DIAGNOSIS AND MANAGEMENT OF STROKE-ASSOCIATED PNEUMONIA: A MIXED-METHODS STUDY

MOHAMMED HUSSEIN ALI HUSSEIN ZAWIAH

UNIVERSITI SAINS MALAYSIA

2023

DIAGNOSIS AND MANAGEMENT OF STROKE-ASSOCIATED PNEUMONIA: A MIXED-METHODS STUDY

by

MOHAMMED HUSSEIN ALI HUSSEIN ZAWIAH

Thesis submitted in fulfilment of the requirements
for the degree of
Doctor of Philosophy

June 2023

ACKNOWLEDGEMENT

I would like to begin by expressing my deepest gratitude to Allah Subahanahu Wata'ala for providing me guidance, blessings, knowledge, and patience throughout my PhD journey. Without his support, I would not have been able to accomplish this work.

I am incredibly grateful to my supervisor, Dr. Amer Hayat Khan, for his unwavering support and guidance throughout the entire process. His expertise and encouragement have been invaluable, and I could not have achieved this without his mentorship. I would also like to express my sincere appreciation to my two co-supervisors, Assoc.Prof. Rana Abu Farha and Dr. Abubakar Usman, for their insightful comments and constructive criticism that have greatly contributed to the development and improvement of my research.

I would like to thank my mother and father for their unwavering love and support throughout my life. Their sacrifices have not gone unnoticed, and I am forever grateful for their constant encouragement and understanding. Their love and support have been a constant source of strength, and I am truly blessed to have them in my life.

I would like to express my sincerest gratitude and appreciation to my lovely wife for her support and understanding throughout my journey. Her patience, encouragement, and belief in me have been a constant source of strength and inspiration. She has been my rock and my partner in every sense of the word. My gratitude goes to my children, Aya and Osaid. They have been my little rays of sunshine. Their presence in my life has been a constant source of joy, motivation, and inspiration.

My gratitude goes to my sisters. They have always been there for me as a shoulder to lean on. Their love and support have been an essential part of my success, and I am forever grateful to have such amazing sisters.

I would like to thank my friend and brother Fahmi Al-Ashwal for his support, encouragement, and companionship throughout my PhD journey. His friendship and support have been invaluable to me, providing a sounding board for my ideas, a source of inspiration and motivation, and a reminder to maintain perspective. I would also like to thank my friends Haggam Dawghan and Ahmad Nawras for their friendship and support during this journey. Their encouragement and companionship have meant a lot to me.

My deepest gratitude goes to Dr. Khawlah Abu Hamour for her endless support and to my research assistants Marwa, Rawand, and Zahra'a, who have dedicated their time and effort to collecting the data. I am grateful for their contribution to this project and for the insights and perspectives they have provided. I would also like to acknowledge Jordan University Hospital and Applied Science Private University for providing the necessary resources and support for this research project.

Lastly, I would like to express my sincere gratitude and appreciation to the Institute of Postgraduate Studies at Universiti Sains Malaysia for supporting me through the provision of a fellowship during my PhD studies.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AFIB	Atrial Fibrillation
AIS	Acute Ischemic Stroke
ARBs	Angiotensin Receptor Antagonists
ASA	Aspirin
ATSIDS	American Thoracic Society and Infectious Diseases Society
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Bisphosphonate
BUN	Blood Urea Nitrogen
CAP	Community-Acquired Pneumonia
CDC	Centres For Disease Control and Prevention
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed-Tomography
CXR	Chest X-Ray
DAMP	Damage-Associated Molecular Patterns
DM	Diabetes Mellitus
DPP-4	Dipeptidyl Peptidase-4
GBD	Global Burden of Disease
GCS	Glasgow Coma Scale
HAP	Hospital-Acquired Pneumonia
Hb	Haemoglobin

HBA1C	Haemoglobin A1c
Hc	Haematocrit
HCI	Hyperacute Cerebral Infarction
Hem	Haemorrhagic
HI	High Income
HR	Hazard Ratio
HTN	Hypertension
ICU	Intensive Care Unit
IFN-c	Interferon-C
IHD	Ischemic Heart Disease
IL	Interleukin
IM	Internal Medicine
INR	International Normalized Ratio
IQR	Interquartile Range
Isch	Ischemic
IV	Intravenous
JUH	Jordan University Hospital
LI	Low Income
MENA	Middle East and North Africa
MLR	Monocyte To Lymphocyte Ratio
MRI	Magnetic Resonance Imaging
MV	Mechanical Ventilation
N	Number
N-BP	Nitrogen Based Bisphosphonates
NGT	Nasogastric Tube
NLR	Neutrophil To Lymphocyte Ratio
NOS	Newcastle Ottawa Scale

NPAR	Neutrophil Percentage to Albumin Ratio
NPPM	Number Of Patients Per Month
O2sat	Oxygen Saturation
OR	Odds Ratio
PLR	Platelet To Lymphocyte Ratio
PLT	Platelet
PN	Physician’s Number
PPIs	Proton Pump Inhibitors
Pt	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cells
RBS	Random Blood Sugar
RC	Retrospective Cohort
RCT	Randomized Clinical Trial
RD	Registry Data
ROC	Receiver Operating Characteristic
RR	Respiratory Rate
SAP	Stroke Associated Pneumonia
SCr	Serum Creatinine
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference
Th 1	T Helper Cells Type 1
Th 2	T Helper Cells Type 2
TIA	Transient Ischemic Attack.
TNF-a	Tumour Necrosis Factor-a
TSOS	Time From Stroke Onset to Sampling

UMI	Upper Middle Income
VAP	Ventilator-Acquired Pneumonia
VIF	Variance Inflation Factors
WBC	White Blood Cells
WHO	World Health Organization
YI	Youden’s Index
YP	Years In Practice

LIST OF APPENDICES

DIAGNOSIS DAN PENGURUSAN PNEUMONIA BERKAIT STROK: SUATU KAJIAN KAEDAH CAMPURAN

ABSTRAK

Pneumonia berkaitan strok (SAP) ialah komplikasi yang biasanya berlaku dalam minggu pertama strok kritikal dan dikaitkan dengan rawatan hospital yang berpanjangan dan peningkatan kematian. Proses diagnosis dan rawatan SAP adalah mencabar kerana kekurangan kriteria standard utama. Penyelidik telah menyiasat kedua-dua jenis ubat pencegahan antibiotik dan bukan antibiotik untuk SAP. Walau bagaimanapun, antibiotik didapati tidak berkesan dalam mencegah SAP, dan keberkesanan ubat bukan antibiotik masih menjadi kontroversi. Selain itu, ramalan biomarker juga telah dikaji, tetapi prestasinya tidak konsisten. Tesis ini mengandungi tiga bahagian. Pertama, terakhir melibatkan kajian semula sistematik dan meta-analisis untuk mensintesis bukti mengenai perkaitan antara nisbah neutrofil-ke-limfosit (NLR), nisbah monosit-ke-limfosit (MLR), dan nisbah platelet-ke-limfosit (PLR), dan SAP. Kedua, kajian retrospektif telah dilakukan untuk mengenal pasti kelaziman dan peramal SAP di Jordan dan untuk menyiasat potensi penggunaan semula N-bisphosphonates (N-BPs) untuk pencegahan SAP. Bahagian kajian kualitatif telah dijalankan untuk meneroka pengalaman pakar perubatan dalam mendiagnosis dan merawat SAP. Untuk meta-analisis, dua belas kajian yang terdiri daripada 6302 orang pesakit strok telah dimasukkan. Analisis terkumpul mendedahkan bahawa pesakit dengan SAP mempunyai tahap NLR, MLR, dan PLR yang jauh lebih tinggi daripada kumpulan bukan SAP. Perbezaan min piawai (SMD), 95% CI, nilai-p, dan I2 untuk mereka masing-masing dilaporkan sebagai (0.88, 0.70-1.07, 0.00001, 77%); (0.94, 0.43-1.46, 0.0003, 93%); dan (0.61, 0.47-0.75, 0.001, 0%). Sejumlah 406 pesakit strok telah dimasukkan ke dalam kajian retrospektif, dan kekerapan SAP adalah 19.7%.

Dapatan menunjukkan bahawa jantina lelaki (nisbah ganjil [OR] = 5.74, selang keyakinan 95% [CI] = 2.04 - 16.1, p <0.001), disfagia (OR= 5.29, 95% CI = 1.80 - 15.5, P = 0.002), hemiparesis (OR = 3.27, 95% CI = 1.13 - 9.47, P = 0.029), Skala Koma Glasgow (GCS) yang lebih rendah (OR = 0.730, 95% CI = 0.585 – 0.910, p = 0.005), NLR lebih tinggi (OR , 95% CI = 1.07 - 1.24, P <0.001) MLR (OR = 1.49, 95% CI = 1.13 - 1.96, P = 0.004) dan peratusan neutrofil kepada nisbah albumin (NPAR) (OR=1.53, 93% CI= 1.53 - 1.76, P <0.001). Adalah peramal tidak bersandar bagi SAP. Apabila membandingkan keupayaan nisbah yang berbeza untuk meramalkan SAP, menariknya, NPAR mempunyai kawasan yang sangat baik dan lebih tinggi di bawah lengkung daripada kedua-dua NLR (0.939 berbanding 0.865, Z = 3.169, p = 0.002) dan MLR (0.939 berbanding 0.842, Z = 3.940, p < 0.001) nisbah. Dari segi pendedahan N-BP dan SAP, kajian mendapati pesakit strok yang terdedah kepada N-BP kurang berkemungkinan untuk mengembangkan SAP (aOR = 0.253; 95% CI = 0.070 – 0.920; p = 0.037) berbanding dengan bukan terdedah. Kajian kualitatif menghasilkan dua tema dan lapan subtema yang muncul: Terminologi dan pendekatan diagnostik SAP yang terlibat; tiada istilah yang pasti, kebergantungan pada kedua-dua bukti klinikal dan penemuan X-ray untuk membuat keputusan , kebergantungan pada bukti klinikal sahaja untuk mengesyaki SAP dan memulakan terapi empirikal, dan diagnosis berlebihan bagi SAP. Strategi rawatan termasuk; rawatan awal SAP, merawat SAP sama seperti CAP/HAP, liputan anaerob utama, dan rawatan berlebihan SAP. Kesimpulannya, kajian ini menekankan potensi NPAR, NLR, dan MLR, sebagai biomarker yang teguh untuk mengenal pasti SAP awal, sementara juga mencadangkan bahawa N-BP mungkin menawarkan jalan yang menjanjikan untuk mengurangkan kejadian SAP. Selain itu, terdapat pelbagai pendekatan diagnostik dan rawatan untuk SAP di kalangan pakar perubatan.

DIAGNOSIS AND MANAGEMENT OF STROKE-ASSOCIATED PNEUMONIA: A MIXED-METHODS STUDY

ABSTRACT

Stroke-associated pneumonia (SAP) is a complication that commonly occurs within the first week of an acute stroke and is associated with prolonged hospitalization and increased mortality. Diagnosing and treating SAP is challenging due to the lack of gold-standard criteria. Researchers have investigated both antibiotics and non-antibiotic preventive medications for SAP. However, antibiotics have been found to be ineffective in preventing SAP, and the effectiveness of non-antibiotic drugs is still controversial. Additionally, predictive biomarkers have also been studied, but their performance has been inconsistent. This thesis consists of three parts. First, meta-analysis to synthesize evidence on the association between the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), and SAP incidence. Second, a retrospective study was performed to identify the prevalence and predictors of SAP in Jordan and to investigate the potential repurposing of N-bisphosphonates (N-BPs) for decreasing SAP incidence. The last part involved a qualitative study was conducted to explore physicians' experiences in diagnosing and treating SAP. In the meta-analysis, twelve studies comprising 6302 stroke patients were included. The pooled analyses revealed that patients with SAP had significantly higher levels of NLR, MLR, and PLR than the non-SAP group. The standardized mean difference (SMD), 95% CI, p-value, and I^2 for them were respectively reported as (0.88, 0.70-1.07, 0.00001, 77%); (0.94, 0.43-1.46, 0.0003, 93%); and (0.61, 0.47-0.75, 0.001, 0%). A total of 406 stroke patients were included in the retrospective study, and the frequency of SAP was 19.7%.

Findings showed that male gender (odds ratios [OR] = 5.74, 95% confidence interval [CI] = 2.04 - 16.1, p <0.001), dysphagia (OR= 5.29, 95% CI = 1.80 - 15.5, P = 0.002), hemiparesis (OR = 3.27, 95% CI = 1.13 - 9.47, P = 0.029), lower Glasgow Coma Scale (OR = 0.730, 95% CI = 0.585 – 0.910, p = 0.005), higher NLR (OR = 1.15, 95% CI = 1.07 - 1.24, P <0.001) MLR (OR = 1.49, 95% CI = 1.13 - 1.96, P = 0.004) and neutrophil percentage to albumin ratio (NPAR) (OR=1.53, 95% CI= 1.33 - 1.76, P <0.001). were independent predictors of SAP. When comparing the ability of different ratios to predict SAP, interestingly, the NPAR had an excellent and higher area under the curve than both the NLR (0.939 versus 0.865, Z = 3.169, p = 0.002) and MLR (0.939 versus 0.842, Z = 3.940, p < 0.001) ratios. In terms of N-BPs exposure and SAP, the study found that stroke patients who exposed to N-BPs were less likely to developed SAP (aOR = 0.253; 95% CI = 0.070 – 0.920; p = 0.037) compared to the non-exposed. The qualitative study resulted in two themes and eight emerged sub-themes: Terminology and diagnostic approach of SAP involved; no definite terminology, reliance on both clinical evidence and X-ray findings to make a decision, reliance on clinical evidence alone to suspect SAP and initiate empirical therapy, and SAP overdiagnosis. The treatment strategies include; early treatment of SAP, treating SAP the same as CAP/HAP, predominant anaerobe coverage, and SAP overtreatment. In conclusion, this study emphasizes the potential of NPAR, NLR, and MLR, as robust biomarkers for early identifying SAP, while also suggesting that N-BPs may offer a promising avenue for reducing SAP incidence. Additionally, it is found a wide range of diagnostic and treatment approaches for SAP among physicians.

CHAPTER 1

INTRODUCTION

1.1 Stroke Definition

The term ‘stroke’ refers to complex neurological dysfunction caused by occlusion or haemorrhage of blood vessels supplying the brain (Lo, Dalkara & Moskowitz, 2003). The World Health Organization (WHO) defined stroke as " rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin" (Aho *et al.*, 1980). Then, the American Heart Association and American Stroke Association proposed a new definition of stroke for the 21st century that incorporates both clinical and tissue criteria. This definition is broader, and it includes any evidence of permanent cell death in the brain, spinal cord, or retina that can be attributable to a vascular cause through neuropathology, neuroimaging, and/or clinical symptoms (Sacco *et al.*, 2013).

1.2 Global Burden of Stroke

The Global Burden of Disease (GBD) data demonstrated that stroke is ranked the second leading cause of mortality accounting for 11.6% of the total deaths worldwide. Stroke is the third leading cause of mortality and disability combined, as expressed by disability-adjusted life years lost (DALYs) and represented 5.7% of the total DALYs worldwide (Feigin *et al.*, 2021, 2022). The global total healthcare cost associated with stroke is estimated to be over USD 891 billion which is equivalent to 1.12% of the world's gross domestic product (Owolabi *et al.*, 2021). Globally, more than 12.2 million new stroke cases and 6.55 million deaths are reported each year. In

addition, there are currently over 101 million stroke survivors worldwide with about 143 million DALYs due to stroke. Furthermore, evidence has shown that one in four people over the age of 25 will experience a stroke in their lifetime. The number of stroke-related deaths has decreased by 9.0% in high-income countries as against a 72 – 78% increase in low-income and low to middle-income countries (Feigin *et al.*, 2021, 2022). In Malaysia, stroke, is the third most common cause of death. In 2019, there were 47,911 incident reported cases, 443,995 prevalent cases and 19,928 deaths due to stroke (Tan & Venketasubramanian, 2022).

Overall, 47% of all stroke cases occur in men, while 53% occur in women. The point estimates of prevalent and incident strokes were higher in women (56.4 million prevalent stroke cases and 6.4 million incident stroke cases) than in men (45.0 million prevalent stroke cases and 5.8 million incident stroke cases), despite the absolute number of DALYs attributable to stroke in men (77.0 million) being higher than for women (66.0 million) worldwide in 2019 (Feigin *et al.*, 2022).

1.3 Stroke in Jordan

The recent GBD estimates revealed that stroke is the second most common cause of death and the fourth most common cause of DALYs in the Middle East and North Africa (MENA) region, representing 10.07% and 4.86% of the total deaths, and DALYs, respectively (Jaberinezhad *et al.*, 2022; Shahbandi *et al.*, 2022). According to a recent systematic analysis that summarised the most recent estimates of prevalence, incidence, deaths, and DALYs for neurological diseases in 21 MENA countries, stroke was the leading cause of neurological DALYs (45 2%) and deaths (70.8%) in the MENA region (Avan *et al.*, 2022). From 1990 to 2019, the stroke burden due to all risk factors combined increased in the MENA region from 3.7 million

to 6.8 million. In 2019, high systolic blood pressure, a high body mass index, and ambient particulate air pollution were the three largest contributors to the stroke burden in the MENA region, with proportions of 53.5%, 39.4%, and 27.1%, respectively (Jaberinezhad *et al.*, 2022; Shahbandi *et al.*, 2022).

In Jordan, which is one of the MENA countries, stroke is ranked as the second leading cause of death after ischemic heart diseases, accounting for 10.44% of the total deaths. In addition, stroke is the fifth leading cause of DALYs, representing 4.05% of the total DALYs. In 2019, there were 15,457 new stroke cases, 134,580 prevalent stroke cases, 3367 deaths from stroke, and 86,118 DALYs due to stroke (Jaberinezhad *et al.*, 2022; Shahbandi *et al.*, 2022).

1.4 Types of Stroke

Stroke is generally classified into ischemic and haemorrhagic stroke. The latter includes intracerebral and subarachnoid haemorrhage (Donkor, 2018). Ischemic stroke is a neurological dysfunction due to infarction at the cerebral, spinal, or retinal sites (Sacco *et al.*, 2013). Intracerebral haemorrhage is defined as a focal blood collection in the brain parenchyma/ventricular system, not due to trauma. However, Subarachnoid haemorrhage is a non-traumatic stroke caused by bleeding into the subarachnoid site of the brain (Sacco *et al.*, 2013). In general, ischaemic stroke accounts for approximately 80% of all strokes, while haemorrhagic stroke accounts for 20%, but the proportions vary depending on the population (Donkor, 2018). Data from the INTERSTROKE study covering 22 countries reported that Africa had a proportion of ischemic and haemorrhagic strokes of around 66% and 34%, respectively, compared to high-income countries, which had a proportion of ischemic strokes of about 91% and haemorrhagic strokes of 9% (O'donnell *et al.*, 2010). The

authors explained that the variations in the incidence of stroke types could be attributed to the differences in the risk factors among different population.

1.5 Risk Factors of Stroke

A considerable amount of literature has identified several risk factors predisposing people to stroke. A large INTERSTROKE study listed ten risk factors that account for 90% of all stroke including hypertension, dyslipidaemia, cigarette smoking, use of alcohol, diabetes mellitus, obesity, stress, heart disease, physical inactivity, and unhealthy diet (O'donnell *et al.*, 2010). More recently, a GBD study covering data from 204 countries reported five leading risk factors for stroke: high systolic blood pressure, a high body mass index, high fasting plasma glucose, ambient particulate matter pollution, and cigarette smoking (Feigin *et al.*, 2021). These aforementioned risk factors are modifiable, which makes stroke highly preventable. There are few non-modifiable risk factors for stroke, including genetic, age and gender (Boehme, Esenwa & Elkind, 2017; Donkor, 2018).

1.6 Stroke Presentation, Evaluation and Management

The presentation of stroke can vary depending on the type, location, and factors such as ethnicity and gender (Powers *et al.*, 2019). A study by Rathore et al. assessed the clinical presentation of 474 strokes patients (85% of them ischemic and 15% haemorrhagic) and found that the majority of patients were presented with most common presentation was hemiparesis, followed by sensory deficits (Rathore *et al.*, 2002). The study mentioned other several symptoms, including headache, gait imbalance, seizures, vertigo, speech deficits, and vision disturbances. The authors also found that hemiparesis was less common in white people compared to black people,

gait disturbance was less common in females compared to males, and haemorrhagic stroke patients were more likely to experience headaches and seizures compared to those with ischemic events (Rathore *et al.*, 2002). Hemorrhagic stroke typically manifests acutely and progresses rapidly, characterized by symptoms including sudden onset headache, vomiting, neck stiffness, elevated blood pressure, and rapidly developing neurological signs (Sanyasi and Pinzon, 2018). The specific symptoms experienced can provide valuable insights into the extent and location of the hemorrhage (Unnithan and Mehta, 2020)

Brain ischemia symptoms may be transient (lasting seconds to minutes), persistent for long periods, or remain indefinitely if the brain damage is irreversible and infarction occurs (Sanyasi and Pinzon, 2018). Unfortunately, neurological symptoms do not accurately indicate the occurrence of infarction, and the tempo of symptoms does not predict the ischemia cause. This is a crucial issue since precise identification of symptom causes is necessary for effective treatment (Powers *et al.*, 2019).

In the initial phase of acute stroke assessment and management, the primary goals are to ensure medical stability, rapidly reverse conditions that contributed to the patient's problem, determine if the patient with an ischemic stroke is candidate for reperfusion treatment, and uncovering the pathophysiological basis of the neurologic symptoms (Powers *et al.*, 2019). There are important guideline based-recommendations (Powers *et al.*, 2019) which include;

a) Evaluating vital signs and ensuring breathing, airway, and circulation stability.

b) Getting a quick yet accurate history and examination to differentiate between stroke and other disorders.

c) Acquiring urgent neuroimaging such as computed-tomography scan (CT) or magnetic resonance imaging (MRI), in addition to neurovascular imaging such as CT angiography and/or magnetic resonance angiography.

d) Managing electrolyte imbalances and volume depletion.

e) Checking and correcting serum glucose if needed. If the serum glucose level is low (<60 mg/dL), it should be adjusted rapidly. It is recommended to treat hyperglycaemia if the serum glucose level is >180 mg/dL, keeping the goal of glucose levels within a range of 140 to 180 mg/dL.

f) Evaluation of swallowing and prevention of aspiration.

g) Optimising the position of the head of the bed. It is recommended to elevate the bed's head to 30 degrees while maintaining the head in neutral alignment with the body for patients who are at risk for aspiration, intracranial pressure elevation, oxygen desaturation, or cardio-pulmonary decompensation. For patients with stroke who are not at risk for such complications, it is recommended to keeping the head of the bed in the most comfortable position.

h) Blood pressure management depends on the stroke type. Antihypertensive therapy is recommended for ischemic stroke patients who will receive thrombolytic therapy so that blood pressure is ≤185/110 mmHg before treatment and <180/105 mmHg for the initial 24 hours after treatment. For patients who are not candidates for

thrombolytic therapy, treating high blood pressure is suggested only in certain circumstances, such as if the patient has a systolic blood pressure of >220 mmHg or a diastolic blood pressure of >120 mmHg or if the patient has another apparent reason such as heart failure, active ischemic coronary disease, aortic dissection, pre-eclampsia or eclampsia, or hypertensive encephalopathy. In haemorrhagic stroke, the approach to lowering blood pressure must consider both the potential benefits, such as preventing further bleeding, and the risks, such as decreasing cerebral perfusion.

i) For patients with ischemic stroke who are candidates for thrombolytic therapy, intravenous alteplase should be started within 4.5 hours of the onset of stroke symptoms. Patients who have an acute ischemic stroke caused by proximal large artery occlusion and can be treated within 24 hours of onset should be evaluated to see if they are candidates for mechanical thrombectomy.

j) Other treatments for ischemic stroke besides reperfusion therapy have been linked to less disability, complications, or recurrence of stroke. These include: Antithrombotic medications, such as aspirin, should be taken within 48 hours of stroke onset; thromboprophylaxis for pulmonary embolism and deep venous thrombosis; and initiating or continuing statin therapy as soon as patients can take oral medications safely.

k) With regards to haemorrhagic stroke screening, CT is typically the initial diagnostic modality used in the evaluation of haemorrhage (Greenberg *et al.*, 2022). In the hyperacute phase, the attenuation of the

haemorrhage on CT increases from 30-60 Hounsfield units (HU) to 80-100 HU within a matter of hours (Unnithan and Mehta, 2020). However, in the presence of anaemia and coagulopathy, the attenuation may be decreased. Vasogenic enema surrounding the hematoma can progressively increase for a duration of up to 2 weeks. While CT is widely regarded as the "gold standard" for detecting acute haemorrhage due to its high sensitivity, gradient echo and magnetic resonance imaging (MRI) sequences exhibit comparable sensitivity to CT in detecting acute haemorrhage. Moreover, these MRI sequences demonstrate superior sensitivity to CT in identifying previous haemorrhagic events (Unnithan and Mehta, 2020).

l) The treatment and management of haemorrhagic stroke encompass various approaches and considerations. BP management is a crucial aspect, and gradual reduction of BP to 150/90 mmHg using specific medications like beta-blockers (labetalol, esmolol), angiotensin-converting enzyme inhibitors (enalapril), calcium channel blockers (nicardipine), or hydralazine is recommended (Ojaghihaghighi *et al.*, 2017). Regular monitoring of BP is advised, and studies have shown that early intensive BP-lowering treatment can attenuate hematoma growth (Unnithan and Mehta, 2020). Elevated BP has been associated with neurological deterioration and adverse outcomes (Greenberg *et al.*, 2022). In cases of raised intracranial pressure (ICP), initial treatment involves elevating the head of the bed and administering osmotic agents (mannitol, hypertonic saline). Monitoring ICP using parenchymal or ventricular catheters is recommended for patients with

a Glasgow Coma Scale score below 8 or evidence of transtentorial herniation or hydrocephalus (Greenberg *et al.*, 2022). The aim is to keep cerebral perfusion pressure between 50 to 70 mmHg. Hemostatic therapy is employed to minimize hematoma progression and address coagulopathy, utilizing interventions such as vitamin K, prothrombin complex concentrates, recombinant activated factor VII, and fresh frozen plasm. Surgery, including craniotomy, decompressive craniectomy, and aspiration procedures, may be considered based on individual patient characteristics (Unnithan and Mehta, 2020; Greenberg *et al.*, 2022).

1.7 Stroke and Infections

Infections are common and life threatening medical complications after a stroke (Bustamante *et al.*, 2017). There is controversy regarding the frequency of post stroke infections. Most research mainly reports the wide variation in any infection rates post stroke, ranging from 5 to 65% (Weimar *et al.*, 2002; Aslanyan *et al.*, 2004; Heuschmann *et al.*, 2004; Chamorro *et al.*, 2005; Vargas *et al.*, 2006; Kwan & Hand, 2007; Vermeij *et al.*, 2009), which is attributable to factors such as heterogeneity of the study populations and diagnostic criteria for post-stroke infection (Westendorp *et al.*, 2011). A large meta-analysis of 87 studies with 137,817 participants showed that the pooled infection rate was 30% (95% CI = 24 – 36%). Pneumonia and urinary tract infections are the most frequent infective complications after stroke (Westendorp *et al.*, 2011).

1.8 Pathophysiology of Stroke Associated Pneumonia

Stroke associated pneumonia (SAP) has traditionally been considered only secondary to aspiration (Lim *et al.*, 2001; Huang *et al.*, 2006; Teramoto, 2009). Different clinical studies have identified aspiration and its associated risk factors, including impaired level of consciousness and dysphagia, as significant risk factors for SAP (Hoffmann *et al.*, 2017; Mandell & Niederman, 2019; Pacheco-Castilho *et al.*, 2019; Eltringham *et al.*, 2020). Most stroke patients have impaired swallowing, resulting in the aspiration of oral content while they sleep, which is thought to be related to dopamine transmission abnormality (Teramoto, 2009). An experimental study found that blocking D1 dopamine receptors in guinea pigs inhibits the swallowing reflex and results in a decreased substance P (SP) in the peripheral organs (Jia *et al.*, 1998). A low level of SP in the sputum was also observed in old patients with aspiration pneumonia (Nakagawa, 1995), and a high serum level of SP was found in stroke patients after treating them with angiotensin converting enzyme inhibitor with accompanying improvement of aspiration suggesting SP plays a role in aspiration (Arai *et al.*, 2003). However, the higher rate of pneumonia in stroke patients compared to other people who have dysphagia or a compromised consciousness level, as well as the fact that pneumonia is predominant in the acute phase of stroke when the neurological deficit is present, suggest that another mechanism such as an immunological alteration may be involved in the SAP pathogenesis (Hannawi *et al.*, 2013).

Beyond the aspiration theory, the subacute immunosuppression following stroke has been strongly associated with the increased risk of SAP among stroke patients (Liu *et al.*, 2018). Basically, the stroke progression is divided into three phases (Figure 1.1). In the hyperacute phase, rapid activation of the peripheral immune system begins within minutes of a stroke (Simats & Liesz, 2022). Immunoactive molecules

(damage-associated molecular patterns; DAMP) originate from stressed or dying cells within the injured brain or are actively secreted from macrophages and other immune cells during activation (Schulze *et al.*, 2013; Richard *et al.*, 2016; Hackshaw *et al.*, 2018; Schuhmann *et al.*, 2021; Simats & Liesz, 2022). DAMPs in the bloodstream rapidly activate peripheral immune cells and trigger a massive expression and release of pro-inflammatory cytokines (Simats & Liesz, 2022). Stroke also induces the mobilization of leukocytes from the two major reservoirs of immune cells, including bone marrow and spleen (Seifert *et al.*, 2012; Courties *et al.*, 2015), as well as the activation of neurogenic pathways such as the sympathetic nervous system (SNS), parasympathetic nervous system (PSN), and hypothalamic–pituitary–adrenal (HPA) axis (Ajmo Jr *et al.*, 2009; Simats & Liesz, 2022). Recently, the gastrointestinal tract has been found to be another crucial reservoir of immune cells, from which leukocytes are also mobilized to the bloodstream after stroke (Benakis *et al.*, 2020; Brea *et al.*, 2021). Enriching data also reveals that the intestinal microbiota have crucial role in the phenotypic modulation of the immune system in the acute inflammatory response to stroke (Benakis *et al.*, 2016; Singh *et al.*, 2016; Battaglini *et al.*, 2020; Lee *et al.*, 2020).

Within hours to days of stroke onset, state of subacute systemic immunodepression rapidly follows the initial activation of the immune system (Simats & Liesz, 2022). The prolonged overactivation of SNS, HPA axis, PNS, DAMP, and other pro-inflammatory mediators gradually induce lymphopenia as a result of massive cell death and a subsequent bias towards monocyte differentiation pathway in the bone marrow (Ajmo Jr *et al.*, 2009; Courties *et al.*, 2015, 2019; Engel *et al.*, 2015; Wang *et al.*, 2015; Liu *et al.*, 2018; Simats & Liesz, 2022). The other feature of subacute immunosuppression is the shift from a proinflammatory Type 1 (Th1) response to an

anti-inflammatory Type 2 (Th2) response of helper T cells. This phenomenon is reflected by an increase in the levels of anti-inflammatory cytokines in the circulation like interleukin (IL) - 4 and IL - 10, and a consequent decrease in pro-inflammatory mediators, such as TNF-a and IFN-c. During this phase, circulating monocytes are also less able to provide the costimulatory signals that are required for T cells activations (Jiang *et al.*, 2017). According to a preclinical study, when monocytic function is lost following an experimental stroke, there is also a decrease in the expression of genes that are linked to the ability to recognize pathogens (TLR genes) and macrophage activation status (MHC Class II genes) (McCulloch, Alfieri & McColl, 2018). In humans, the stroke-related loss of monocytic function is characterized by a decrease in the expression of genes, namely CD64 and human leukocyte antigen D-related (HLA-DR), on monocytes and dendritic cells (Krishnan *et al.*, 2021).

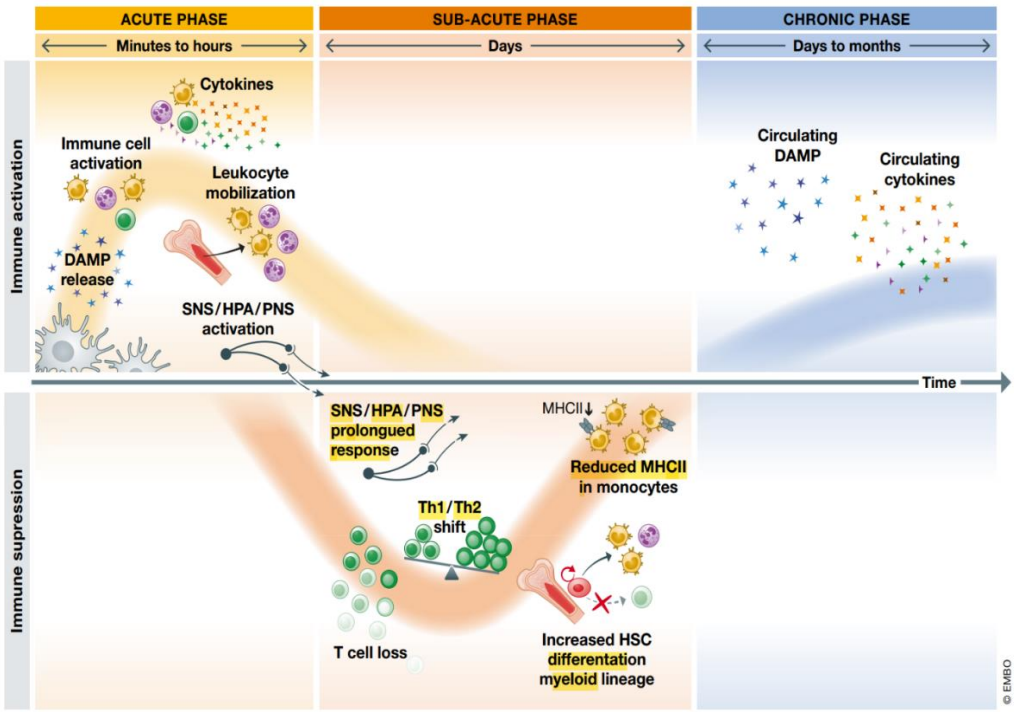

Figure 1.1 Immunological Responses after Stroke

Adapted from https://www.embopress.org/doi/full/10.15252/emmm.202216269, accessed on 11/11/2022 (Simats & Liesz, 2022).Systemic inflammation after stroke: implications for post-stroke comorbidities.

1.9 Problem Statement and Rationale of Study

Stroke imposes a massive burden on society, accounting for 11.6% of global deaths, making it the second leading cause of death after ischaemic heart disease (Feigin *et al.*, 2021). In Jordan, stroke is also ranked as the second leading cause of death after ischemic heart diseases, accounting for 10.44% of the total deaths. SAP is a common clinical complication that occurs commonly within the first week of an acute stroke (Kishore *et al.*, 2015). It is associated with poor functional outcomes, prolonged hospitalization, and increased mortality (Suda *et al.*, 2018; Teh *et al.*, 2018). Furthermore, the occurrence of SAP has an economic burden on stroke patients and the health system. It independently increased the cost of acute care by £5817 (95% CI = 2513–9210, p = 0.001) per patient (Ali *et al.*, 2018).

Diagnosis and treatment of SAP is challenging for many reasons. First, the clinical presentation may be nonspecific (Harms *et al.*, 2012); cough may be impaired due to neurological deficit (Ward *et al.*, 2010). Fever and leukocytosis can occur in response to the acute phase of stroke without infectious aetiologies (Naritomi *et al.*, 2002; Saand *et al.*, 2019). Fever might also be masked by frequent use of antipyretics such aspirin and paracetamol in acute stroke (Kallmünzer *et al.*, 2010); and hypoxia may result from other comorbidities (Ferdinand and Roffe, 2016). Second, the quality of chest radiography may be affected by diaphragmatic impairment and reduced ability to have a deep inspiration (Esayag *et al.*, 2010). Third, difficulties in acquiring sputum samples in non-ventilated stroke patients and the low diagnostic sensitivity of other available culture samples make identifying the microbiological aetiology of SAP difficult, and limit definite antibiotic therapy depending on microbial sensitivities (Campbell *et al.*, 2003; Ranzani *et al.*, 2019).

A specific diagnostic approach is essential for decision-making in SAP management. There are currently no gold-standard criteria for the diagnosis and treatment of SAP despite the availability of such criteria for CAP, HAP, and VAP (Torres *et al.*, 2017; Metlay *et al.*, 2019). Given the challenges associated with the diagnosis and treatment of SAP and the inconsistency of diagnostic criteria in the stroke research, a collaborative group, PISCES, was created firstly to propose standardized terminology and operational diagnostic criteria for SAP based on CDC criteria (Smith, Kishore, *et al.*, 2015). Furthermore, a second PISCES -2 group has convened to formulate antibiotic treatment recommendations for SAP (Kishore *et al.*, 2019). Despite these two recent initiatives, there are some limitations and they are intended as a starting point for both clinical practice and stroke research. The proposed criteria from the PISCES -1 still need a rigorous evaluation of their validity and reliability to evaluate their usefulness in hospital-based clinical practice and stroke research and assessment of their impact on the physicians' behaviours, including prescribing antibiotics and clinical outcomes (Smith, Kishore, *et al.*, 2015). The recommendations from PISCES-2 were not commissioned guidelines, so they should not be used as a clinical guideline (Kishore *et al.*, 2019).

Due to the difficulties in diagnosing and treating SAP, clinical trials were conducted to evaluate the efficacy of prophylactic antibiotics such as ceftriaxone in preventing SAP. However, these trials were unsuccessful in preventing SAP (J. Vermeij *et al.*, 2018; J.-D. Vermeij *et al.*, 2018). It is possible that the immunosuppressive effects resulting from stroke could have impacted the antibiotics' efficacy (Faura *et al.*, 2021). Additionally, attractive strategy for researchers to combat this complication recently included biomarkers prediction, however, the performance

of the current biomarkers for predicting SAP remain inconsistent. Therefore, it is crucial to synthesize the evidence on the most studied biomarkers, including neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, in order to evaluate their association with SAP incidence." Furthermore, Immunomodulator-based preventive interventions were investigated to prevent SAP; however, findings of such studies are still controversial (Maier *et al.*, 2015, 2018; Sykora *et al.*, 2015). In this field, it is important to investigate research on the new immunomodulating medications for preventing SAP. Given the evidence of the immunomodulating and anti-inflammatory effects of nitrogen-based bisphosphonates (N-Bps) and their ability to reduce pneumonia and mortality rates in non-stroke patients, it is worth investigating the possibility of repurposing these medications for the prevention of SAP.

Although stroke is a major cause of mortality and SAP has substantial implications for stroke outcomes, the economy, and mortality, there is a lack of research on SAP in Jordan (Ali *et al.*, 2018; Suda *et al.*, 2018; Teh *et al.*, 2018). It is crucial to fill this gap and investigate SAP within the Jordanian context. By conducting a study in Jordan, we can assess the prevalence and impact of SAP predictors within the local population, considering cultural, genetic, and healthcare system differences (Al-Hawary, 2012; Jabbour *et al.*, 2012; Elbarazi *et al.*, 2017). This will provide valuable insights into specific risk factors and their interactions, enabling the development of targeted prevention and management strategies.

Despite the importance of accurate diagnosis and treatment of SAP, there is a scarcity of literature on physicians' experiences in clinical practice (Harms *et al.*, 2012; Westendorp *et al.*, 2015). Existing studies have highlighted the overestimation of SAP by physicians, leading to unnecessary antibiotic prescriptions for stroke

patients(Harms *et al.*, 2012; Westendorp *et al.*, 2015). However, there is a need for further investigation into the factors influencing physicians' decision-making process in improving SAP diagnosis. Bridging this research gap would provide valuable insights into optimizing the diagnostic and treatment strategies for SAP in clinical practice. There is also a notable research gap within Jordan and across Arab countries. No studies have been conducted in these regions to investigate physicians' experiences in diagnosing and treating SAP. This knowledge gap hinders our understanding of the specific challenges and factors influencing clinical decision-making regarding SAP in the local context. Additionally, the lack of research within Jordan limits the generalizability of findings from studies conducted in other regions. Bridging this gap by conducting research within these settings would provide crucial insights into the unique perspectives, practices, of physicians' in diagnosing and treating SAP in Jordan.

1.10 Research Objectives

1.10.1 General Objectives

The main objective of this study is to assess predictors and investigate a repurposed preventive medication for SAP, while also exploring physicians' experiences in the diagnosis and treatment of SAP. Furthermore, to assess the impact of SAP and N-bisphosphonates use on mortality rate of acute stroke patients.

1.10.2 Specific Objectives

(1) To synthesize the evidence evaluating the association between biomarkers (neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio, and platelet-lymphocyte ratio) and SAP incidence. (Meta-analysis).

(2) To evaluate the prevalence and predictors of SAP among hospitalized acute stroke patients. (Retrospective Study).

(3) To investigate the association between SAP and mortality rate of acute stroke patients. (Retrospective Study).

(4) To investigate the association between nitrogen-based bisphosphonates exposure and SAP incidence. (Retrospective Study).

(5) To investigate the association between nitrogen-based bisphosphonates use and mortality rate of acute stroke patients. (Retrospective Study).

(6) To explore physicians' experience regarding the diagnosis and treatment SAP among hospitalized acute stroke patients. (Qualitative study).

1.11 Conceptual Framework

The conceptual framework of this project was presented by reporting the problem statements and the corresponding study designs and objectives to address research gaps (Figure 1.2)

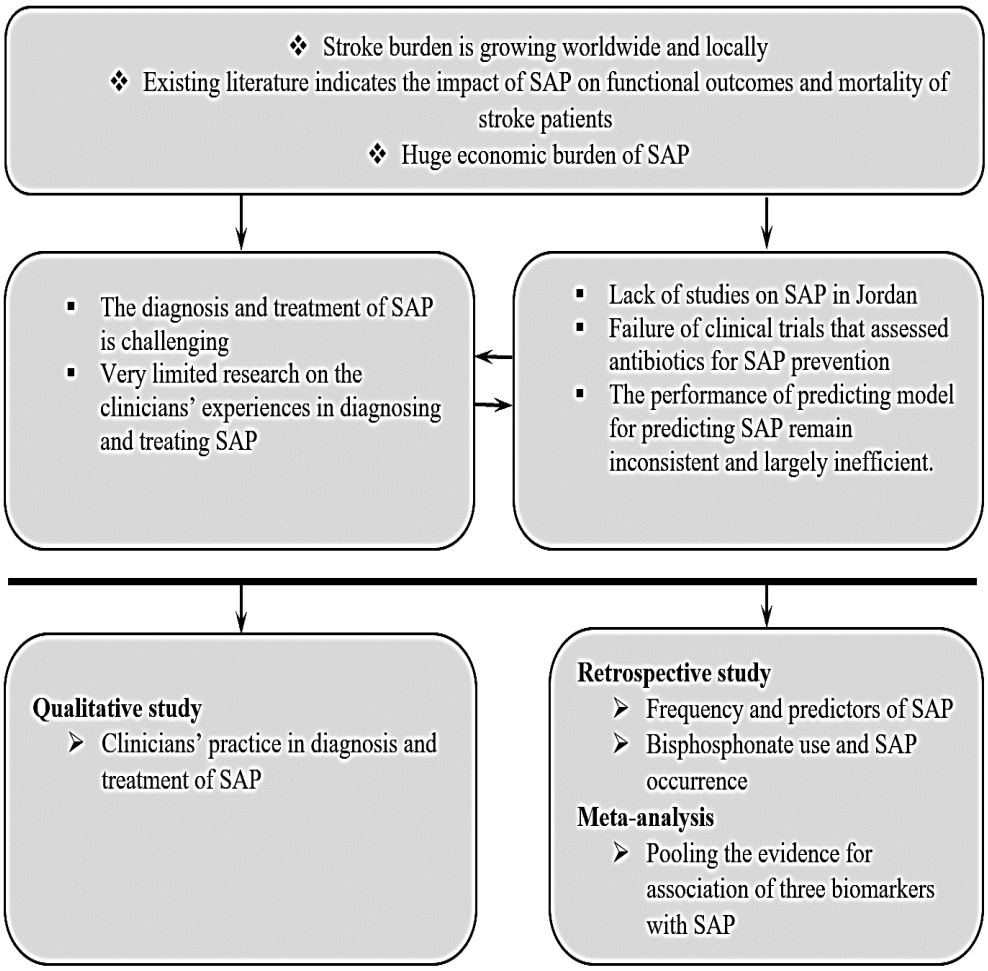

Figure 1.2 Conceptual Framework

CHAPTER 2

LITERATURE REVIEW

2.1 Literature Search

To ensure a comprehensive and thorough literature search aligned with the search objectives, a three-group search strategy was implemented. The first group focused on exploring literature related to the prevalence and predictors of SAP. The second group involved searching for papers that evaluated the diagnosis, treatment, and roles of immunomodulating medications in preventing SAP in stroke research. The third and final group focused on identifying literature evaluating the diagnosis and treatment of SAP in clinical practice.

Electronic databases, including Medline, Scopus, Web of Science, Science Direct, Cochrane Library, and Google Scholar, were searched from their inception to January 2021. The literature search and review process remained ongoing throughout the study to include the latest research. Various types of clinical studies, such as clinical trials, prospective cohorts, retrospective cohorts, retrospective case-control studies, and cross-sectional studies, were included in the literature review. The search terms used encompassed keywords related to stroke, stroke complicating infections, stroke complicating pneumonia, diagnosis, treatment, predictors, risk factors, bisphosphonate, and pneumonia. Boolean operators such as AND, OR, and NOT were employed to refine search results as necessary. Additionally, the reference lists of identified articles were examined to identify any additional relevant literature.

2.2 Prevalence of Stroke Associated Pneumonia

A considerable amount of literature has been reported on the prevalence of pneumonia after stroke. Westendorp and colleagues conducted the first systematic review and meta-analysis aimed at pooling rates of post-stroke infections and assessing their impact on stroke outcomes and mortality. (Westendorp *et al.*, 2011). The meta-analysis included 87 studies of 137817 stroke patients, with the majority of these studies conducted in high income countries. The authors included observational cohort or randomized clinical studies on ischemic or hemorrhagic strokes that reported infection rates in the acute phase of stroke. The definition of infection was based on any criteria mentioned in the studies that were recruited. The authors found that the frequency of pneumonia ranged from 0.8% to 48%, with an overall pooled proportion of 10% (95% CI = 9–10). Patients in ICU studies showed higher rates of pneumonia (28%, 95% CI, 18–38%) than those in non-ICU studies, with a rate of 9% (95% CI, 9–10%). The higher rate of pneumonia in ICU patients was attributed to the severity of the stroke and the frequency of invasive procedures such as mechanical ventilation, which might increase the risk of infection (Walter *et al.*, 2007; Westendorp *et al.*, 2011).

Badve et al. performed another systematic review and metaanalysis to determine the frequency of post-stroke pneumonia (Badve *et al.*, 2019). The meta-analysis included 47 studies of 139,432 patients. The study's inclusion criteria were prospective observational studies, a minimum age of 18 years, and admission within 30 days of a stroke. The authors selected studies that defined post stroke pneumonia by any diagnostic method. Based on the study findings, the proportion of post-stroke pneumonia ranged from 1.4% to 56.82%, with an overall pooled frequency of 12.3% (95% CI = 11.1–13.6; I2 = 98%). Stratifying studies based on the location of acute

care showed that the pooled frequency of pneumonia in patients managed in the ward and stroke unit was 13.1% (95% CI= 11.3–14.9; I2 = 98%; n = 28 studies; participants = 111,409); and this was statistically higher than the pooled proportion in the patients only treated in the stroke units, which was 8% (95% CI = 7.1–9.0; I2 = 78%; n = 14 studies; participants = 26,942) (P interaction = 0.001). Moreover, the overall occurrence of pneumonia among ICU patients was 30.3% (95% CI=12.9%-47.6%; I2 14 97%; n= 4 studies; 798 participants), which was significantly higher than the other pooled proportions based on care location (stroke units and ward). The lowest pooled frequency of pneumonia in stroke units suggests that the care provided in stroke units may be more effective in preventing pneumonia. This might be due to the better facilities and standard clinical protocols in such units, including effective screening and management of dysphagia and preventing aspiration (Govan, Langhorne and Weir, 2007; Langhorne, Ramachandra and Collaboration, 2020). Further subgroup analysis according to the stroke type showed that the pooled proportions were 16.8% (95% CI=15.8–17.8), 11.7% (95% CI==9.2–14.1), and 11.7% (10.3%–13%) for studies involved haemorrhagic stroke, ischemic stroke, and both haemorrhagic and ischemic strokes respectively with p interaction of 0.37 (Badve *et al.*, 2019).

Furthermore, Eltringham et al. recently conducted a systematic review of 11 studies to assess the risk factors of SAP among only dysphagic patients. The included studies were retrospective cohort, prospective cohort, and randomized control trials. The definition of pneumonia was variable, using either physician diagnosis or algorithmic criteria, or not mentioned at all. The authors found that the rates of SAP ranged from 3.9% to 56.7% (Eltringham *et al.*, 2020).

Despite the wide range of SAP rates, the three systematic reviews discussed above revealed a comparable overall range of SAP occurrence. Because the first two

previous systematic reviews and meta-analyses did not include the studies that defined pneumonia by the PISCES group definition and only a very few studies were included in the review of Eltringham et al., we will further report the updated studies that used the PISCES diagnostic criteria (Table 2.1).

Table 2.1 Studies Reporting the Prevalence of Stroke Associated Pneumonia Based on PISCES Diagnostic Criteria

Author, year	Country	N	Design	Income	Age Mean/ Median	Male %	NIHSS Mean /Median	Site of care	ICU %	Time from stroke onset	SAP %	Stroke type
(Soares *et al.*, 2022)	Portugal	525	R	HI	71	64	NA	Stroke unit	NA	NA	31.5	Hem
(Schaller-Paule *et al.*, 2022)	Germany	4281	RD	HI	74	45.2	NA	Ward/ICU	NA	NA	19.4	Isch
(Assefa *et al.*, 2022)	Ethiopia	325	CS	LI	65.2	46.8	NA	Ward	NA	24h	36	Isch/Hem
(Song *et al.*, 2022)	China	887	R	UMI	67.1	66.4	3	Ward	NA	24h	9.9	Isch
(Lin *et al.*, 2022)	China	932	R	UMI	67	63	3	Ward	NA	24h	10.7	Isch
(Huang *et al.*, 2022)	China	766	R	UMI	71	53.7	4	ward	NA	24h	11.9	Isch
(Dai *et al.*, 2022)	China	3416	R	UMI	68.9	64.6	3	Ward	NA	NA	12.4	Isch
(Yan *et al.*, 2021)	China	3173	R	UMI	67.97	62	4	Ward	NA	NA	13.1	Isch
(Qiu *et al.*, 2022)	China	920	R	UMI	63	64.7	2.8	Ward/ICU	0.9	NA	13.4	Isch
(Li and He, 2022)	China	295	R	UMI	69.5	66.4	3.7	Ward	NA	72h	13.6	Isch
(L. Chen *et al.*, 2022)	China	5173	R	UMI	67.7	63.8	2	Ward	NA	NA	17.3	Isch
(B. Zhang *et al.*, 2022)	China	46	RCT	UMI	63.1	63.4	6	Stroke unit	NA	48h	19.5	Isch
(Li *et al.*, 2022)	China	2366	R	UMI	71	64.8	NA	Stroke unit	NA	72h	19.4	Isch
(Deng *et al.*, 2022)	China	420	P	UMI	68	68	NA	Stroke unit	NA	24h	21.9	Isch
(Tao *et al.*, 2022)	China	2039	R	UMI	69.8	63.4	5	Ward	NA	NA	26.14	Isch/Hem
(R. Wang *et al.*, 2022)	China	351	R	UMI	56	34.20%	NA	ICU	100	48h	27.4	Hem
(Ji *et al.*, 2022)	China	1,964	RD	UMI	56.8	67.6	11	Ward/ICU	NA	24h	29.3	Hem
(Xu *et al.*, 2022)	China	50	R	UMI	57	48	NA	Ward/ICU	86	48h	52	Isch/Hem
(Guo *et al.*, 2022)	China	328	P	UMI	68	56.4	16	Ward/ICU	NA	NA	52.4	Isch
(Yu *et al.*, 2022)	China	205	R	UMI	66.3	33.2	5.1	Ward/ICU	NA	NA	27.8	Isch
(Ning *et al.*, 2021)	Pakistan	285	CS	LMI	56.8	51.5	NA	Ward	NA	72h	17.9	Isch
(Cheng *et al.*, 2021)	China	734	R	UMI	63.9	63.5	NA	Ward	NA	NA	7.1	Isch

Table 2.1 (Continued)

Author, year	Country	N	Design	Income	Age Mean/ Median	Male %	NIHSS Mean /Median	Site of care	ICU %	Time from stroke onset	SAP %	Stroke type
(Yuan *et al.*, 2021)	China	451	P	UMI	67	65.2	NA	Ward	NA	NA	21.7	Isch
(Xia *et al.*, 2021)	China	188	P	UMI	59.6	66.5	5.5	Ward	NA	48h	27.7	Isch
(Cao *et al.*, 2021)	China	399	R	UMI	64	63.2	5.9	Ward/ICU	NA	24h	29.1	Isch/Hem
(Xu *et al.*, 2021)	China	329	R	UMI	67.5	67.5	19	ICU	100	72h	37.7	Isch/Hem
(Zhao *et al.*, 2021)	China	200	P	UMI	56	48	NA	ICU	100	72h	42.5	Isch/Hem
(B. Zhang *et al.*, 2021)	China	258	R	UMI	63.3	65.5	14	Ward/ICU	NA	24h	46.5	Isch
(Gens *et al.*, 2021)	Belgium	514	R	HI	75	53.8	7.7	Stroke unit	NA	24h	15.4	Isch
(Sun *et al.*, 2021)	China	803	R	UMI	69	53.7	NA	Ward	NA	72hr	15.1	Isch
(Cheng *et al.*, 2020)	China	972	R	UMI	67	63.7	3.4	Ward	NA	NA	10.7	Isch
(J. Yang *et al.*, 2020)	China	398	R	UMI	62	59.8	NA	Ward	NA	24h	17.6	Isch
(Jiao, Geng and Zhang, 2020)	China	276	R	UMI	70.3	63.7	6.4	Ward/ICU	NA	NA	24.2	Isch/Hem
(Zhu *et al.*, 2020)	China	112	R	UMI	62	67.9	15	Ward/ICU	NA	6h	27.7	Isch
(X. Yang *et al.*, 2020)	China	798	R	UMI	66.9	48.3	NA	Ward	NA	24hr	30.2	Isch
(Zapata-Arriaza *et al.*, 2019)	Spain	41	p	HI	75	51.2	20	Stroke unit	NA	24	19.5	Isch
(Huang *et al.*, 2019)	China	863	R	UMI	66.2	63.8	5	Ward	NA	24	11.8	Isch
(Nam *et al.*, 2018)	Korea	1317	R	HI	67	60	3.7	Ward	NA	7d	8.5	Isch
(Tu *et al.*, 2017)	Singapore	731	R	HI	NA	60.5	6	Stroke unit	NA	4.5	5.5	Isch

Note. Hem: haemorrhagic stroke; HI; high income; ICU: intensive care unit; Isch: ischemic stroke; LI: lower income; NIHSS: National Institutes of Health Stroke Scale SAP: stroke associated pneumonia; UMI: upper middle income