respiratory failure, tracheal intubation, need of trachesotomy), recurrent hospital acquired

infection (HAP), prolonged hospital stays, higher Modified Rankin Scale (MRS) score on discharge and inpatient mortality, $p< 0.05$.

Conclusion: The significant independent associated factors for developing SAP are CAD, high random blood glucose on admission, nasogastric tube feeding and high A^2DS^2 score. SAP is significantly associated with adverse outcomes which are organ impairments, recurrent HAP, prolonged hospital stays, poor MRS score on discharge and inpatient mortality. Thus, preventive measure of these significant associated factors needs to be done to reduce incidence of SAP.

Keyword: *Stroke associated pneumonia, acute ischaemic stroke*

INTRODUCTION

Stroke is one of the major causes of morbidity and mortality in both developed and developing countries. According to Department of Statistic Malaysia, stroke is the third leading cause of death in Malaysia in year 2019 which account 8%, after ischaemic heart disease (15%) and pneumonia (12.2%).

One of the complications of acute ischaemic stroke is infection, mainly pneumonia and urinary tract infection. Up to date, the is no gold-standard criteria for diagnosing or categorising lower respiratory tract infection in acute stroke. Pneumonia in Stroke Consensus (PISCES) Group recommended stroke associated pneumonia (SAP) as the terminology used for the spectrum of pneumonia complicating the first 7 days after stroke onset in nonventilated patients [1]. This includes the spectrum of acute lower respiratory tract syndromes complicating stroke, which may or may not meet radiological criteria for pneumonia, and may even be noninfective (eg, aspiration pneumonitis). This consensus agreed pneumonia as the operational terminology due to widespread acceptance and familiarity of the pneumonia concept in acute stroke care, and lack of accepted definitions for alternative terms such as stroke-associated chest infection, stroke-associated LRTI, and stroke-associated acute respiratory syndrome. Pneumonia which occurred after first week of stroke in hospitalised patient is defined as hospital-acquired pneumonia [1]. According to American Heart Association (AHA) guideline, PISCES Group recommended the diagnosis of SAP in acute stroke patient is based on modified CDC criteria for clinically defined pneumonia [1]. Definite SAP is defined as all CDC criteria are met, including diagnostic CXR changes. Meanwhile, probable SAP is defined as all CDC criteria are met, but initial CXR and repeated CXR nonconfirmatory (or not undertaken), and no alternative diagnosis or explanation.

The reported prevalence of stroke associated pneumonia ranged from 5.2% - 15.2% [2,3,4,5,6]. These variations of rates were due to differences in patient populations and study design.

There are diverse factors contributed to SAP were identified from previous studies including dysphagia [3,4,7,8], high NIHSS on admission [3,4,7,9], high blood glucose on admission [3], atrial fibrillation [5,10] and older age [9,11]. One of the tools to predict post-stroke pneumonia is A^2DS^2 score which is developed based on routinely collected data with a good discrimination and calibration properties. It consists of 10 score (Age ≥ 75 years = 1, Atrial fibrillation = 1, Dysphagia = 2, male Sex = 1, stroke Severity, National Institutes of Health Stroke Scale 0–4 = 0, 5–15 = 3, ≥ 16 = 5) [12].

Post-stroke infection is associated with high morbidity and mortality. Previous studies showed post-stroke pneumonia was associated with prolonged hospital stay [13,14] with mean length of stay was 20.8 days [15]. Upon discharged, patient with SAP had reduced functional outcome [2,15] with MRS score 3 – 6 [13]. SAP increase risk of death with pooled odds ratio for in-hospital mortality was 3.62 [6], and one of independent predictor for 30-day mortality [3,15,16].

The data regarding SAP in our population is scarce. In this study, we would like to determine the proportion, associated factors, and clinical outcomes of SAP among acute ischaemic stroke patient in our setting, Hospital Universiti Sains Malaysia (HUSM) for a of period January 2016 until December 2020.

METHODOLOGY

Study design

This study was a single centre, cross sectional study. There were 2500 patients admitted for acute ischaemic stroke in between January 2016 until December 2020 in our neurology or medical ward. Using systematic sampling method, every 5^{th} number of the lists were selected. If the patient's folder for the selected number was not available, we took the next number. Ethical approval was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia (USM/JEPeM/21010111).

Subjects

We selected 446 patients above 18 years old who admitted to neurology or medical ward for acute ischemic stroke (based on WHO definition) by clinical or radiological, either first episode or recurrent ischaemic stroke. Patient with SAP (the spectrum of low respiratory tract infections complicating stroke in the first week in nonventilated patient) were included in this study. The diagnosis of SAP based on modified CDC criteria, both probable (all CDC criteria met, but initial and repeated CXR nonconfirmatory or not undertaken) and definite (all CDC criteria met including diagnostic CXR changes) SAP included in this study. Modified CDC criteria for diagnosis of pneumonia are: at least one of following (fever more than 38^0 C with no other recognised cause, leucopenia (<4000 WCC/mm^3) or leucocytosis (>12 000 WCC/mm^3) and for ≥70 years old, altered mental status with no other recognised cause); and at least 2 of the following (new onset of purulent sputum or change in character of sputum over a 24 hour period or increased respiratory secretions, or increased suctioning requirement, new onset or worsening cough, or dyspnea, or tachypneic (respiratory rate > 25/min), rales, crackels or bronchial breath sounds and worsening gas exchange (eg O_2 desaturation, increase oxygen requirement)); and ≥ 2 serial chest radiographs with at least 1

of the following (new or progressive and persistent infiltrate, consolidation or cavitation). Exclusion criteria for patient's selection were those with haemorrhagic stroke or other neurological disease such as brain tumour, meningitis, or encephalitis, or patient with respiratory failure due to other causes such as heart failure, pulmonary embolism or pulmonary oedema. Patient with abnormal CXR at baseline or developed respiratory symptoms prior to stroke also excluded from this study.

Data collection

The list of patients who admitted to neurology or medical ward Hospital USM from January 2016 until December 2020 was obtained from record office. Patients were selected using systematic sampling method. The data from patient's record were collected based on pro forma which including sociodemographics, co-morbidities, clinical presentations, treatment, and clinical outcomes. The clinical presentations including stroke characteristics (e.g. stroke subtypes and vascular territory of stroke), clinical features (e.g. fever, cough, shortness of breath, blood pressure, SPO_2, random blood glucose on admission, GCS on admission, dysphagia and upper motor neuron lesion (UMNL) facial nerve palsy), investigations (white cell count (WCC), C-Reactive protein (CRP), chest X-ray (CXR)), severity score (NIHS score, A^2DS^2 score and pneumonia CURB-65 score). Treatment prescribed to patient includes oral hygiene, types of feeding either nasogastric or oral feeding, proton pump inhibitor usage were also obtained therein. Antibiotic either started within or after 48 hours of SAP diagnosis were obtained in the treatment section. The clinical outcomes section including organ impairment (e.g septic shock, AKI, liver dysfunction, respiratory failure, tracheal intubation and need of tracheostomy), recurrent HAP, length of stay, MRS score on discharge and inpatient mortality.

Statistical Analysis

For statistical analysis, categorical data presented as frequency and percentage while numerical data presented as mean and standard deviation (SD).

For univariate analysis, we used parametric test for normally distributed data and non-parametric test for skewed data.

1. For categorical variables, we used non-parametric test which were Chi-square test for gender, comorbidities, GCS, dysphagia, facial nerve palsy, blood pressure, SPO2, nasogastric tube feeding, on PPI, antibiotics within 48 hours, septic shock, AKI, liver dysfunction, respiratory failure, intubation, tracheostomy, recurrent HAP, MRS score and mortality; and Fisher Exact test for oral hygiene.
2. For numerical variables (age, random blood sugar, A^2DS^2 score, WCC, CRP and length of stay), all data were normally distributed. We used parametric test which was independent T-test.

For multivariate analysis, forward logistic regression (LR) and backward LR method by SPSS software were used to automatically select among significant factors from univariate analysis to develop a model for multivariate analysis. Variables with $p<0.25$ (age, hypertension, diabetes, dyslipidaemia, recurrent stroke, CAD, heart failure, AF, COPD, stroke subtypes, random blood glucose on admission, GCS, dysphagia, UMNL facial palsy, NIHS score, A^2DS^2 score, nasogastric tube feeding, on PPI and oral hygiene) were selected for MLR to analyse association of factors and SAP.

All assumptions for the tests were met. Variables comparison with p-value less than 0.05 was considered as significant. The data was analysed using SPSS software version 26.

RESULTS

There were 446 subjects selected in this study using systematic sampling method who met the inclusion criteria from January 2016 until December 2020. Out of 446 selected subjects, 102 (22.9%) had SAP.

Table 1.1 shows the descriptive analysis of baseline sociodemography and co-morbidities. Mean age for SAP patient was 61 years old, which was lower compared to non-SAP patient, 67 years old. Male patient predominantly in both group, 59.8% and 62.8% for SAP and non-SAP respectively. The percentage of patients who had co-morbidities of diabetes (n=60, 58.8%), dyslipidaemia (n=52, 51%), recurrent stroke (n=23, 22.5%), coronary artery disease (n=36, 35.3%) and atrial fibrillation (n=32, 31.4%) are higher in those who had SAP compared to non-SAP subjects. Our patients who developed SAP also had other co-morbidities such as chronic kidney disease (n=6), goitre (n=1) and hyperthyroid (n=1).

For the subtypes of stroke, there were 41(40.2%) patients cardioembolic cause, followed by lacunar (n=37, 36.3%) and large atherosclerotic disease (LAD) (n=24, 23.5%). In contrast to non-SAP patients, most of them were lacunar (n=229, 66.6%) cause. Middle cerebral artery (MCA) involvement was predominantly in both group, 85(83.3%) and 281 (81.7%) for SAP and non-SAP respectively. The results of baseline stroke characteristics are summarised in Table 1.2.

Among patient who developed SAP, most of them presented with fever (n= 62, 60.8%) and desaturation with SPO_2 less than 95% (n= 69, 67.6%), followed by cough (n= 38, 37.3%) and shortness of breath (n= 22, 21.6%). Upon diagnosis of SAP, only 5 (4.9%) patients had hypotensive episode (BP<90/60 mmHg). Glasgow coma scale (GCS) is a validated tool used to assess conscious level. Total score of 13-15 is mild, 9-12 is moderate

and 3-8 is severe GCS impairment. Upon presentation to emergency room, patients who developed SAP presented with lower GCS score which 53(52%) of them mild GCS impairment and 43(42.2%) patients moderate GCS impairment, compared to non-SAP which most of them presented with mild GCS score (n=313, 91%) impairment. Among patients who developed SAP, 79.4% (n= 81) had dysphagia, which was higher compared to non-SAP patients who only 21% (n= 72) had dysphagia, this is statistically significant using chi square test $p<0.001$. Mean for random blood glucose on admission was higher in SAP (11.35 mmol/L, ± 4.64) than non-SAP (9.38 mmol/L, ± 4.31), statistically significant using independent T- test $p<0.001$. The results of baseline clinical presentation are tabulated in Table 1.3.

Results of severity score are summarised in Table 1.4. Upon admission to emergency room, NIHS score was used to assess severity of stroke. Our results show patients who developed SAP presented with higher NIHS score, which 52 (51%) moderate score and 22 (21.6%) moderate-severe score. Only 19 (18.6%) among SAP patient presented with mild NIHS score, in contrast to those who did not developed pneumonia which most of them presented with mild NIHS score (n=203, 59%). A^2DS^2 score was used to predict development of pneumonia which consist of 5 components: age, atrial fibrillation, dysphagia, male sex and NIHSS. Mean for A^2DS^2 score was higher (mean= 5.7, ± 2.47) among patient who developed SAP compared to non-SAP (mean= 2.45, ± 1.99), this is statistically significant using independent T-test $p<0.001$. CURB-65 score was used to assess severity of pneumonia. Score 0-1 is mild, 2 is moderate and ≥ 3 is severe pneumonia. Fourty-five percent (n=45) of SAP patients had mild, followed by moderate (n= 35, 35%) and severe pneumonia (n= 20, 20%).

In term of investigations, mean white cell count (WCC) among patient who had SAP was 14.27 X 10^9 (± 4.51), which is higher than non-SAP (mean 8.94, ±2.89), this is statistically significant by independent T-test $p<0.001$. Mean for CRP among SAP patients

was 45.96 mg/L (± 26.3). Most of SAP patient had patchy CXR finding (n= 79, 77.5%). The results are summarised in Table 1.5.

Table 1.6 summarised the treatments given to patients. Among SAP patients, most of them were given feeding through nasogastric tube (n= 86, 84.3%). It contrasts to non-SAP patients which only 27.7% (n= 95) given nasogastric tube feeding. For oral hygiene care, only 6 (5.9%) and 4 (1.2%) patients were given oral hygiene care for SAP and non-SAP group respectively. This small percentage is contributed by lack of documentation regarding oral hygiene care in the patient's folder. Majority of patients from both groups were prescribed with proton pump inhibitor, SAP (n= 92, 90.2%) and non-SAP (n= 256, 74.6%) respectively. All patients with SAP were started on antibiotics within 48 hours (n=102, 100%). Two (0.6%) non-SAP patients were started on antibiotics for thrombophlebitis. All these given treatments were statistically significant using Chi square test, $p<0.005$.

Association of factors and SAP were analysed using simple logistic regression (SLR). We found there was significant association of age and SAP ($p<0.01$) which showed in Table 2.1. For co-morbidities, there were significant associations of dyslipidemia, recurrent stroke, CAD, heart failure, AF and COPD with SAP ($p<0.05$), the result is tabulated in Table 2.1. Table 2.2 shows there were significant association of stroke subtypes with SAP ($p<0.05$). For the clinical presentations, there were significant association of random blood glucose on admission, all GCS score and dysphagia with SAP ($p<0.01$), the results are tabulated in Table 2.3. Table 2.4 shows NIHS score and A^2DS^2 score were significant associated with SAP ($p<0.01$). In term of treatments that given to the patients; nasogastric tube feeding, patients who on proton pump inhibitor and oral hygiene care were significant associated with SAP ($p<0.05$), the result are showed in Table 2.5.

To ascertain the independent factors associated with SAP in this study, the analysis was proceeded with multiple logistic regression (MLR) test. The significant independent variables ($p<0.25$) included in MLR analysis were age, dyslipidaemia, recurrent stroke, CAD, heart failure, atrial fibrillation, COPD, stroke subtypes, dysphagia, random blood glucose on admission, GCS, NIHS score, A^2DS^2 score, nasogastric tube feeding, PPI usage and oral hygiene. The test was statistically significant and correctly classified 86.5% of cases with 88.4% of area under receiver operating characteristics (ROC) curve.

The four significant independent factors associated with SAP were CAD, random blood glucose on admission, nasogastric tube feeding and A^2DS^2 score. The results are summarised in Table 2.6. A patient with CAD had 2.286 odds of getting SAP when random blood glucose on admission, nasogastric tube feeding and A^2DS^2 score variables were adjusted (95% CI (1.12,4.68), $p = 0.024$). Every 1 mmol increased of glucose had 1.152 risk of SAP when CAD, nasogastric tube feeding and A^2DS^2 score were adjusted (95% CI (1.081,1.23), $p<0.001$). A patient with nasogastric tube feeding had 4.04 risk of SAP when CAD, random blood glucose on admission, and A^2DS^2 score variables were adjusted (95% CI (1.91,8.56), $p<0.001$). Every increased of A^2DS^2 score had 1.58 risk of SAP when CAD, random blood glucose on admission, and nasogastric tube feeding variables were adjusted (95% CI (1.35,1.85), $p<0.001$).

The results for clinical outcomes are summarised in Table 3. In term of organ impairments due to SAP, 6 (5.9%) of them had septic shock, 22 (21.6%) AKI, 4 (3.9%) liver dysfunction, 25 (24.5%) respiratory failure, 8 (7.8%) required tracheal intubation and 7 (6.9%) need tracheostomy. One patient from non-SAP group required tracheal intubation for dropping GCS due to malignant infarct. Thirteen (12.7%) of SAP patients had recurrent HAP during that admission. MRS score is a scale used to measure functional outcome, which score of 0-2 consider as good and score 3-6 is poor MRS score. Our analysis shows proportion of

poor MRS score was higher than good MRS in SAP patients, and it was significantly associated with SAP. Inpatient mortality among SAP patients were 4.9% (n=5) which was higher than non-SAP patients 1.2% (n=4). They died because of septic shock, respiratory failure and recurrent HAP. Patient with SAP had prolonged hospital stay 3 times higher than non-SAP group, which the mean was 15 days and 5 days for SAP and non-SAP respectively. Further analysis using chi square and independent T test found SAP is statistically significant associated with all adverse clinical outcomes that we studied ($p<0.05$).

DISCUSSION

There were 446 patients selected in this study who met the inclusion criteria. Out of 446 selected patients, proportion of patients who had SAP is 102 (22.9%). This high proportion is possibly contributed by our sampling method and might not reveal the true prevalence of SAP in our centre. Previous prospective study at one local centre which included all acute ischaemic stroke patient (n=120), the prevalence of SAP is 15.2% [3] and a previous meta-analysis of 87 studies showed prevalence of 10% [6].

The four most significant independent factors associated with SAP are CAD, random blood glucose on admission, nasogastric tube feeding and A^2DS^2 score ($p<0.05$).

Co-morbidities which have significant association with SAP are dyslipidemia, recurrent stroke, coronary artery disease, heart failure, AF and COPD ($p<0.05$). When we proceed with MLR test, CAD is one of the independent factors for SAP. A patient with CAD has 2.286 odds of getting SAP when random blood glucose on admission, nasogastric tube feeding and A^2DS^2 score variables are adjusted (95% CI (1.12,4.68), $p = 0.024$). Our finding is contrast to other study done in Indian which showed CAD is not significant associated with

SAP [17]. We cannot explain this observation at this point of time and need a larger cohort in future study to arrive at any definite conclusion.

We found co-morbid of diabetes is not significant associated with SAP (p=0.248), similar finding to previous study [12]. Mean random blood glucose on admission was higher among patients who had SAP, 11.35 (± 4.64) mmol/L compared to 9.38 (± 4.31) mmol/L for those who were non-SAP. From our MLR analysis, it shows every 1 mmol increase of glucose has 1.152 risk of SAP when CAD, nasogastric tube feeding and A^2DS^2 score are adjusted (95% CI (1.081,1.23), p<0.001). Previous study done in Malaysia also reported random blood glucose on admission is significant independent factors for SAP (p=0.013) [3]. This may be explained by stress induced hyperglycaemia during acute stroke. Hyperglycaemia in acute ischaemic stroke is caused by two mechanisms: the activation of the sympathetic and parasympathetic nervous system, and the immune response of the hypothalamic-pituitary-adrenal axis [18, 19]. Furthermore, leucocytes bactericidal ability is reduced by hyperglycaemia which increased risk for pneumonia [20]. Hyperglycaemia within 24 hours of acute stroke also associated with expansion of infraction and worsen functional outcome [21].

We found nasogastric tube feeding is one of the significant independent factors for SAP with adjusted OR of 4.04 (95% CI (1.91,8.56), p<0.001). This was supported by other studies which showed nasogastric tube feeding among stroke patients associated with high risk of pneumonia [20, 22, 23]. The mechanisms for aspiration in patients with nasogastric feeding tube are loss of anatomical integrity of the upper and lower esophageal sphincters, increase in the frequency of transient lower esophageal sphincter relaxations, and desensitization of the pharyngoglottal adduction reflex [22].

Our study shows mean A^2DS^2 score among patients who developed SAP is higher (mean= 5.7, ± 2.47) than non-SAP (mean= 2.45, ± 1.99). This consistent with other study which reported means for SAP (mean = 7.02 ± 1.40) is higher than non-SAP (mean = 4.75 ± 1.92), p = 0.0001 [17]. Our MLR analysis shows A^2DS^2 score is a significant independent variable for SAP with every increase of A^2DS^2 score has 1.58 risk of SAP when CAD, random blood glucose on admission, and nasogastric tube feeding variables were adjusted (95% CI (1.35,1.85), p<0.001). Previous study showed higher A^2DS^2 score was associated with higher risk of SAP (OR: 9.68, 95% CI (6.12–15.30)) [24]. A^2DS^2 score is a simple and effective tool to predict SAP during hospitalization, which was proposed by Hoffmann et al. This has been verified in China [24, 25], the United Kingdom [26], France [27], and Spain [28]. Based on study done in Indian, A^2DS^2 score >5 to predict SAP had sensitivity of 82.6% and specificity of 65.1%[17]. It consists of 10 score (Age ≥ 75 years = 1, Atrial fibrillation = 1, Dysphagia = 2, male Sex = 1, stroke Severity, NIHSS 0–4 = 0, 5–15 = 3, ≥ 16 = 5). From our univariate analysis, we found 4 components out of 5 A^2DS^2 components are significantly associated with SAP which are age, atrial fibrillation, dysphagia and NIHS score.

Our univariate analysis shows age has significant association with SAP (OR: 1.047, 95% CI (1.025, 1.070), p<0.01). Previous study also supported that age (OR: 1.096, 95% CI (1.023 – 1.174)) is one of the predictors for SAP [11]. Older age is associated with higher incidence of SAP [24, 29], as they have lower immunity and age-related organ-specific physiological changes which predisposed them to infection [30].

Among our patients who had SAP, there were more male (n=61, 59.8%) patients than female (n=41, 40.2%). But we found there is no significant association between gender and SAP, similar to previous study [17]. However, one study reported male gender was associated with SAP (OR 1.71, CI 95% (1.22, 2.39)) [9].

Our SLR analysis shows AF has significant association with SAP, crude OR 4.78 (95% CI (2.73, 8.39), p < 0.001), similar to previous studies [5,10,17]. Irregular cardiac activities of AF cause decreased cardiac output and pulmonary congestion which promote pulmonary infection [10].

Dysphagia has significant association with SAP which showed from our univariate analysis. Few studies reported dysphagia is one of the strong predictors for SAP [3, 4, 7, 8,11,17]. Our study shows the patient with dysphagia is 14 times higher (OR: 14.03, 95% CI (8.41, 25.06), p<0.001) risk to developed SAP, while other study report there was seven [31] and twenty [32] risk fold for aspiration pneumonia. The risk of pneumonia in aspiration patients are varies between the studies suggesting of other factors that influence SAP. This was supported by a study which reported dysphagia is a factor for SAP but it is not sufficient to cause pneumonia unless other factors are present as well [33]. Oral feeding by family members prior to admission may contribute to SAP, unfortunately we did not look for it and this may need further study to be done. Patient with stroke developed dysphagia because the swallowing musculature is asymmetrically represented in both motor cortices. Hence, stroke which affect the dominant swallowing projection hemisphere will results in dysphagia [31]. Oropharyngeal dysphagia is best defined as a disruption of bolus flow through the mouth and pharynx, while aspiration is defined as incursion of food material into the airway and below the true vocal cords [31].

NIHS scale is a validated tool used to assess severity of stroke which consists of conscious level, gaze, visual, facial palsy, motor power, sensory, dysphasia, dysarthria and neglection. Score 1 – 4: minor, 5 – 15: moderate, 16 – 20: moderate to severe and 21 – 42: severe stroke. Our SLR analysis shows NIHS score is a significant independent factor for SAP (p <0.001) which is similar to other studies [3, 9]. Patient with moderate-severe NIHS score is at 33 risk (OR: 33.56, 95% CI (12.71-88.74), p< 0.001) and severe NIHS score at 19

risk (OR: 19.23, 95% CI (5.86 – 63.22), p<0.001) to develop SAP. This is consistent with a meta-analysis which reported NIHSS >15 points (moderate and severe) had OR:14.63 of getting SAP [7]. Patient with a higher NIHS score at higher risk of developing pneumonia due to decrease conscious level or position-induced gastroesophageal reflux [34].

Regarding adverse clinical outcomes of SAP, we studied about organ impairments (e.g. septic shock, acute kidney injury, liver dysfunction, respiratory failure, need of tracheal intubation and tracheostomy), recurrent HAP, length of stay, MRS score on discharge and inpatient mortality. We found all the clinical outcomes had significant associations with SAP (p<0.05).

There is significant association of SAP and organ impairment (p<0.001). The most common complication of severe stroke was pulmonary infection which cause multiple organ dysfunction syndrome [35].

Our analysis shows proportion of SAP patient who had poor MRS score (n=98, 96.1%) on discharge is higher than good MRS, and it is significantly associated with SAP (p<0.001). Our finding is consistent with other study which reported post stroke pneumonia had worse functional outcome with MRS 3- 6 (OR 7.17; CI: 5.44- 9.45) [13]. The other study also supported our findings which they reported only 12.3% (95% CI 7.0–17.7) of pneumonia patients were independent at hospital discharge (MRS <3) compared to 38.2% (95% CI 37.3%–39.1%) of patients without pneumonia [15].

Our study shows significant association of SAP and inpatient mortality (p=0.018). According to an observational study on impact of SAP on mortality including 9238 patients, the mortality remained significant at 3 time periods; inpatient (OR 5.87, 95%CI (4.97-6.93)), 0-90 days (OR 2.17 (1.97-2.40)), and 91-365 days (OR 1.31 (1.03-1.67)) [14]. This contrast to a multicentre retrospective cohort study involved 8,251 patients which reported SAP not

increased mortality 7-day, but increase 30-day (OR: 2.2, 95% CI (1.8–2.7)) and 1-year mortality (OR: 3.0, 95% CI (2.5–3.7)) [15]. Another study also reported SAP increase 30 days mortality [3,16]. In our study, we unable to look at the mortality in 30 days and 1 year as we only collect the data during admission, and did not follow up the patient until 30 days or 1 year after being discharged. A previous study regarding predictor of mortality and disability of SAP reported the mortality is associated with non-modifiable patient characteristics including increasing age, haemorrhagic stroke sub-type, pre-stroke disability and comorbidities (dementia, lung cancer and previous transient ischaemic attack) [36]. However, in our study we did not look at the causal relationship between predictor factors and mortality, and this may need further study to be done.

SAP prolonged hospitalization with mean length of stay was 15 days (± 12.21) compared to 5 days (± 2.76) for non-SAP patient. It consistent with previous study which reported SAP prolonged hospital stay, with adjusted relative length of stay extension was 1.80 (95% CI 1.54 – 2.11)[13] and higher odds of long length of stay (OR 1.93; CI: 1.67-2.22)[14]. Most of acute ischaemic stroke patient without pneumonia were discharged after blood pressure and glucometer being well controlled and reviewed by physiotherapist, speech therapist and neurorehabilitation teams. However, patient with SAP required longer stay for completion of antibiotics, and inpatient rehabilitation as they associated with high stroke severity. This increased the cost of hospitalisation, but we did not look at the cost in our study. Further study needs to be done to compare the cost for patient with SAP and non-SAP.

CONCLUSION, LIMITATION OF STUDY AND RECOMMENDATIONS

Conclusion

In conclusion, the proportion of SAP in our study is 22.9%. CAD, high random blood glucose on admission, nasogastric tube feeding, and high A^2DS^2 score are significant independent factors associated with SAP. SAP is significantly associated with adverse outcomes which are organ impairments, recurrent HAP, prolonged hospital stays, poor MRS score on discharge and inpatient mortality. Thus, preventive measure of these significant associated factors needs to be done to reduce incidence of SAP.

Study limitations

There are few limitations in our study.

1. This study is a retrospective study. The data were restricted to what has been written in the folder.
2. There are 2500 patients who admitted for acute ischaemic stroke from January 2016 until 2020 in our centre. However, in view of time limitation, we used systematic sampling method which the patients were selected in every 5^{th} number from the lists. This high proportion of SAP as compared to other centre is possibly contributed by our sampling method and did not reveal the true prevalence of SAP in our centre.
3. This study is an observational study which do not establish causal relationship between independent and outcome variables. Further study is required to confirm the hypothesis.

Recommendations

Preventive measure needs to be done to reduce incidence of SAP:

1. Early management of hyperglycemia should be highlighted since patient at emergency room as random blood glucose on admission is one of predictor of SAP.
2. Patient who on nasogastric tube feeding need to be referred to speech therapist early for proper assessment of dysphagia to prevent prolonged nasogastric tube feeding.

Future research

1. A larger cohort prospective study which include all 2500 stroke patients needs to be done to establish causal relationship between optimal preventive treatment and clinical outcomes of SAP.
2. As no local data regarding cost of SAP, a study regarding the cost of SAP compared to non-SAP among stroke patient worth to be done.
3. A study regarding oral feeding prior to hospital presentation associated with SAP should be done to look for any significant association.

REFERRENCES

1. Smith, C.J., Kishore, A.K., Vail, A., Chamorro, A., Garau, J., Hopkins, S.J., Di Napoli, M., Kalra, L., Langhorne, P., Montaner, J. and Roffe, C., 2015. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group. *Stroke*, *46*(8), pp.2335-2340

2. Vermeij, F.H., op Reimer, W.J.S., De Man, P., Van Oostenbrugge, R.J., Franke, C.L., De Jong, G., De Kort, P.L. and Dippel, D.W., 2009. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands Stroke Survey. *Cerebrovascular Diseases*, *27*(5), pp.465-471.

3. Adina, A.N., Ahmad, M.A., Uduman, A. and Hamidon, B.B., 2012. Predictors of stroke-associated pneumonia after the first episode of acute ischaemic stroke. *Malaysian Journal of Medicine and Health Sciences*, *8*(1), pp.37-43.

4. Sari, I.M., Soertidewi, L., Yokota, C., Kikuno, M., Koga, M. and Toyoda, K., 2017. Comparison of characteristics of stroke-associated pneumonia in stroke care units in Indonesia and Japan. *Journal of Stroke and Cerebrovascular Diseases*, *26*(2), pp.280-285.

5. Matz, K., Seyfang, L., Dachenhausen, A., Teuschl, Y., Tuomilehto, J. and Brainin, M., 2016. Post-stroke pneumonia at the stroke unit–a registry based analysis of contributing and protective factors. *BMC neurology*, *16*(1), pp.1-8.

6. Westendorp, W.F., Nederkoorn, P.J., Vermeij, J.D., Dijkgraaf, M.G. and van de Beek, D., 2011. Post-stroke infection: a systematic review and meta-analysis. *BMC neurology*, *11*(1), pp.1-7.

7. Yuan, M.Z., Li, F., Tian, X., Wang, W., Jia, M., Wang, X.F. and Liu, G.W., 2015. Risk factors for lung infection in stroke patients: a meta-analysis of observational studies. *Expert review of anti-infective therapy*, *13*(10), pp.1289-1298.

8. Martino, R., Foley, N., Bhogal, S., Diamant, N., Speechley, M. and Teasell, R., 2005. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *stroke*, *36*(12), pp.2756-2763.

9. Aslanyan, S., Weir, C.J., Diener, H.C., Kaste, M., Lees, K.R. and GAIN International Steering Committee and Investigators, 2004. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. *European journal of neurology*, *11*(1), pp.49-53.

10. Zhu, J., Zhang, X., Shi, G., Yi, K. and Tan, X., 2015. Atrial fibrillation is an independent risk factor for hospital-acquired pneumonia. *PLoS One*, *10*(7), p.e0131782.