IN THE CONTEXT OF ANEURYSMAL SUBARACHNOID HAEMORRHAGE (aSAH), INCREASED LEVEL OF SERUM INFLAMMATORY MARKERS IS ASSOCIATED WITH A HIGHER MODIFIED FISHER SCORE AND A WORSE WFNS AND HUNT AND HESS SCORE.

Morena Nthuse Mpanza
Student Number: 1320955

University of the Witwatersrand, Health Sciences Faculty, Master of Medicine, Department of Neurosurgery, Johannesburg, 2020

DECLARATION

I, Morena Nthuse Mpanza, declare that this research report is my own work. I am submitting this research report for the degree of Master of Medicine in the branch of Neurosurgery at the University of the Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other University.

Signature

6th day of November 2020

DEDICATION

I dedicate this work to God, my creator and one who sustains my life and all its endeavours; my wife, Noloyiso; my children, Nkanyezi Thulisile, Morena Nthuse and Luyana Omolemo; my parents, Jameson Muntu and Mirriam Nthabiseng; my dearest and most fearless late aunt Josephine Mantoa Mohlakoana; and my late grandmother Grace Matlopo Mohlakoana for their unwavering support, love and cheer.

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Last, and not least, I thank the patients themselves, and their families and next-of-kin for their understanding and granting consent, without which this study would have not been possible.

ABSTRACT

AIM

To evaluate the relationship between Inflammatory Biomarker Levels and the Modified Fisher Score in patients with Spontaneous Subarachnoid Haemorrhage at the Johannesburg Academic Hospitals.

METHOD

This was a prospective, descriptive cross-sectional three-centre study involving patients with aneurysmal subarachnoid haemorrhage (aSAH) diagnosed on CT and CTA scans. The patients had blood samples taken in order to measure the levels of serum inflammatory biomarker CRP (and others), and test whether there was a relationship between biomarker levels and the amount of aneurysmal bleed as determined by the Modified Fisher Score on initial CT scan, as well as the clinical grading scores (Hunt and Hess and WFNS). When all inclusion criteria were met their records were reviewed and data pertinent to the study was extracted for statistical analysis.

RESULT

A Total of 67 patients were screened, of which only 49 met the inclusion criteria. Their ages ranged from 18 to 77 with a mean of 50 (SD +/- 15,2 years). More females were affected than males (65 vs 35%). Blacks made up 88% of the study population, Caucasians 8% and Indians 4%. Risk factors (hypertension, smoking and family history of stroke) were probed and,

although having no statistically significant relationship with aSAH grading systems, there was a trend. Clinical presentation of aSAH (sentinel headache, seizures) in this study was consistent with findings in literature. More than half of the study population presented with moderate to severe aSAH assessed by clinical (Hunt and Hess, and WFNS) and radiological (Modified Fisher) Scores. The death rate was 14,3% - with an average time of 3 days from admission to demise. Hydrocephalus was present in 51% of the study population as a whole and also showed higher presence in those with more severe scores clinically and radiologically. Aneurysm characteristics (location, laterality and size) revealed a total of 59 singular aneurysms from which 11 locations were derived – the most common of which were located on the ICA (29%), MCA (23%), ACoA (22%) and ACA (19%). Aneurysm location and size did not show any preponderance for aSAH severity in this study. The biomarkers considered for the current study, and in particular CRP, largely proved to have a non-significant relationship with the Hunt and Hess, WFNS and Modified Fisher Scores. Albumin at Day 0 showed a significant relationship to the Modified Fisher Score; while ESR and platelets at Day 0 correlated to the Day 0 Hunt and Hess Score; and ESR at Day 0 correlated to Day 0 WFNS.

CONCLUSION

There was insufficient evidence in the current study to prove that a relationship existed between the level of serum inflammatory markers and the Modified Fisher, Hunt and Hess and WFNS Scores. Challenges with data collection, referral protocols and patient education may have influenced the final outcomes.

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ABBREVIATIONS

ACA	Anterior Cerebral Artery
ACoA	Anterior Communicating Artery
AIDS	Acquired Immunodeficiency Syndrome
Alb	Albumin
aSAH	Aneurysmal Subarachnoid Haemorrhage, also Subarachnoid Haemorrhage (SAH)
BA	Basilar Artery
CRP	C-reactive protein (inflammatory marker)
CSF	Cerebrospinal Fluid
CTB	Computerised Tomography, (CT brain, CT)
CTA	Computerised Tomography Angiography
CV	Cerebral Vasospasm, herein also includes Angiographic (AV) and Symptomatic Vasospasm (SV)
DALYs	Disability-Adjusted Life-Years
DBI	Delayed Brain Injury
DCI	Delayed Cerebral Ischaemia
DINDs	Delayed Ischaemic Neurological Deficits, herein also includes Delayed Neurological Deterioration (DND)
DSA	Digital Subtraction Angiography
EBI	Early Brain Injury
ESR	Erythrocyte Sedimentation Rate
GBD	Global Burden of Disease
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Scale (score)
H&H	Hunt and Hess Scale (Score)
HACAA	HIV-Associated Cerebral Aneurysmal Arteriopathy
HIV	Human Immunodeficiency Virus
HS	Haemorrhagic Stroke
ICA	Internal Carotid Artery
IHD	Ischaemic Heart Disease
IS	Ischemic Stroke
MCA	Middle Cerebral Artery

mFS	Modified Fisher Score
mRS	Modified Rankin Score
PCA	Posterior Cerebral Artery
Pcom	Posterior Communicating Artery
PCT	Procalcitonin
PI	Principal Investigator
Plt	Platelets
StatsSA	Statistics South Africa
TCD	Transcranial Doppler
VCT	Voluntary Counselling and Testing
WCC	White Cell Count
WFNS	World Federation of Neurosurgeons Score
WHO	World Health Organisation
YLDs	Years Lived with Disability
YLLs	Years of Life Lost

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CHAPTER ONE

INTRODUCTION

1.1 Stroke: Background

Stroke is defined as a cessation of blood flow to the brain secondary to obstruction, subsequent to clot formation; or haemorrhage as a result of blood vessel rupture, as in the case of an aneurysm.[1]

Stroke has rapidly made its mark and is deserving of its own category as a major non-communicable disease (NCD), with significant impact on global health as well as economic development, unlike previously being included within the 'cardiovascular diseases' group.[2]

The WHO interval reports for 2000 and 2016 listed stroke as second only to ischaemic heart disease (IHD) as a leading cause of death overall.[3,4] Whilst surpassed by infectious (communicable) diseases in the lower-income countries (respiratory, diarrhoeal, HIV/AIDS), it remains high in the list of leading causes of death in those regions; and notably remains higher than tuberculosis, malaria, and road injuries, all three of which are very common in the South African context.[3,4] In a 2013 report compiled by StatsSA, cerebrovascular diseases (4.9%) were listed fourth as the leading cause of death in South Africa, following TB (8.8%), influenza and pneumonia (5.2%) and HIV (5.1%) based on ICD-10 codes.[5] It is predicted that stroke will remain the second leading cause of death by the year 2040, after IHD.[6]

Coupled with its high mortality rate is the overwhelming morbidity that stroke places on survivors. In 2016 alone, neurological disorders listed as the leading cause of disability-adjusted life-years (DALYs) worldwide; and stroke constituted the majority (42.2%), with migraine following at a much lower 16.3%.[7] DALYs were defined as the total of years of life lost (YLLs) and years lived with disability (YLDs).[7] Thus, for every person rendered disabled due to migraines, a very common presentation in clinical practice, stroke was over two and a half times more prevalent in people with disabilities. Bertram et al. reported 75 000 new stroke cases in South Africa for the year 2008 alone, a third of those suffering mortality within the first month; and 350 000 individuals living with stroke as of the year 2007, 35% of them suffering moderate to severe disability.[8] They reported South Africa's burden of disease as a consequence to stroke to be 564 000 DALYs, with YLDs constituting 17%.[8] This estimate, though marginally lower, is similar to the WHO estimations for South Africa.

Considering the age group(s) affected by stroke – by way of incidence, mortality and morbidity – the cumulative impact on persons of productive age is significantly high, assuming productive age to be above 15 years of age and up to 60.[4,8,9] The current global incidence of stroke patients between the ages 18–50 is estimated at 2 million annually, and the total number of those living with stroke and its sequelae is projected to be on the rise, due to both rising incidence and long term survival.[9-12] This is attributed to the rise in global population through time together with the rise in the aging population.[10] A study on Global and Regional Burden of Disease in 2010 found that young and middle-aged adults (20–64 years old) from low-income and middle-income countries, of which South Africa is listed under, contributed 4 million (78%) to the global burden of stroke.[11]

The long-term sequelae of stroke on these otherwise potentially productive persons impose a strangulating socioeconomic cost on both the individual and society at large.[9-12] Furthermore, the tendency to affect younger age groups is higher, and on the rise, in developing countries compared to the first world.[12] This cost manifests itself firstly in rendering a significant number of persons unable to return to work.[13] Secondly, it implies the need for long-term care,[13] the burden of which falls squarely on relatives and the wider socioeconomic and healthcare systems (mainly the state, and or the employer).[14] Louw et al. estimate the cost of post-stroke care in the thousands of rands per patient; and propose that a work-place rehabilitation programme for stroke survivors in South Africa could result in a significant financial relief on the state budget.[14] Theirs remains a hopeful proposition, however, as it would rely on better employment rates, together with better and more sustainable employment benefits including access to health. Yet from their study we appreciate very well how post-stroke care is simply not affordable for the majority of patients and their families in South Africa considering the country's socioeconomic ills.[14,25,26] As such, a large majority of stroke patients will be left to the mercies of the public health care system, which is mostly short-handed when it comes to human resources, and other resources needed for stroke prevention, in-hospital treatment, as well as post-stroke rehabilitation strategies.[22,24-29]

1.2 Haemorrhagic Stroke

Haemorrhagic stroke occurs as a result of intracranial bleeding: whether parenchymal, within the overlying subarachnoid spaces, or deep within the cerebrospinal fluid (CSF) channels (ventricles and/or cisterns).[15]

The *GBD 2013 Study* showed rising global trends on incidence and prevalence of haemorrhagic stroke (HS); and a reduction in the rates of death and DALYs globally, save for the developing countries where they are on the rise.[12] According to the same report HS accounted for 33% of new strokes, 29% stroke survivors, 49% stroke mortality and 42% stroke DALYs. South Africa had the age-standardised prevalence and mortality rates of 0–39/100 000 and 32–64/100 000 person-years respectively.[12]

1.3 Subarachnoid Haemorrhage (SAH)

Subarachnoid haemorrhage (SAH) denotes a pathologic neurological condition in which blood enters the subarachnoid space (SAS), otherwise naturally occupied by CSF.[1,16] SAH is sub-classified as traumatic or spontaneous, with traumatic being the leading cause.[16] This study focuses on spontaneous SAH.

SAH is a critical health challenge globally, with significant socioeconomic implications, despite it making up only 5% of all strokes; considering the younger population group it impacts compared to ischaemic stroke, and its elevated mortality and disability rates coupled with poor clinical outcomes.[13,17-20] It is estimated that 10-20% of SAH patients demise before presenting to a health care facility, and of those who get medical attention 33% demise in the initial 48 hours and 50% in the first month post-ictus and admission; and half of those who survive face permanent disability twice more pronounced than with ischaemic stroke.[18,46] It is estimated that only 1 in 4 SAH survivors will recover to normal life.[20]

The majority (85% cases) of spontaneous SAH results from rupture of a cerebral aneurysm (aSAH);[20,21] Accounting for 10% of SAH cases are perimesencephalic non-aneurysmal

entities, whereby computerized tomographic angiography (CTA) is negative for aneurysmal foci, and subarachnoid blood occurs from basal cistern venous bleeding.[13] Less commonly, one in twenty (5%) persons will suffer a SAH due to miscellaneous medical states such as arteriovenous malformation, intracranial artery dissections, mycotic aneurysms, bleeding abnormalities, Ehlers-Danlos syndrome, polycystic kidney disease, reversible cerebral vasoconstriction syndrome, vasculitis, moyamoya disease, amyloid angiopathy, or drug abuse.[13,16]

1.4 Challenges with aSAH: Presentation, Diagnosis and Treatment

A significant number of patients present to the emergency department with signs and symptoms that may point to aSAH, the most common being headache, nausea and vomiting, meningism, as well as loss of consciousness.[13,154-156] The headache may be the only symptom in the event of aSAH; presenting frequently as the pathognomonic "worst headache of my life", or even as a simple headache.[13,19]

A fair proportion of these patients will be found to indeed have SAH on computed tomography (CT) scan; and upon further investigation by way of angiographic computed tomography (CTA) or DSA (Digital Subtraction Angiography), will be found to have a ruptured cerebral aneurysm.[62,172,173] Concerning the competencies required for prompt recognition of aSAH at presentation, culminating in expedient investigation, diagnosis and treatment, many regions in the world continue to face challenges in standard of care.[19,20] This was evidenced by a large proportion of hospitals in the United Kingdom as being able to achieve a good standard of care in only 58% of the cases.[19,20]

The areas of concern (in need of improvement) were cited as complete failure to diagnose aSAH in close to 50% of patients at primary care level; delayed diagnosis in 10% at primary or secondary levels of care; lack of (proper) recording of the neurological findings in 20% at secondary level; delay of initial assessment in 7.4% patients; a 66% failure rate to provide necessary investigation(s) (CT) promptly; and a 50% failure to prescribe nimodipine as indicated by treatment guidelines.[19,20] These shortcomings are worsened in the context of healthcare facilities lacking standardised aSAH management protocols.[19,20] Last but not least is the alarming lack of adequate rehabilitation for aSAH patients, even in a healthcare system, the United Kingdom with 27 regional specialised units, geared to providing best results for the large majority of the population.[19,20]

1.5 Access to Health Care in SA

Patients who suffer aneurysmal subarachnoid haemorrhage (aSAH) benefit from urgent transfer to a facility that is adequately equipped and has a full complement of a specialised multidisciplinary team. Being adequately equipped means having a CT scanner, a high-care or intensive-care unit with ventilators and life-support equipment, and a laboratory for serological (blood) investigations. A full complement of specialised staff should include competent personnel in the emergency medical, neurological, neurosurgical, radiological, neurointervention, intensive/high care, and anaesthetic units; as well as competent nursing and rehabilitation teams. These provisions, although provided for by state and law, particularly in South Africa, remain tremendously scarce, both here at home and through the entire African continent.[22]

This often means referral to a tertiary, or quaternary, hospital. Gauteng Province (South Africa) has only five centres which enjoy the fullest complement of these; and only two centres that offer neurointervention for aneurysm obliteration. In Johannesburg, Africa's economic hub, Charlotte Maxeke Johannesburg Academic (CMJAH), Chris Hani Baragwanath Academic (CHBAH), and Helen Joseph Hospitals (HJH) – all affiliated with Witwatersrand University – offer a full complement of treatment to aSAH patients; with only the former two offering neurointervention. Pretoria, South Africa's administrative capital, has Steven Biko Academic (University of Pretoria) and Dr George Mukhari (Sefako Makgatho Health Sciences University) Hospitals; none which offer neurointervention. These five hospitals are mandated to serve a vast drainage area, covering the Gauteng, Limpopo, Mpumalanga and North West provinces. The 2019 population size estimates in these provinces are 15 176 115 (25,8% of the South African population), 5 982 584 (10,2%), 4 592 187 (7,8%) and 4 027 160 (6,9%) respectively; and a total of 29 778 046 (50,7%).[23]

Having to service half the country's population, and facing the very imposing reality of migration patterns, with high population influx including that of undocumented foreign nationals, these public hospitals are easily overwhelmed with having to deliver a good standard of care for aSAH patients, notwithstanding being underequipped, short staffed and poorly organised, despite well intended political-administrative policies.[23-26] This burden does not even account for the mixed terrain from which patients must be transported, rural and peri-urban, and the implied factors of a challenged infrastructure and hospital transportation system (Emergency Medical Services) among others.[26-29] In a report on *"The health and health system of South Africa"*, Coovadia et al. provide a succinct yet elaborate map *(Figure 5 in their report)* of health and development indicators in the country's respective provinces.[25]

It is in this context that access to health care for aSAH patients in the region must be understood. While "access to health care for all" is mandated by South African law, it often remains an illusion for the majority, for reasons that are rooted in the current and historical socioeconomic inequalities of the country.[25-29] Distance, and transportation cost and time, to reach specialised treatment has been cited as one of the major challenges to availability of and access to care.[27-29] Furthermore, Vergunst et al., looking at one of South Africa's largest rural population, described how disparities in access to health care affect the disabled most severely, particularly in a rural setting.[29] Their contribution is noteworthy from the point of view that, including for the peri-urban communities, people who suffer disability consequent to aSAH face the inevitability of becoming even more marginalised and deprived of access to health care, for both rehabilitation and ongoing and new onset illnesses.[28-31] Public and academic hospitals certainly experience high volumes of loss to follow-up for many of the patients who become incapacitated after suffering aSAH – most of whom never even continue with a rehabilitation program once discharged.

It therefore stands to reason that due to our country's current socioeconomic climate, as described above, as well as the intense challenges posed by disease patterns that result from the extremes of poverty, an improved means of detecting, diagnosing and managing patients with aSAH remains merely an ideal that is far from being realised.[12,32-36] Furthermore, improving on our solution (prevention, detection and treatment) to the challenge of aSAH will mean answering to the mammoth task of capacitating and deepening the country's health care system at both primary and secondary levels, which will require novel ideas as well as a gallant political and administrative will.[12,37-39]

1.6 Considerations in aSAH: A Historical Overview

Hippocrates is recognised as the first to describe SAH clinically: *"...when persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days, unless fever comes on."*[40-42] Since then several authors have further contributed to its understanding and the clarity of its definitions from the clinical presentation to the pathological and causal processes.[13,43-45] It is by these terms, and in keeping with them, that patients who present with "a worst headache of my life", "thunderclap headache", and some accompanied with loss of consciousness, are investigated by way of a CT brain scan to rule out or diagnose subarachnoid haemorrhage and the potential causal cerebral aneurysm.

Several considerations have been proposed and studied over the years in an attempt to describe the pathophysiology, causes of mortality and morbidity, and thus management, of aSAH.[47-55] Several authors have contributed to the concepts of "early brain injury" (EBI) as well as "delayed neurological deterioration" (DND) as the major causes of death and morbidity in aSAH.[47,48,50-55] Although these two terms seek to delineate the cascade of events which occur at different time periods post aSAH ictus, they are believed to be more related than not.[50-55] During the early phase (EBI) the complex mechanisms believed to play a role are: (i) loss of cerebral autoregulation involving intracranial pressure (ICP), cerebral perfusion pressure (CPP) and cerebral blood flow (CBF); (ii) inflammation; (iii) loss of neuroprotection involving excitotoxicity, cortical spreading depolarization (CSD) and ionic imbalance; (iv) oxidative stress; (v) cerebral oedema and; (vi) cell death.[50-55] Delayed neurological deterioration (DND), which occurs after 72hours from aSAH onset, involves: (i) delayed cerebral vasospasm; (ii) microcirculatory spasm; (iii) microthrombosis and; (iv) cortical spreading ischaemia.[50-53,56,57]

Furthermore, the added complications of aSAH which contribute to mortality and morbidity are: (i) rebleed; (ii) acute and chronic hydrocephalus; (iii) seizures and; (iv) multiorgan dysfunction and failure.[58-63]

Despite the advances in the understanding of aSAH, and the much appropriate attempts to manage the complexity of the pathophysiological mechanisms involved, the clinical outcomes remain largely poor after successful aneurysmal treatment.

It is important and beneficial that several means of prognosticating have been established – these have led in many a breakthrough in the appropriate and efficient triaging and management of aSAH patients both in the acute phase and thereafter post aneurysmal rupture. These prognosticating tools include: clinical grading systems (Hunt and Hess, World Federation of Neurosurgeons Score, Glasgow Coma Score);[64-67] radiological grading systems (Fisher Grade),[68,69] as well as correlations such as CSF and serological/or blood markers (glucose,[70] free fatty acid,[71] bradykinin,[72] TNF-$\propto$,[73,74] neuropeptide Y,[75] B-type natriuretic peptide,[76] Interleukin-6,[77] CRP[78,79])

This study sought to correlate mainly two prognosticating variables: the amount of blood volume as demonstrated on the CT scan (the modified Fisher Score) in relation to plasma CRP levels.

CHAPTER TWO

2.1 LITERATURE REVIEW

2.1.1 aSAH: Definition and Aetiology

Sub-arachnoid haemorrhage (SAH) denotes a pathologic neurological condition in which blood enters the subarachnoid space (SAS), otherwise naturally occupied by cerebrospinal fluid (CSF).[16] SAH is sub-classified as traumatic or spontaneous, with traumatic being the leading cause.[16] The focus of this study was on spontaneous SAH.

The majority (85% cases) of spontaneous SAH results from rupture of a cerebral aneurysm.[21] Accounting for 10% of SAH cases are perimesencephalic non-aneurysmal entities, whereby computerized tomographic angiography (CTA) is negative for aneurysmal foci, and subarachnoid blood occurs from basal cistern venous bleeding.[13] Less commonly, one in twenty (5%) persons will suffer a SAH due to miscellaneous medical states such as arteriovenous malformation, intracranial artery dissections, mycotic aneurysms, bleeding abnormalities, Ehlers-Danlos syndrome, polycystic kidney disease, reversible cerebral vasoconstriction syndrome, vasculitis, moyamoya disease, amyloid angiopathy, or drug abuse.[13,16]

2.1.2 Epidemiology

The global incidence from most population studies is 6–7 per 100,000 person-years.[21,80,81,82] The incidence varies between regions, with much higher estimates in Finland and Japan (20 per 100,000).[21,80,81,83] Furthermore, the World Health Organization (WHO) estimates an annual incidence of aSAH to be between 2.0 cases in China to 22.5 cases in Finland per 100,000.[13,62,83] A 2009 review reported an overall incidence of 2 to 16 per 100,000 population; with low- to middle-income countries showing nearly twice as high as the incidence in the high-income countries.[84] However, there are conflicting incidence reports in the United States of America (USA) with some stating 9.7 per 100,000 persons,[85] while a 2003 Nationwide Inpatient Sample revealed it to be 1.5 times as much based on hospital discharges.[86]

Age is reported to have a directly proportional relationship with the incidence, with studies reporting an increase in incidence with increasing age till a peak incidence of 22.1 per 100,000 person-years in the 50-55year age group.[13,80] Several authors have pointed out very importantly that half the sufferers were in the productive years (younger than 55).[82] Gender also plays a role as females tend to have higher incidence rates than males.[13,83,87] It is observed that race and ethnicity also exhibit different trends in aSAH incidence, with non-Caucasian Americans showing a greater incidence than Caucasians.[62]

Importantly, consideration should be given to pre-admission aSAH related deaths which are estimated to be in the region of 12% to 15% of cases.[18,46,88,89] Thus the true incidence of aSAH may be greater.[62,88,89]

2.1.3 Mortality and Morbidity

Global mortality associated with aSAH remains high,[84] despite showing trends of marginal decrease over the last three decades.[62,90] Population-based studies are quoted as showing a 50% case mortality rate.[21] Some studies also showed that one out of six deaths occur upon aSAH ictus.[13] Mortality rates as stated above, are influenced by vastly unaccounted pre-hospital aSAH related deaths.[13,21,62] Thus under-reporting might have occurred. Gender and race are also thought to influence mortality rates associated with aSAH:[62] some authors have suggested that women are at greater risk of death,[89,91,92] and that the risk is greater in blacks, Hispanics, American Indians/Alaskan Natives, and Asians/Pacific Islanders as compared to Caucasians.[62,93,94]

2.1.4 Causes of Mortality Associated with aSAH

Lantigua et al. investigated potential causes and mode of death amongst inpatients admitted for aSAH.[95] Overall mortality was 18% and there was a relationship between the risk of death and clinical grade (Hunt & Hess). Furthermore, the mode of death, or outcome severity, was related to: effects of the ictus or primary haemorrhage (55%), aneurysm rebleed (17%), medical complications (15%), cerebral oedema (5%) and Delayed Cerebral Ischaemia (DCI) (5%). In addition, the well-established predictors of mortality at presentation are age, loss of consciousness (LOC) at ictus, and admission Glasgow Coma Scale (GCS);[67] Modified Fisher Score, the World Federation of Neurosurgeons (WFNS) and Hunt and Hess scores,[62,64,65] aneurysm size, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) physiologic sub-score.

2.1.5 Predictors of Mortality and Morbidity for aSAH

2.1.5.1 Clinical Parameters

The well-established clinical parameters for predicting morbidity and mortality in aSAH patients are the Hunt and Hess and the World Federation of Neurosurgeons (WFNS) scores.[64,65] The Hunt and Hess scale, first described in 1968, is the most widely used to classify aSAH severity (Appendix 1).[66] It assesses the patient's wakefulness after aSAH – combined with headache, nuchal rigidity and focal deficit (including cranial nerve palsy). The increasing score from 1 to 5 indicates worsening clinical severity. It is criticised, however, for its inter-observer variability and failure to have clear distinction between some of its grades.[66,96] In 1988 the WFNS score was described,[65] which accounts for the patient's GCS,[67] as well as presence of motor deficit, with the increasing grades from 1 to 5 indicating clinical severity of aSAH (Appendix 2).

2.1.5.2 Radiological Parameters

The most recognised radiological tool, developed in 1980, for assessing prognosis in patients with aSAH is the Fisher Score (Appendix 3). It categorises the severity of aSAH by measuring the amount of blood visible on the initial non-contrasted CT scan taken post ictus. Investigating 47 cases of confirmed aneurysmal rupture, Fisher et al. posited that a focal clot or column of blood greater than 1mm thick was strongly predictive of cerebral vasospasm, and thus poor clinical outcome.[68] They also discovered that severe vasospasm almost did not occur when aSAH was not detected or was of a diffuse nature. Frontera and colleagues subsequently described a modified Fisher scale by accounting for thick cisternal and ventricular blood, and proving the modified scale to be more precise at predicting symptomatic cerebral vasospasm after subarachnoid haemorrhage compared to the original Fisher scale (Appendix 4).[69]

2.1.5.3 Inflammatory Biomarkers

Inflammation (neuroinflammation) has been shown to be a significant factor in the advent of SAH, impacting on patients' functional and cognitive prognosis.[98-101] Blood entering the subarachnoid space triggers inflammatory cascades including those of vascular and cellular nature.[98-101] The subsequent early brain injury (EBI) which occurs within the initial 72 hours has fatal outcomes manifesting as increased intracranial pressure, acute hydrocephalus, microvascular alterations and transient global ischemia.[50-55,97] Approximately, a third of the survivors from the initial ictus suffer delayed cerebral deterioration, which generally appears 3–14 days later and is defined by delayed cerebral ischemia (DCI) and delayed neurological deficits (DNDs).[97,] Delayed neurological deterioration (DND) involves: (i) delayed cerebral vasospasm; (ii) microcirculatory spasm; (iii) micro-thrombosis and; (iv) cortical spreading ischaemia.[50-53,56,57]

Studies have postulated that a synergistic combination of factors, such as blood–brain barrier disruption, microvascular spasm, arteriolar constriction and thrombosis, along with cortical spreading depolarization, rather than vasospasm alone are involved in the development of DNDs.[50-53,56,57] The subsequent inflammation is thought to both play a vital contributing role as well as being consequent to DCI.[97] These neuro-inflammatory processes are considered vital towards better management and outcomes of SAH sufferers. Thus, several serum biomarkers have been studied and related to outcome after SAH namely: glucose, free fatty acid, bradykinin, neuropeptide Y, B-type natriuretic peptide (BNP), C-reactive protein (CRP), tissue necrosis factor alpha (TNF-α), Interleukins (-1,-6,-8), catecholamines and microalbuminuria.[70-79] Also associated with inflammation in SAH, but not outcome, are procalcitonin (PCT) and myeloperoxidase (MPO).[102]

CRP, an acute phase inflammatory marker, is utilised to evaluate sepsis. It is synthesised by hepatocytes in response to inflammation and cytokine activation. It is accepted as one of the most useful septic markers in the critically ill, notwithstanding its variable sensitivity and specificity.[102] CRP offers better sensitivity and specificity when used together with other markers of sepsis, such as temperature.

It has also been shown that CRP is associated to vasospasm and poor outcome in SAH. Fountas et al. were the first to study CRP in relation to SAH outcomes, analysing the levels thereof in blood as well as CSF. They found that high CRP values were related to vasospasm and poor outcomes at discharge.[103] Subsequently, several published literature suggested that CRP has a role as a marker of poor outcome in SAH. Badjatia et al. showed that elevated high sensitivity CRP (hsCRP) in the first 14 days post-ictus was an independent predictor of delayed cerebral ischaemia (DCI) and therefore delayed ischaemic neurological deterioration (DIND) in SAH.[104] Kubo et al. demonstrated that at days 0 and 7, raised hsCRP was associated with DIND.[105] Likewise, Romero and colleagues found that elevated serum CRP was related to SAH severity as well as poor prognosis on discharge.[106] Their findings were supported by work done by Frontera and colleagues in the same year.[107] Jeon et al. looked particularly at SAH patients who were to undergo surgical intervention. They found that pre- and post-procedure CRP values were related to outcome. Their study showed that on postoperative days 1 to 2, raised CRP values were related to severe neurological deterioration at presentation, cerebral infarction, intracerebral haemorrhage and surgical decompression.[108]

The direct role of CRP in SAH, however, remains largely undefined: whether CRP invades the central nervous tissue causing direct insult or is merely a systemic marker of SAH severity is unknown. Moreover, it is not clear if CRP reliability in predicting SAH outcomes is impacted

by confounding complications such as lower respiratory infections, cardiac and other complications.

Recently, Kapoor et al. prospectively investigated the value of nutritional biomarkers haemoglobin, serum protein as well as albumin in SAH prognosis. They found that all the aforementioned factors decreased in the first week post-ictus after measuring them within the first 24 hours as well as day 7 post-haemorrhage. They also found lower serum albumin values at presentation to be predictive for poor outcome as defined by neurological deficits (52% vs 20%), infarct (35% vs 23%), mortality (28% vs 16%) and unfavourable Glasgow Outcome Score (GOS) (38% vs 25%). Multivariate data showed lower admission albumin and Fisher grade to contribute strongly to neurological deficits, while a percentage fall in albumin over the first week was predictive for neurological deficits and poor GOS.[109]

2.2 MOTIVATION FOR THE STUDY

2.2.1 Biomarkers vs Radiology

Several studies have looked at inflammation after aSAH, by examining serum markers, and its potential relation to patient outcomes. While these studies provide significant proof on the role of inflammation in the disease process, there is very little literature on the direct correlation between serum inflammation marker levels and the quantity of blood present on CT scan as graded by the Modified Fisher Score.

For the purposes of this research it was hypothesised that a larger volume of SAH as quantified by the Modified Fisher Score would lead to higher serum inflammatory marker levels and

worse patient outcomes. Of particular interest was the observation whether a large volume SAH with low inflammatory marker levels would have comparably equal poor patient outcomes or not. Clarifying this relationship would then potentially make possible the combined use of serum inflammatory markers and the Modified Fisher Score as synergistic useful prognostication tools. In a resource limited environment, a proven relationship may add value such that the serum biomarker in question (CRP) could be used as a triage tool for patients with aSAH. Furthermore, surrogate serum markers could also have the potential benefit of being used as ongoing monitoring tools of the disease process. This study therefore aimed to elucidate a relationship between inflammatory markers and the Modified Fisher Score in patients who present with spontaneous SAH.

2.2.2 Hypothesis

In the context of aneurysmal subarachnoid haemorrhage (aSAH), increased level of serum inflammatory markers is associated with a higher modified Fisher score and worse WFNS and Hunt and Hess Scores.

2.2.3 Aims and Objectives

Aim

The aim of the study was to evaluate the relationship between Inflammatory Biomarker (CRP) Levels and the Modified Fisher Score in patients with Spontaneous Subarachnoid Haemorrhage at the Johannesburg Academic Hospitals.

Objectives

i. To describe the sociodemographic characteristics of patients with aSAH

ii. To evaluate the relationship between the inflammatory markers CRP, ESR, PCT, WCC, Platelets and albumin and the category of Modified Fisher Score

iii. To evaluate the relationship between the inflammatory markers CRP, ESR, PCT, WCC, Platelets and albumin and the Hunt and Hess and WFNS Scores

iv. To evaluate the relationship between the inflammatory markers CRP, ESR, PCT, WCC, Platelets and albumin and socio-demographic (such as age, gender, ethnic group, smoking status) and comorbid (such as hypertension history, HIV status, family history of aSAH) factors

v. To determine the relationship between duration of aSAH diagnosis and the inflammatory markers CRP, ESR, PCT, WCC, Platelets and albumin

CHAPTER THREE

MATERIALS AND METHODS

3.1 Research Design

This was a prospective, descriptive cross-sectional three-centre study involving patients with aneurysmal subarachnoid haemorrhage (aSAH) diagnosed on computed tomography (CT) scan and computed tomographic angiography (CTA) scan. The same patients had blood samples taken in order to measure the serum inflammatory biomarker CRP levels (and others), and test whether there was a relationship between this biomarker levels and the amount of aneurysmal bleed as determined by the Modified Fisher Score on initial CT scan.

3.1.1 Methods

This study was carried out at the Departments of Neurosurgery at Chris Hani Baragwanath Academic (CHBAH), Charlotte Maxeke Johannesburg Academic (CMJAH) and Helen Joseph Hospitals (HJH), all in the greater Johannesburg, South Africa. The departments were ideal recruitment sites for the study as they are the final referral centres for the treatment of patients with proven aSAH.

HJH has between 500 and 700 beds in total, including 12 in ICU and 6 in the High Care/Step down unit. The Neurosurgical Department there, fully functional since early 2017, shares a ward with the Department of Internal Medicine and enjoys just a little over 10 beds with only basic facilities and nursing staff. CHBAH, the largest hospital in Africa and according to some

reports the third largest in the world, has approximately 3400 beds, with the Neurosurgical Department occupying about 72 beds, including a 12 bed ICU/High Care area. CMJAH has slightly over 900 beds, with the Neurosurgical Department occupying a 20-bed ward – 8 ICU and 12 High Care beds.

Apart from directly admitting patients from communities in their immediate surrounds, these hospitals are also specialist referral (and training) centres for hospitals and clinics in the greater Johannesburg region, the greater southwestern to eastern Gauteng Province, as well as parts of the neighbouring North West and Mpumalanga provinces. The 2019 population size estimates in these provinces were 15 176 115 (25,8% of the South African population), 4 592 187 (7,8%) and 4 027 160 (6,9%) respectively; a total of 29 778 046 (40,5%).[23] Whilst not serving these population numbers in total, due to the existence of two more academic hospitals in the northern Gauteng Province region (i.e. Pretoria), namely Dr George Mukhari and Steven Biko Hospitals, both of which also provide full neurosurgical services, it goes without saying that Johannesburg, as the hub of the South African and Africa's economy, has a much larger share of the population size. The greater Johannesburg City alone is quoted to have a population size of 8 million people, which rises to 10,5 million if the West Rand and Lenasia (south) are included.[110]

The study population were referred by colleagues from the lower level (district) hospitals in the region as detailed above as well as by the medical, neurological and emergency units from within the hospitals designated as study sites. Patients diagnosed with aSAH by way of non-contrast CT and CT angiography scans, either at the study-site hospitals or otherwise, were referred to the respective Departments of Neurosurgery. A protocol, detailing which investigations were to be undertaken for the purposes of the study, was outlined and distributed

to all the emergency units at the recruiting sites (hospitals), as well as among colleagues on call in the respective Neurosurgical Departments (Appendix 5). This protocol was instituted at an ongoing and consecutive manner upon each aSAH patient's referral, assumed to be day 0 of admission post aneurysmal bleed, starting from the time permission was granted to conduct the study.

The inclusion criteria for the study was SAH proven on CT scan and an aneurysm proven on subsequent CT angiography in adult patients. Once these were satisfied informed consent was obtained from each patient and/or his/her next-of-kin for those who were not compos mentis. Information documents concerning the study were printed and given to each patient and/or his/her next-of-kin to read through, and a discussion was held with each, after which a consent form was signed and witnessed. The information sheets and consent forms (for primary participant and Next-Of-Kin respectively) are included as Appendices 6, 7, 8 and 9. Granting consent meant the patient approved him/herself being included in the study by way of use of their records (the patient bed letters), radiological examination and blood/serological investigation results. Voluntary Counselling and Testing (VCT) for HIV/AIDS was also conducted, separately, as an added interest in the study to observe whether this co-morbidity impacted on aSAH and how. It was, however, made clear to the patients that this part of the consenting process was not mandatory for the study and would not impact negatively on their treatment. The study data sheet was produced and explained to each patient, with which the history-taking part of the study data, for instance headache, smoking and hypertension, provided there was collateral, and/or the patient was compos mentis, was reinforced if not obtainable from the patient bed letters (Appendix 10).

After all ethical considerations were satisfied, relevant information was extracted from the patients' bed letters and their radiological and blood/serological findings were captured. Where appropriate, information missing from the patient bed letter such as history of headache, smoking, hypertension, HIV/AIDS was obtained by asking the participant and/or his/her next-of-kin where possible.

There was also a link data sheet produced for the purposes of separating the participant's identifying data such as name and surname, hospital and hospital reference numbers, as well as demographics, from the scientific data (Appendix 11). This added a layer of protection to the anonymity of our participants and their information.

The information collected was as follows:

A. **Demographic data**: Name, age, gender, hospital and reference number, admission date, patient allocation tracking number (link data sheet).
B. **Clinical data**: Clinical data pertaining to risk factors associated with aneurysm development and rupture were captured as follows: history of hypertension, smoking, family history of aSAH, HIV status (VCT approved), sentinel bleed (headache), day of sentinel bleed to presentation, day of SAH ictus. On history taking the presence of risk factors was captured as "Yes", "No" and/or "Unknown". This largely depended on whether the patients were compos mentis or not over the study period, and on reliable collateral report where applicable. Hypertension and smoking were captured categorically as "Yes" or "No", notwithstanding how long the patients had been hypertensive or smoking; and as "Unknown" where the patients had reduced levels of consciousness and/or where there was no reliable collateral. Circumstances

surrounding aSAH presentation were probed directly from the patients, and/or next-of-kin or legal guardian who could provide good collateral on behalf of those who were not compos mentis. The history of a sentinel bleed (evidenced by a characteristic headache) was captured categorically as "Yes", "No" or "Unknown"; and an estimation of the number of days lapsing between the occurrence of such a headache and presenting to hospital was recorded for those who reported "Yes". This was not totally reliable as it depended on communication between patient and accompanying next-of-kin or legal guardian. aSAH ictus (proper) was taken as the day the patient suffered a strong enough headache, or neurological fallout, to result in him/her presenting at the emergency department. Seizures on presentation Day 0 and on Day 5 were recorded categorically as "Yes" or "No" regardless of number and/or duration.

C. **Examination data**: The Glasgow Coma Score (GCS), Hunt and Hess score (H&H) and the World Federation of Neurosurgeons score (WFNS), recorded on Days 0 and 5 of admission respectively, were used for measuring the clinical severity of aSAH. For the purposes of the study the GCS was deemed improved if it increased by ≥2 points on Day 5; and worse if it decreased by the same. An improved or worse GCS was also defined as crossing the categories of "mild", "moderate" and "severe" head injury. Improvement and/or worsening of the Hunt and Hess and WFNS scores was judged as a change of 1 point respectively. For the purposes of clarity, those who demised were recorded separately from those who worsened without demising by admission Day 5.

D. **Radiological data**: Radiological investigations were performed by way of baseline CT brain scan and CT angiography done upon patient presentation (admission Day 0). CT scans were thoroughly studied by the Author (Principal Investigator or PI) to obtain the following: Modified Fisher Score on admission day 0; presence of hydrocephalus on day 0; aneurysm location and size. The radiological reports were also studied, and the

reporting Radiology Consultant(s) was consulted, to see if there was any conflict in the scoring of the Modified Fisher scores. Where there was conflict a third party (a Consultant in Neurosurgery for a period of at least 4 years since qualification) was called in to give a final score. As the study was undertaken at three separate hospitals, this would potentially introduce inter-rater variability with regards to assigning the Modified Fisher Scores. Having the same arbitrator (a Consultant in Neurosurgery for a period of at least 4 years since qualification) assign a score, regardless of whether there was a conflict or not between the findings by the PI and those from the Radiology Consultants at the three respective hospitals, was done in an attempt to overcome this challenge. CT angiogram reports were studied to obtain aneurysm size and location where possible. Aneurysm locations were determined for all singular aneurysms, as well as for aneurysms which were reported as "multiple" in a single patient. Where "multiple" aneurysms were reported without defining what those aneurysm locations were, this was labelled Multiple-UD for analysis purposes. Aneurysm size was categorised as <2,5mm; 2,5 – 5,0mm; 5,1 – 10,0mm; and >10mm.

E. **Blood/Serological data**: Blood was obtained by pulling samples from each patient and sending them to the NHLS (National Health Laboratory Services) for analysis. The results were obtained by logging onto the NHLS Labtrack Portal and entering the patient hospital reference numbers. The results captured were of CRP levels on admission days 0 and 5; ESR levels on admission days 0 and 5; PCT levels on admission days 0 and 5; WCC levels on admission days 0 and 5; Platelet levels on admission days 0 and 5; and Albumin levels on admission days 0 and 5.

3.1.2 Ethical and Legal Considerations

Ethical approval (certificate No. M1911168) was obtained from the Human Research and Ethics Committee (HREC) – Witwatersrand University – prior to the commencement of the study (Appendix 12). Informed consent was obtained from each participant and/or his/her next-of-kin. Confidentiality was upheld and maintained by use of initials on data sheets, as well as usage of the link data sheets which separated the patient identification data (names, demographics, hospital references) from the scientific data used in this study. The information collected was kept safe and not distributed; and was only accessed by the principal investigator. The study was observational and not invasive; patients' records and results of their radiological and serological (and blood) investigations were obtained and used without any additional procedure(s) performed. With regards the HIV/AIDS status, the participants were asked to offer this voluntarily and where they consented a full VCT process was followed. Patients who refused HIV/AIDS VCT or to divulge information pertaining to this were still managed according to world class standards of treating aSAH and were not impacted upon negatively. The study protocol (proposal) was vetted by the university protocol committee and copies were submitted to the respective hospitals and approval was granted by the respective CEOs/Clinical Directors to conduct the research as proposed and the CEO/Clinical Director/Medical Advisory Committee Consent were obtained. Written consent was obtained from the Medical Superintendents of the hospitals prior to commencement of the study.

3.2 Study Site

This study was carried out at the Departments of Neurosurgery at CHBAH, CMJAH and HJH respectively. The departments were ideal recruitment sites for the study as they are the largest and final referral centres for the treatment of patients with proven aSAH.

3.3 Study Population

Patients who were referred to the Neurosurgical Departments at CHBAH, CMJAH and HJH for the treatment of aSAH as diagnosed by CT scan and CT angiography scan were the study population.

3.4 Sample Size

The sample size consisted of all the consecutive consenting participants with newly diagnosed aSAH from the time of diagnosis and admission to the 5th day of admission (post aneurysmal bleed). Data was to be collected over a period of three to six months, or until at least 30 cases were achieved, whichever came first. The rationale for this was due to reasons of practicality in achieving an outcome. A power study was conducted in the protocol proposal phase of the research project. The power study revealed that the appropriate study sample size was not going to be attainable in our setting for the time period that the study was to be conducted. As a result of this the University Protocol Approval Committee determined that a time period stipulated above, or attaining at least 30 subjects, was adequate for the purposes of the study.

3.5 Inclusion and Exclusion Criteria

Inclusion criteria were the following:

i. All patients 18 years of age and above who presented with spontaneous SAH proven on computed tomography (CT) scan admitted within 5 days of the ictus (bleed)

ii. The spontaneous SAH must have been proven by CT angiography or Digital Subtraction Angiography (DSA) scans to be caused by aneurysmal rupture
iii. All patients who consented either directly or by way of next-of-kin to participate in the study

Exclusion criteria were the following:

i. Patients with SAH secondary to trauma
ii. Patients with spontaneous SAH secondary to neurological diseases other than aneurysmal; such as hypertensive bleeds, arteriovenous malformation rupture, haemorrhagic infarction, vasculitis, tumour bleeds, etc.
iii. Patients who presented, or were referred from other hospitals, later than 5 days without initial CT scan findings and relevant serum inflammatory marker investigations
iv. All patients who refused consent of participation in the study
v. Patients who were younger than 18 years of age

3.6 Measuring Tool or Instrument

A pre-designed data collection sheet (Appendix 10) was used to record all relevant data including patient demographics, history pertaining to aSAH, examination findings, radiological findings as well as serological/blood results.

3.7 Method and Statistical Analysis

Patients included in the study were those who presented with spontaneous SAH proven to be caused by aneurysmal rupture (aSAH). These patients presented either directly to the hospitals where the study was conducted (CHBAH, CMJAH, HJH); and/or were referred by lower level (district) hospitals. When a patient diagnosed with aSAH was referred to the respective neurosurgical units, s/he was vetted to verify if s/he met the inclusion criteria to participate in the study. Once inclusion criteria were met per participant and informed consent was obtained, the datasheet was explained to each participant and completed first by filling in the details of the participant's presenting history (sentinel headache, smoking, hypertension, family history, seizures). The participant was then informed that the rest of the information for the purposes of our data collection would be obtained from his/her bed letter, the department of radiology for the scan results and report, as well as the National Health Laboratory Services for their blood/serological results. All information was then captured on the pre-designed data collection sheet; and subsequent to being recorded on the Microsoft Excel spreadsheet (Appendix 13) the data was then exported for analysis to "R" Statistical Software. A suspected relationship between the biomarker levels in the blood – CRP, ESR, PCT, platelets and albumin – and aSAH severity scores was investigated through a statistical process, primarily by using ordinal logistic regression model.

A relationship of the form $Y_j = \sum a_i X_{i,}$ regress Y_j on X_i, was tested.

The dependent variables, Y_j, were Hunt & Hess Score, World Federation of Neurosurgeons Score, and Modified Fisher Score. These were all treated as discrete ≠random variables and were regressed on continuous random variables, Xi.

The assumed independent variables, biomarkers (X_i), were CRP, ESR, PCT, WCC, platelets and albumin.

The aim of the investigation was to verify the statistically significant coefficients, a_i, of the regression equation so as to prove that there existed a relationship between the dependent and independent variables. The null-hypothesis being H_0: $a_i = 0$ and alternative hypothesis H_1: $a_i \neq 0$. The significance level, α, is 0.05.

CHAPTER FOUR

RESULTS

4.2 Records Reviewed

A total of 67 patients diagnosed with aneurysmal subarachnoid haemorrhage (aSAH) were identified, of which only 49 were recruited for the study from three hospitals. Their medical, radiological and blood (serological) records were obtained and reviewed. The records were obtained from the respective hospitals as summarised below and shown in Figure 4.1:

- 8 from Helen Joseph Hospital (HJH);
- 19 from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH);
- 22 from Chris Hani Baragwanath Academic Hospital (CHBAH)

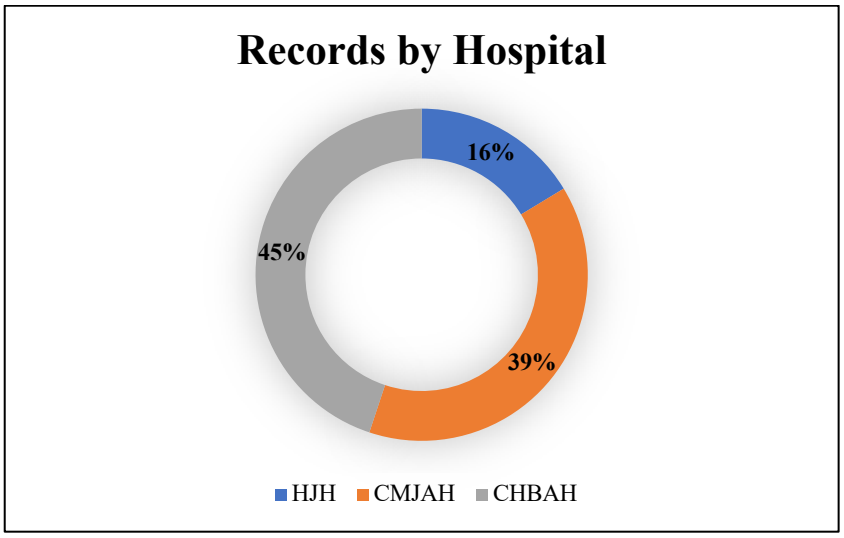


Figure 4.1: Records Reviewed by Hospital (shown in percentage).

4.2 Demographic Profiles

The demographic data of the study population were recorded according to age, gender and ethnicity.

Patients above the legal adult age were recruited for the study. Their ages ranged from 18 to 77 years with a mean of 50 (SD +/- 15,2 years). Age demographics are summarised in Figure 4.2. The highest absolute number of those affected was in the age group 41 – 60. The mean age was 51,1 years for females and 48 years for males. The mean age by ethnic group was 49,5 years in the African group; 45,5 years in the Caucasian group; and 70 years in the Indian group. The mean age by gender and ethnicity was 52,7 years for African females and 42,2 years for African males; 27 years for Caucasian females and 64 years for Caucasian males; and 70 years in the Indian group which comprised only males in this study.

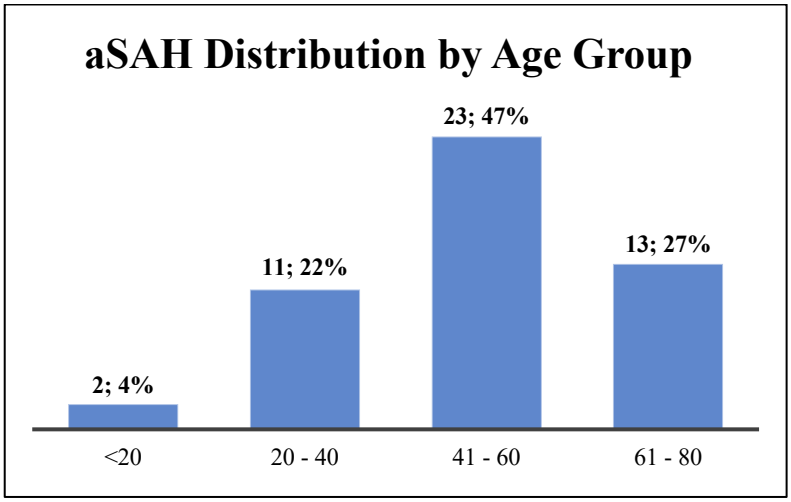


Figure 4.2: aSAH Distribution by Age Group (shown in number and percentage).

Female participants were more affected than males (32 vs 17) – Figure 4.3.

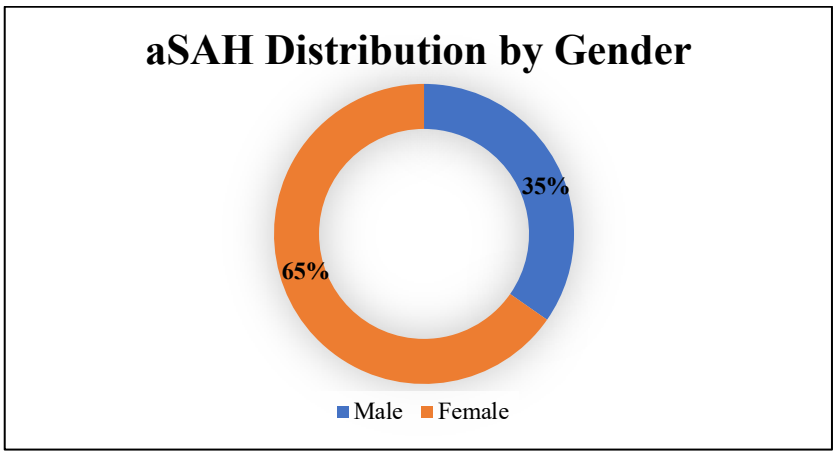


Figure 4.3: aSAH Distribution by Gender (shown in percentage).

The ethnic demographics (Figure 4.4) were categorised as African, Indian and Caucasian – with coloured people included in the African group. Africans made up the vast majority of the study population (n = 43), followed by Caucasians (n = 4) and Indians (n = 2).

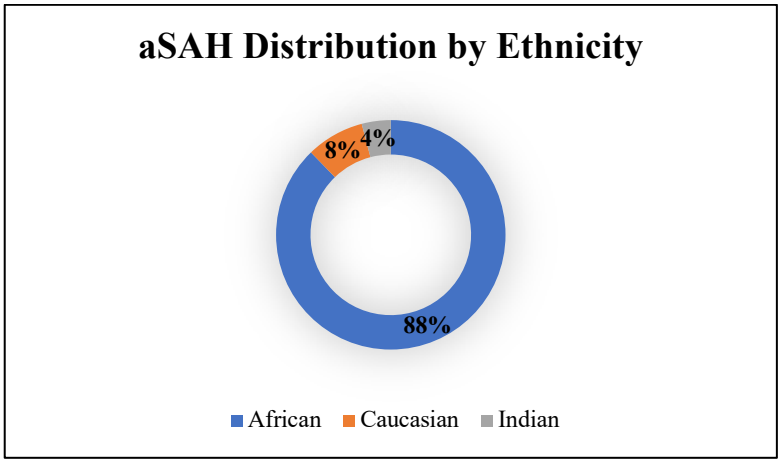


Figure 4.4: aSAH Distribution by Ethnicity (shown in percentage).

aSAH distribution by gender within the respective ethnic groups (Figure 4.5) showed a female preponderance in the African group and an equal distribution in the Caucasian group. There were no Indian female participants.

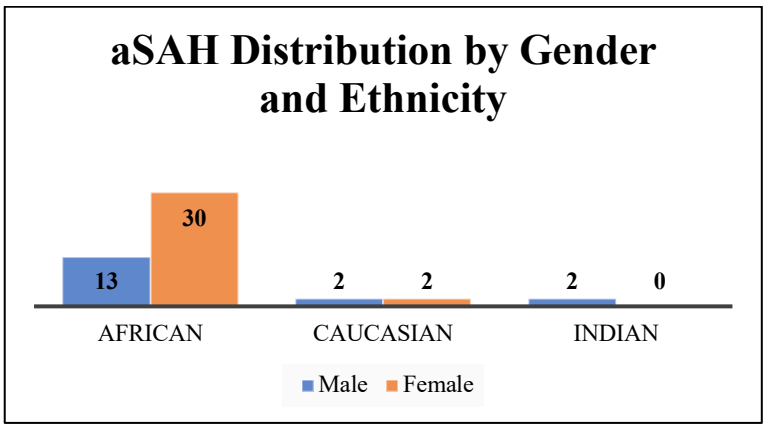


Figure 4.5: aSAH Distribution by Gender and Ethnicity (shown in number).

The Modified Fisher scores of all participants were recorded on Days 0 and 5 of admission. These were averaged and are presented below according to age and gender (Figure 4.6) and according to gender and ethnicity (Figure 4.7) respectively – using the Day 0 admission scores. When looking at the severity of the Modified Fisher score by age and gender, there was no gender bias for the age group below 20 years; in the age group 21–40 females were more severely affected than males; and in the age groups 41 and above males were more severely affected than females. For females, the severity of the Modified Fisher score reduced with increasing age, while it remained the same for males, except for a decline in the age group 21–40.

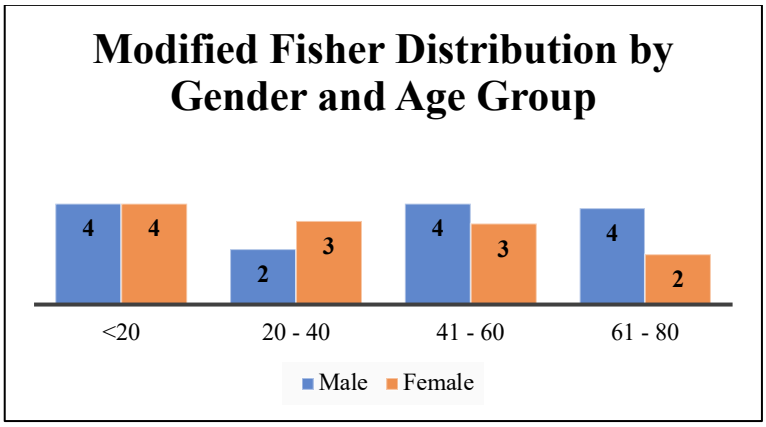


Figure 4.6: Modified Fisher Score Distribution by Gender and Age Group.

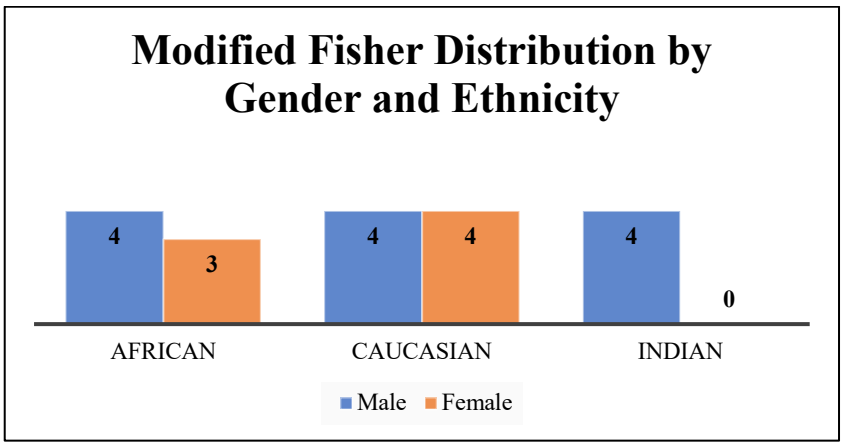


Figure 4.7: Modified Fisher Score Distribution by Gender and Ethnicity.

The mean Modified Fisher score was higher in males in the African group and equal for males and females in the Caucasian group. The Indian group had male participants only. African females overall had the least severe Modified Fisher scores than everyone else.

4.3 Risk Factors Associated with Aneurysm Development and Rupture

4.3.1 Hypertension and Smoking

A history of smoking was positive in 24,5% (n = 12), negative in 40,8% (n = 20) and "Unknown" in 34,7% (n = 17) of the patients. Hypertension was present in 55,1% (n = 27), whilst 24,5% (n = 12) were non-hypertensive and 20,4% (n = 10) were "Unknown".

When pairing hypertension and smoking together (Figure 4.8), hypertension was a leading risk factor in the majority of the participants and in all the categories of smoking history. In the smoking "Unknown" category there was an equal number (n = 6) of hypertensives as those "Unknown" to be.

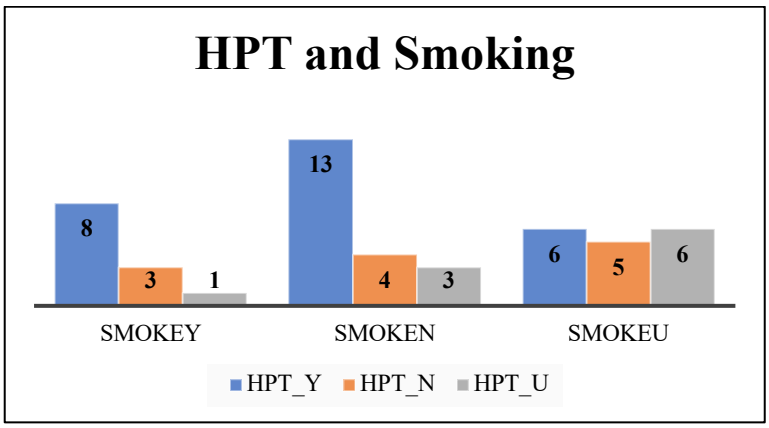
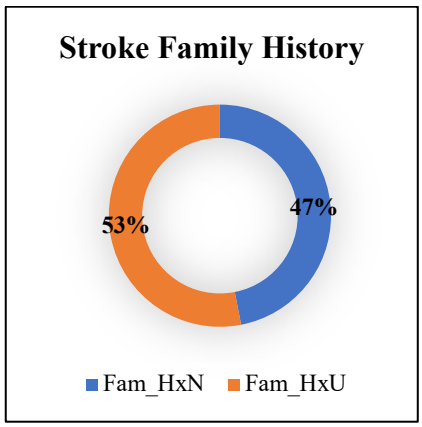


Figure 4.8: Hypertension and Smoking History when Paired Together (shown in numbers). HPT = Hypertension; Y = "Yes"; N = "No"; U = "Unknown".

4.3.2 Family History of Stroke and Hypertension

Figures 4.9(a) and 4.9(b) summarise the characteristics of the family history of stroke in the current study population as well as when family history is paired with hypertension respectively. The family history of stroke was negative in a little more than half of our study population and the rest (including by collateral from their next-of-kin) reported having an unknown family history of stroke. Of those who were hypertensive: 33,3% (n = 9) had no family members who suffered from a stroke; whilst in 66,6% (n = 18) it was not known. In the non-hypertensive group 83,3% (n = 10) reported to have had no family members suffer from a stroke. Lastly, the hypertension "Unknown" group had a 60% rate of unknown strokes occurring in the family.

(a)



(b)

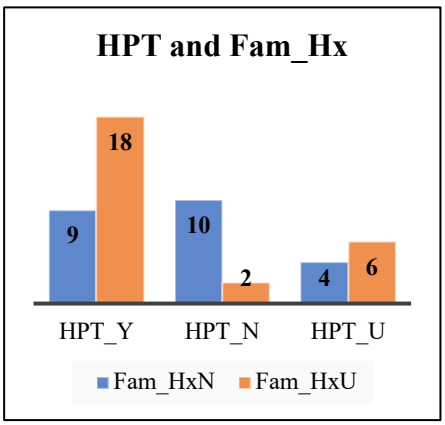


Figure 4.9(a): Family History of Stroke in the Current Study Population (shown in percentages); Figure 4.9(b): Hypertension and Family History of Stroke when Paired Together (shown in numbers). Fam_Hx = Family History; HPT = Hypertension; Y = "Yes"; N = "No"; U = "Unknown".

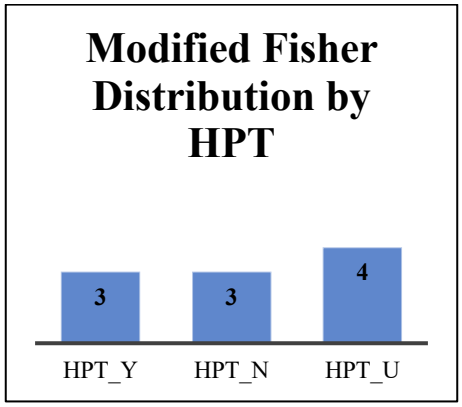
4.3.3 Risk factors in relation to the Modified Fisher score

Figures 4.10(a), (b) and (c) respectively provide summaries of the mean Modified Fisher scores in relation to hypertension; hypertension and smoking paired together; and hypertension and family history paired together.

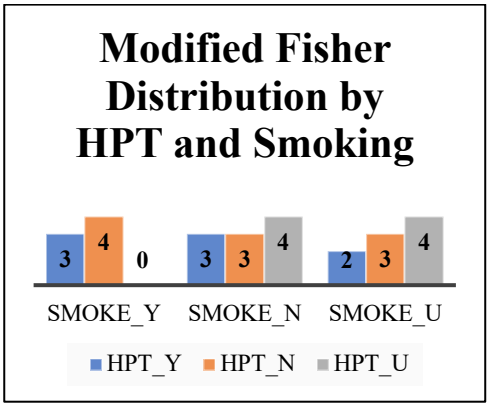
The mean Modified Fisher score by hypertension status was equal (3) in the hypertensive as well as the non-hypertensive groups and highest (4) in those who were undefined ("Unknown"). When pairing hypertension and smoking together, mean Modified Fisher score was highest (4) in the smoking/non-hypertensive, non-smoking/hypertension-unknown, as well as smoking-unknown/hypertension-unknown groups. It was lowest (0) in the smoking/hypertension-unknown group. The hypertensive/smoking-unknown group had a score of 2 and the rest had a score of 3. When hypertension and family history of stroke were paired together, the mean Modified Fisher score was highest (4) in the hypertension-unknown

group regardless of family history of stroke. It was lowest (2) in the non-hypertensive group in whom the history of stroke in the family was unknown. The rest had a score of 3.

(a)



(b)



(c)

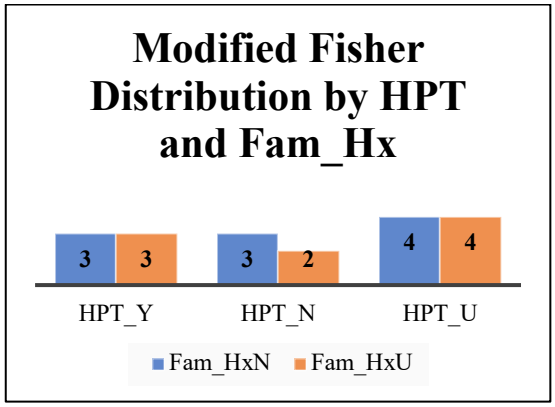


Figure 4.10(a): The Modified Fisher Score Distribution by Hypertension Status; Figure 4.10(b): The Modified Fisher Score Distribution by Hypertension and Smoking Paired Together; Figure 4.10(c): The Modified Fisher Score Distribution by Hypertension Paired with Family History of Stroke. HPT = Hypertension; Y = "Yes"; N = "No"; U = "Unknown"; Fam_Hx = Family History.

4.3.4 HIV/AIDS: A Special Consideration

HIV/AIDS VCT was conducted and only 16 (32,7%) participants consented; 27 (55,1%) refused VCT; and 6 (12,2%) were categorised as "Unknown". Of those who consented, 6

(37,5%) were HIV-positive and 10 (62,5%) were HIV-negative. The mean Modified Fisher score was analysed by HIV status as summarised in Figure 4.11. The score was highest (4) in the HIV positive group, lower (3) and equal in the HIV-negative, "Unknown" and VCT non-consenting groups. When looking at the different groups in detail 70% of the HIV-negative group had a score ≥3, whilst this was the case in 83,3% of the HIV-positive group. In the HIV-unknown group 83,3% had a score ≥3. In the VCT-refusing group 77,7% had a score ≥3.

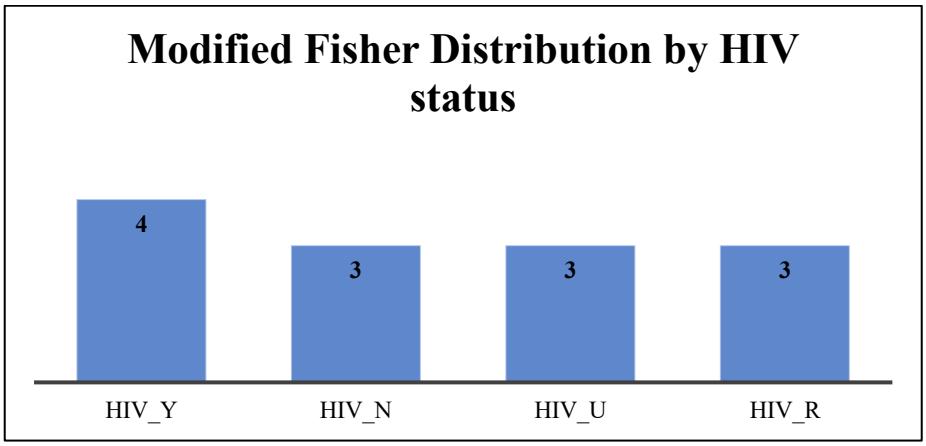


Figure 4.11: The Modified Fisher Score Distribution by HIV Status. Y = "Yes"; N = "No"; U = "Unknown"; R = "Refused".

4.4 Subarachnoid Presentation

4.4.1 Presentation: History Taking

Circumstances surrounding aSAH presentation are summarised in Table 4.1 below.

4.4.2 aSAH Presentation and the Modified Fisher Score

Figures 4.12 and 4.13 below illustrate the relationship between the Modified Fisher scores and sentinel headache and seizures respectively. Of those who reported a sentinel bleed (22,4%; n = 11), 81,8% (n = 9) had a score of 4, the other two having low scores (0 and 1). Of those who reported having no sentinel bleed (38,8%; n = 19), 78,9% (n = 15) had a score of 3 and higher. Of those in the sentinel headache "Unknown" category (38,8; n = 19), 73,7% (n = 14) had a score of 3 and higher.

aSAH Presentation on History							
	N (%)	**Time to Presentation (days): Range; Mean (SD)**	**Compos Mentis: N (%)**	**Collateral (Next-of-kin/legal guardian/none): N (%)**	**Day 5 Status (H&H)**		
					S (%)	**I (%)**	**W (%)**
Sentinel headache (Hx)							
Yes	11 (22,4)	4 – 22; 10,1 (5,8)	7 (63,6)	4 (36,4)	72,7	9,1	18,2
No	19 (38,8)	N/A	6 (31,6)	13 (68,4)	73,7	21,1	5,3
Unknown	19 (38,8)		2 (10,5)	17 (89,5)	57,9	21,1	21,1
Day of Presentation post aSAH							
Day 0	32 (65,3)	0 – 7; 0,6 (1,21)	6 (18,8)	26 (81,3)	65,6	12,5	21,9
Day 1	10 (20,4)		5 (50)	5 (50)	60	30	10
Day 2	6 (12,2)		2 (33,3)	4 (66,7)	83,3	16,7	0
>Day 2	1 (2)		1 (100)	0	100	0	0
Seizures (Hx)							
Day 0 admission	4 (8,2)	0 – 1; 0,25	0	100	50	25	25
Day 5 admission	0	N/A					

Table 4.1: aSAH Presentation on History (Hx) Highlighting the Occurrence of a Sentinel Headache (Bleed); Day of Presentation post aSAH ictus; and Seizure Occurrence. Day 5 Status Refers to Clinical Status by Hunt & Hess Score (compared to Day 0). S = Same; I = Improved; W = Worse.

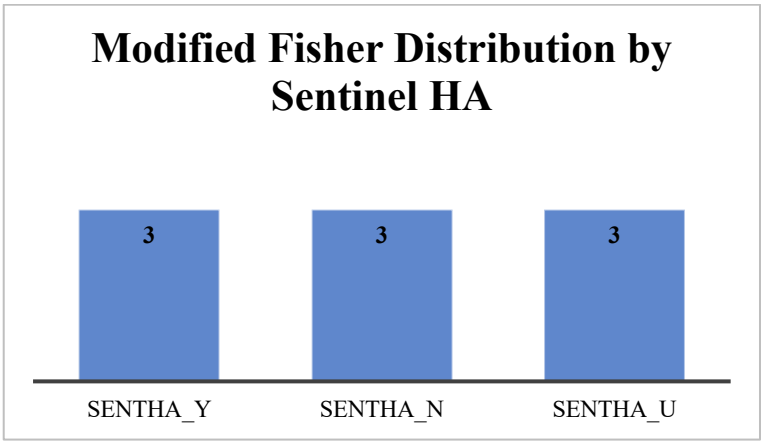


Figure 4.12: Modified Fisher Score Distribution by Sentinel Headache (HA). SENTHA = Sentinel Headache; Y = "Yes"; N = "No"; U = "Unknown".

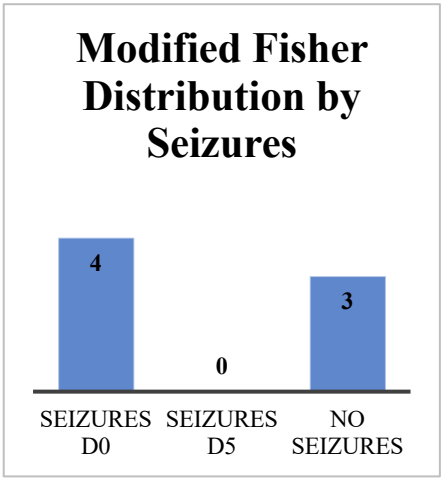


Figure 4.13: Modified Fisher Score Distribution by Seizures. D0 = Day 0; D5 = Day 5.

4.5 Clinical Parameters for Measuring aSAH Severity

The Glasgow Coma Score (GCS), Hunt and Hess score (H&H) and the World Federation of Neurosurgeons score (WFNS) for Days 0 and 5 of admission respectively are summarised in Table 4.2 below; together with the mean Modified Fisher scores associated with these clinical grades as well as the presence of hydrocephalus in each. By Day 5 of the study period 14,3% (n = 7) of the participants had demised; the average time to demise was Day 3 from admission.

aSAH by Clinical Grading Scores

GCS	Day 0: N (%)	Day 5				Modified Fisher D0	HCP D0: N (%)
		Remained the same: N (%)	Improved: N (%)	Worsened: N (%)	Demised: N (%)		
≤8	10 (20,4)	1 (10)	4 (40)	3 (30)	2 (20)	4	6 (60)
9 – 13	16 (32,7)	5 (31,3)	5 (31,3)	3 (18,8)	3 (18,8)	4	11 (68,8)
14 - 15	23 (46,9)	21 (91,3)	0	1 (4,3)	1 (4,3)	3	8 (34,8)

H&H	Day 0: N (%)	Day 5				Mean Modified Fisher D0	HCP D0: N (%)
		Remained the same: N (%)	Improved : N (%)	Worsened: N (%)	Demised: N (%)		
1	5 (10,2)	5 (100)	0	0	0	2	0
2	14 (28,6)	12 (85,7)	2 (14,3)	0	0	3	7 (50)
3	17 (34,7)	8 (47,1)	4 (23,5)	0	5 (29,4)	3	9 (52,9)
4	12 (24,5)	8 (66,7)	2 (16,7)	1 (8,3)	1 (8,3)	4	9 (75)
5	1 (2)	0	0	0	1 (100)	4	0

WFNS	Day 0: N (%)	Day 5				Modified Fisher D0	HCP D0: N (%)
		Remained the same: N (%)	Improved : N (%)	Worsened: N (%)	Demised: N (%)		
1	16 (32,7)	16 (100)	0	0	0	3	4 (25)
2	8 (16,3)	4 (50)	3 (37,5)	0	1 (12,5)	3	5 (62,5)
3	4 (8,2)	2 (50)	1 (25)	1 (25)	0	3	1 (25)
4	17 (34,7)	4 (23,5)	6 (35,3)	3 (17,6)	4 (23,5)	4	13 (76,5)
5	4 (8,2)	1 (25)	0	0	3 (75)	4	50

Table 4.2: A Summary of the aSAH Clinical Grading Scores: GCS, H&H, WFNS. GCS = Glasgow Coma Scale; H&H = Hunt and Hess Score; WFNS = World Federation of Neurosurgeons Score; HCP = Hydrocephalus; D0 = Day 0.

4.6 Radiological Findings

Radiological findings – Modified Fisher score as well as its relationship to hydrocephalus and aneurysm location – are detailed below in Figures 4.14, 4.15 and 4.18 respectively. WFNS score by aneurysm location is also reflected in Figure 4.18. Hydrocephalus was present in 51% (n = 25) of the cases. Aneurysm location was reported in all cases and is summarised in Figure 4.16. A total of 59 singular aneurysms were reported, including each of those that were reported as "multiple" in a single patient. There was also 1 case which was reported as "multiple" aneurysms without defining the locations of those aneurysms; this was labelled Multiple-UD for analysis purposes. From these, eleven aneurysm locations were derived including the Multiple-UD. The eleven aneurysm locations in descending order of frequency were ACoA (22%), R MCA (15%), L ACA 14%, L Pcom (10%), R ICA (9%), L MCA (8%), L ICA (7%), R ACA and VBA (each 5%), R Pcom (3%), and Multiple-UD (2%). Multiple aneurysms (those that were properly defined) were found in 17% of the cases. The lateralisation of the aneurysm locations is summarised in Figure 4.17. MCA and ICA aneurysms had a right sided bias, although this was very slight for the latter. ACA and Pcom aneurysms had a left sided bias. Aneurysm size was reported in 57,1% (n = 28) of the cases and the details are summarised in Table 4.3, together with its association with the clinical and radiological scores of aSAH severity, the presence of hydrocephalus, and mortality rate. The mean aneurysm size was 6,1mm (2,2–21,0mm).

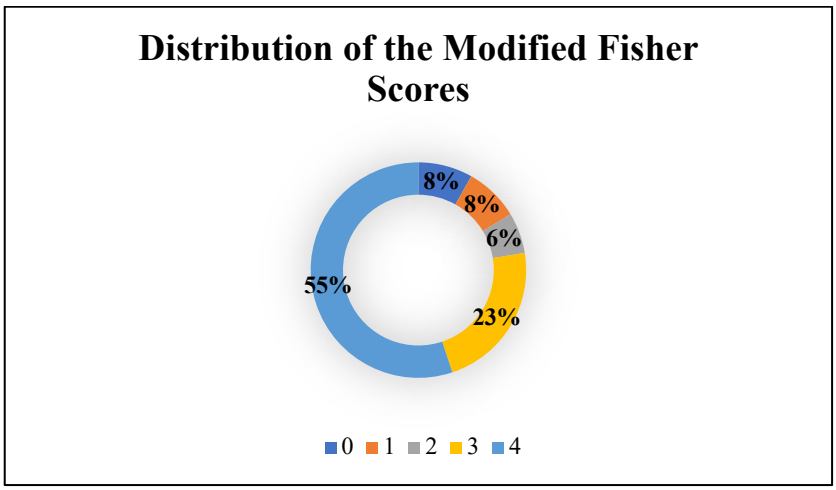


Figure 4.14: Chart Illustrating the Distribution of the Modified Fisher Scores in the Current Study Population.

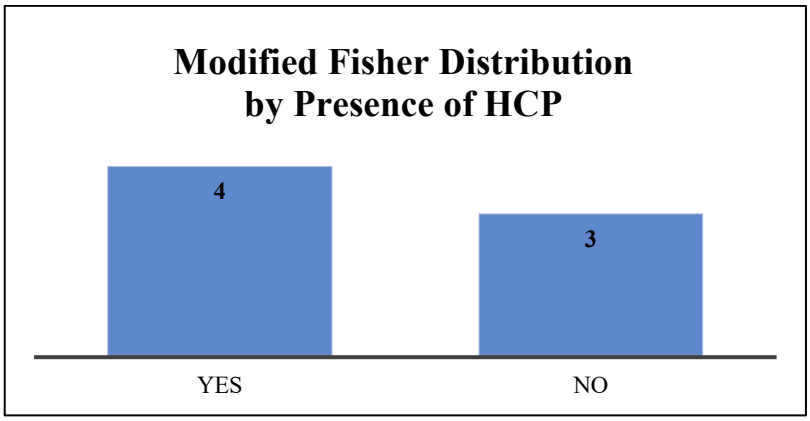


Figure 4.15: The Modified Fisher Score Distribution by Presence of Hydrocephalus (HCP).

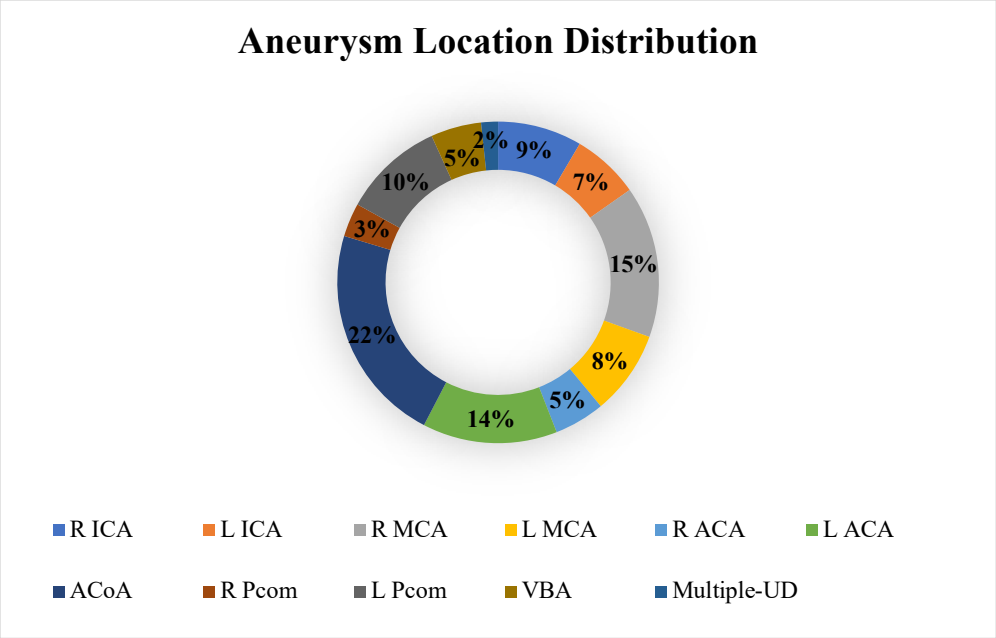


Figure 4.16: Chart Showing Aneurysm Locations by Percentage. R = Right; L = Left; ICA = Internal Carotid Artery; MCA = Middle Cerebral Artery; ACA = Anterior Cerebral Artery; ACoA = Anterior Communicating Artery; Pcom = Posterior Communicating Artery; VBA = Vertebrobasilar arteries; Multiple-UD = Multiple-Undefined.

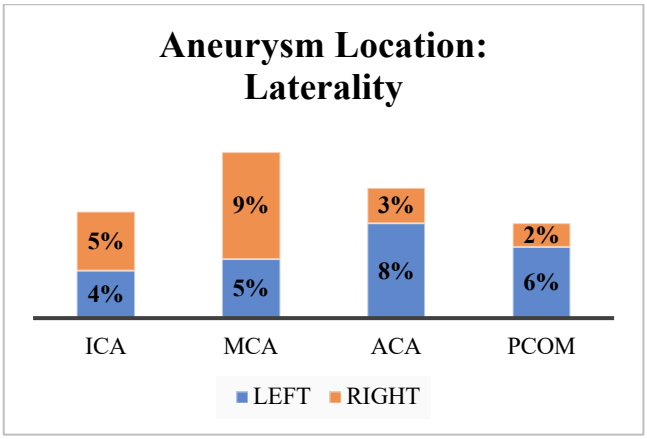


Figure 4.17: Illustrating the Lateralisation of Aneurysm Locations. ICA = Internal Carotid Artery; MCA = Middle Cerebral Artery; ACA = Anterior Cerebral Artery; PCOM = Posterior Communicating Artery.

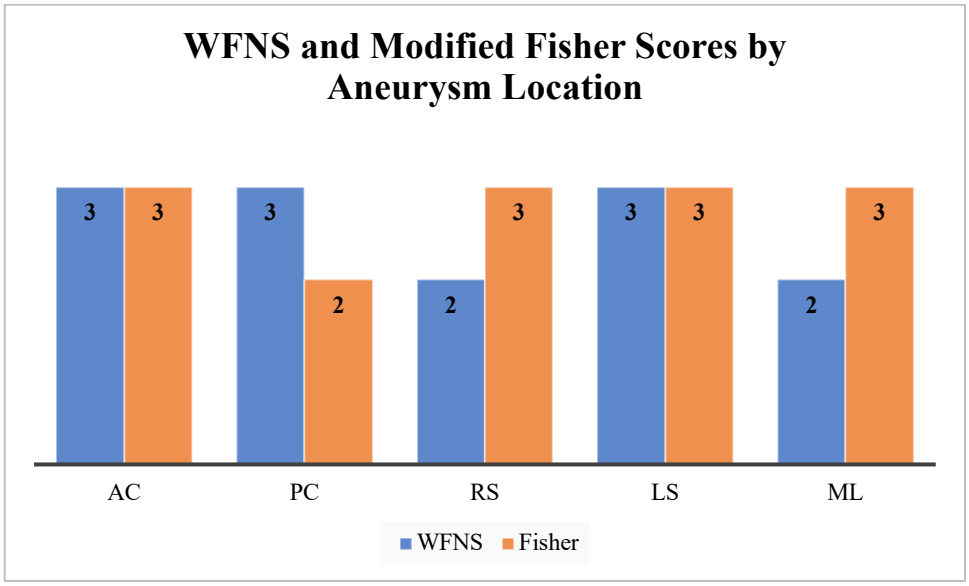


Figure 4.18: WFNS and Modified Fisher Score Distribution by Aneurysm Location. AC = Anterior Circulation; PC = Posterior Circulation; LS = Left Side; RS = Right Side; ML = Multiple.

Aneurysm Size (mm)	**N (%)**	**H&H Score on D0**	**WNFS Score on D0**	**Modified Fisher Score on D0**	**HCP on D0: N (%)**	**Death Rate D0-D5: N (%)**
< 2,5	1 (3,6)	2	1	4	0	0
2,5 – 5,0	15 (53,6)	3	3	4	7 (46,7)	3 (20)
5,1 – 10,0	10 (37,5)	2	2	2	4 (40)	0
> 10	2 (7,1)	4	4	3	1 (50)	1 (50)

Table 4.3: A Summary of Aneurysms by Size and Showing the Associated Hunt and Hess (H&H), World Federation of Neurosurgeons Score (WFNS) and Modified Fisher Scores, Presence of Hydrocephalus (HCP) and Death Rate. HCP = Hydrocephalus; D0 = Day 0; D5 = Day 5.

4.7 Inflammatory Markers and the Hunt and Hess, WFNS and Modified Fisher Scores

4.7.1 Biomarkers

Biomarkers – CRP, ESR, PCT, WCC, Platelets, Albumin - were retrieved and captured from 49 patients for Days 0 and 5 as they presented and aSAH was proven. Table 4.4 below summarises all the biomarker data collected and the success rate thereof. C-reactive protein (CRP) was the central inflammatory marker of interest for the study; ESR, PCT, WCC, Platelets, Albumin were intended for use as surrogate markers so as to provide potential added information. These biomarkers were then tested for correlation to the Hunt and Hess, WFNS and Modified Fisher scores (see section *4.7.2* below).

Biomarkers Retrieved			
Biomarker	**Day 0: N (%)**	**Day 5: N (%)**	**Day 0 and 5: N (%)**
CRP	46 (93,9)	32 (65,3)	30 (61,2)
ESR	18 (36,7)	14 (28,6)	3 (6,1)
PCT	23 (46,9)	15 (30,6)	9 (18,4)
WCC	48 (98)	35 (71,4)	34 (69,4)
Plts	48 (98)	35 (71,4)	34 (69,4)
Alb	37 (75,5)	23 (46,9)	18 (36,7)

Table 4.4: Showing the Biomarkers Retrieved and Captured. CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; WCC = White Cell Count; Plts = Platelets; Alb = Albumin.

4.7.2 Biomarkers and the Clinical and Radiological Scores (Grades)

The assumed independent variables, biomarkers (X_i) CRP, ESR, PCT, WCC, platelets and albumin displayed a very low correlation, as displayed in the correlation matrix in Figure 4.19 below.

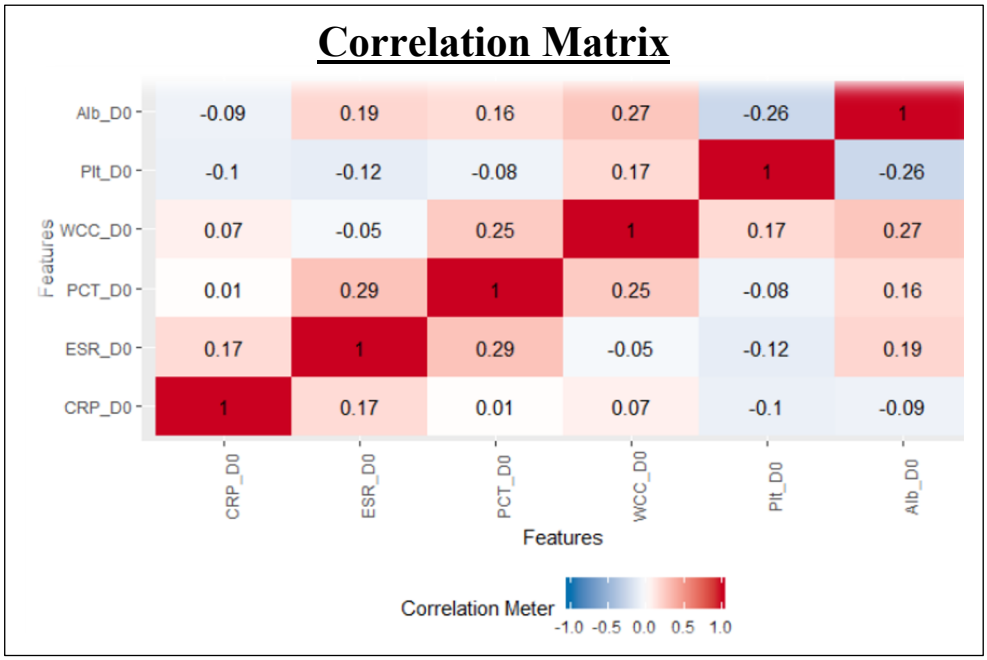


Figure 4.19: Correlation Matrix for Day 0 CRP, WCC, Plt, and Alb. CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; WCC = White Cell Count; Plt = Platelets; and Alb = Albumin.

The results of the regression analyses as well as the graphs comparing the observations in the current study against what would be expected are shown in the Figures below. Figures 4.20 and 4.21 illustrate the regression analysis and comparison graph for the Modified Fisher Score respectively. Figure 4.21 illustrates the comparison (and therefore mismatch) between the Modified Fisher Scores as produced by the statistical model and those produced by the independent variables (the biomarkers) as measured in the current study. The Misclassification error was 0.40816327.

Regression Analysis for the Modified Fisher Score

No.	.rownames	Value	Std.Error	t.value	p.value	Confidence
1	CRP_D0	0.00249062	0.00384151	0.64834279	0.516763262	48%
2	ESR_D0	0.01984221	0.01963192	1.01071176	0.312154407	69%
3	PCT_D0	-1.2309831	1.12939176	-1.0899522	0.275734192	72%
4	WCC_D0	0.12956092	0.0766061	1.69126117	0.090786932	91%
5	Plt_D0	0.00075944	0.00245695	0.30910045	0.757245119	24%
6	Alb_D0	0.04285271	0.01787326	2.39758774	0.016503428	98%
7	0|1	0.15097981	1.1134974	0.13559062	0.892144918	11%
8	1|2	1.03290774	1.06833799	0.96683611	0.333625972	67%
9	2|3	1.51339423	1.07850992	1.40322699	0.160549162	84%
10	3|4	2.90108426	1.15670972	2.50804865	0.012139995	99%

Figure 4.20: Regression Analysis for Day 0 CRP, WCC, Plt, and Alb with the Modified Fisher Score as a Dependent Variable. CRP = C-reactive protein, ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; WCC = White cell count; Plt = Platelets; and Alb = Albumin.

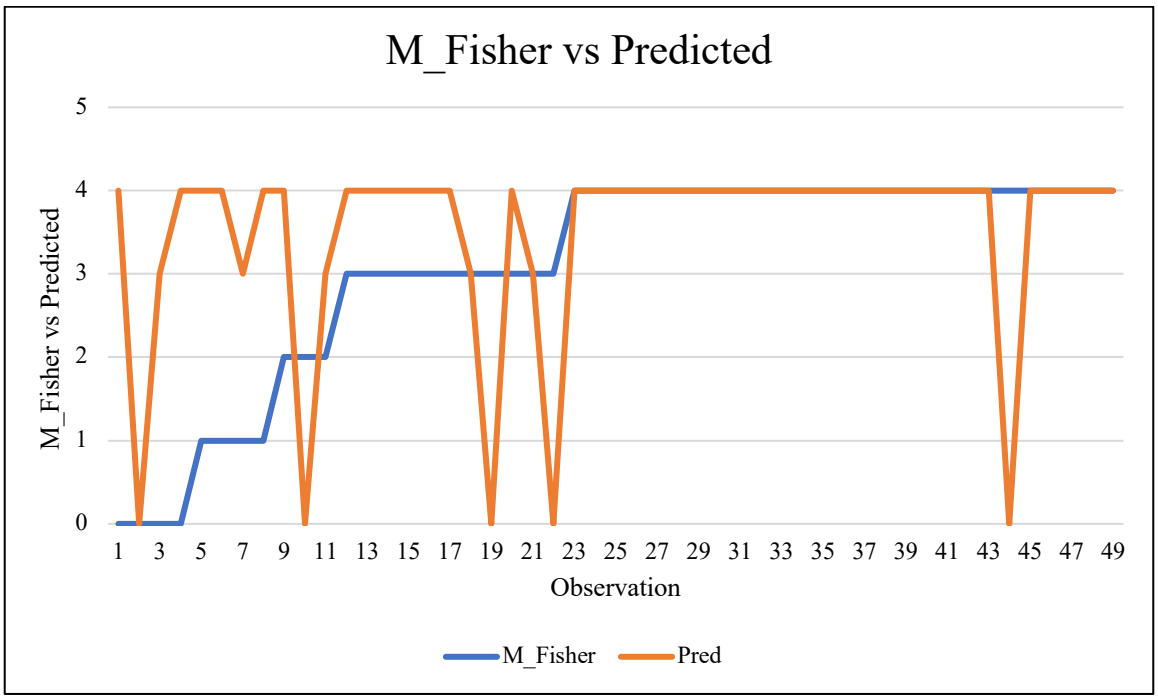


Figure 4.21: A Graph Illustrating the Comparison between the Modified Fisher Score as Expected and the Modified Fisher Scores Produced by the Independent Variables. M_Fisher = Modified Fisher Score; Pred = Predicted.

Figures 4.22 and 4.23 illustrate the regression analysis and comparison graph for the Hunt and Hess Score respectively. Figure 4.23 illustrates the comparison (and therefore mismatch) between the Hunt and Hess Scores as produced by the statistical model and those produced by the independent variables (the biomarkers) as measured in the current study. The Misclassification error was 0.51020408.

Regression Analysis for the Hunt and Hess Score

No.	.rownames	Value	Std..Error	t.value	p.value	Confidence
1	CRP_D0	0.00374044	0.00394406	0.94837184	0.342940188	66%
2	ESR_D0	0.03661437	0.01595594	2.29471792	0.021749295	98%
3	PCT_D0	-0.5971044	1.14046413	-0.5235627	0.60058275	40%
4	WCC_D0	0.03925784	0.05860442	0.66987847	0.502935265	50%
5	Plt_D0	-0.0044931	0.00218964	-2.051977	0.040171897	96%
6	Alb_D0	0.01502278	0.01603411	0.93692654	0.348796347	65%
7	1|2	-2.685169	1.09964923	-2.4418414	0.014612565	99%
8	2|3	-0.6216056	0.97024573	-0.6406682	0.52173829	48%
9	3|4	1.24824253	1.00685338	1.23974608	0.215069328	78%
10	4|5	4.78926834	1.55747729	3.07501647	0.002104909	100%

Figure 4.22: Regression Analysis for Day 0 CRP, WCC, Plt, and Alb with the Hunt and Hess Score as a Dependent Variable. CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; WCC = White Cell Count; Plt = Platelets; and Alb = Albumin.

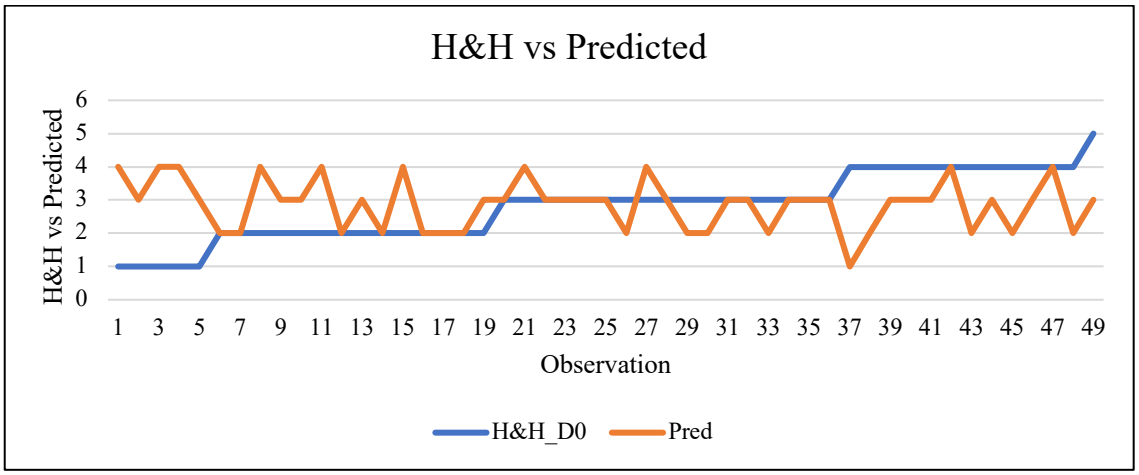


Figure 4.23: A Graph Illustrating the Comparison between the Hunt and Hess Score as Expected and the Hunt and Hess Scores Produced by the Independent Variables. H&H_D0 = Hunt and Hess Score Day 0; Pred = Predicted.

Figures 4.24 and 4.25 illustrate the regression analysis and comparison graph for the WFNS Score respectively. Figure 4.25 illustrates the comparison (and therefore mismatch) between

the WFNS Scores as produced by the statistical model and those produced by the independent variables (the biomarkers) as measured in the current study. The Misclassification error was 0.48979592.

Regression Analysis for the WFNS Score

No	.rownames	Value	Std..Error	t.value	p.value	Confidence
1	CRP_D0	0.00593457	0.00411555	1.44198607	0.149306302	85%
2	ESR_D0	0.03928585	0.01683045	2.33421296	0.019584573	98%
3	PCT_D0	0.06883544	1.35057786	0.05096739	0.959351502	4%
4	WCC_D0	0.02138032	0.05946274	0.35955829	0.719177482	28%
5	Plt_D0	-0.0041668	0.00245323	-1.6984827	0.089416703	91%
6	Alb_D0	0.023915	0.01687393	1.41727488	0.156402576	84%
7	1|2	-0.5754239	1.02993825	-0.5586974	0.57636822	42%
8	2|3	0.30002017	1.02658625	0.29225033	0.770095234	23%
9	3|4	0.70396504	1.03560186	0.67976417	0.496653797	50%
10	4|5	3.50903493	1.19670044	2.93225841	0.003365066	100%

Figure 4.24: Regression Analysis for Day 0 CRP, WCC, Plt, and Alb with the WFNS Score as a Dependent Variable. CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; WCC = White Cell Count; Plt = Platelets; and Alb = Albumin.

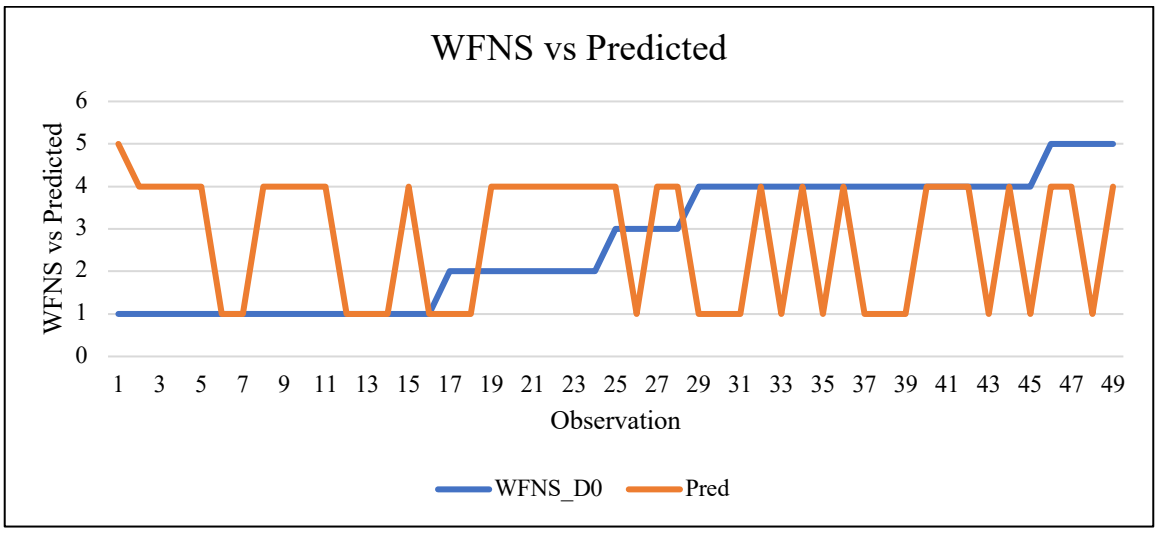


Figure 4.25: A Graph Illustrating the Comparison between the WFNS Score as Expected and the WFNS Scores Produced by the Independent Variables. WFNS_D0 = World Federation of Neurosurgeons Score Day 0; Pred = Predicted.

It was noted that the T-statistic was insignificant for most coefficients in the ANOVA tables for the respective dependent variables (Modified Fisher, Hunt and Hess and WFNS Scores). Added to that were the high misclassification errors in all three regression instances. The lack of data could be a contributing factor to the model being poor, although this may not be the sole reason. The misclassification error remained high after removing the insignificant independent variables (ESR and PCT) under each regression model. There was, therefore, insufficient evidence in this study to reject the null hypothesis. Thus, a significant relationship as hypothesized in the current study, between the dependent variables (Modified Fisher, Hunt and Hess and WFNS Scores) and independent variables (the biomarkers), could not be established.

Also of note is that albumin levels at Day 0 proved to have a significant relationship with the Modified Fisher Score as shown in Figure 4.20 ($p = 0.017$ with CI = 98%) above; while ESR and platelet levels at Day 0 proved to have a significant relationship with the Hunt and Hess

Score at Day 0 as shown in Figure 4.22 (p = 0.022 with CI = 98%; and p = 0.040 with CI = 96% respectively) above; and ESR levels at Day 0 proved to have a significant relationship with the WFNS Score at Day 0 as shown in Figure 4.24 (p = 0.020 with CI = 98%) above. Yet, again it must be emphasised that these findings occurred in the context of very high misclassification errors and therefore when tested did not reproduce a trend (relationship) as expected. A reflection of these trends is summarised by Figures 4.26, 4.27 and 4.28 below.

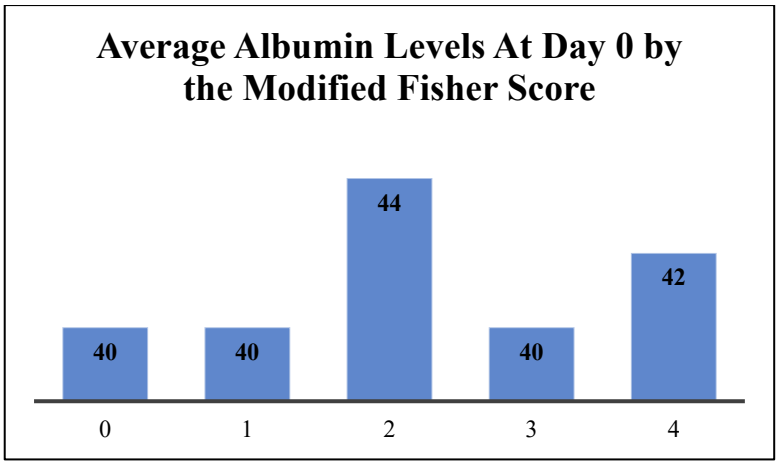


Figure 4.26: Chart Illustrating the Average Albumin Levels in the Blood at Day 0 by the Modified Fisher Scores.

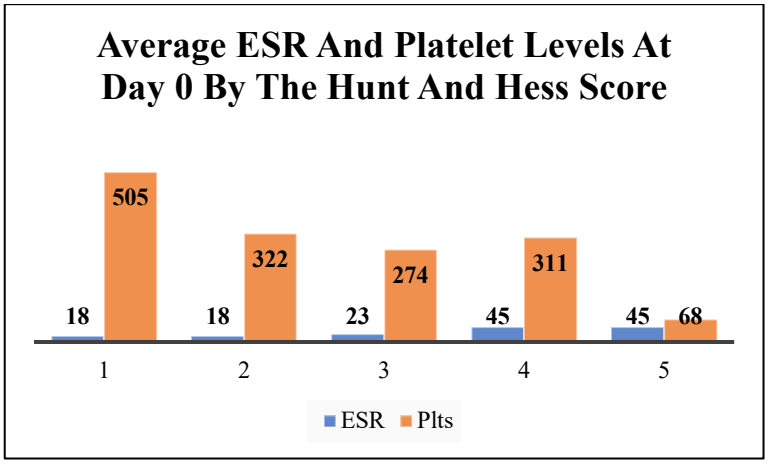


Figure 4.27: Chart Illustrating the Average ESR and Average Platelet Levels in the Blood at Day 0 by the Hunt and Hess Scores. ESR = Erythrocyte Sedimentation Rate; Plts = Platelets.

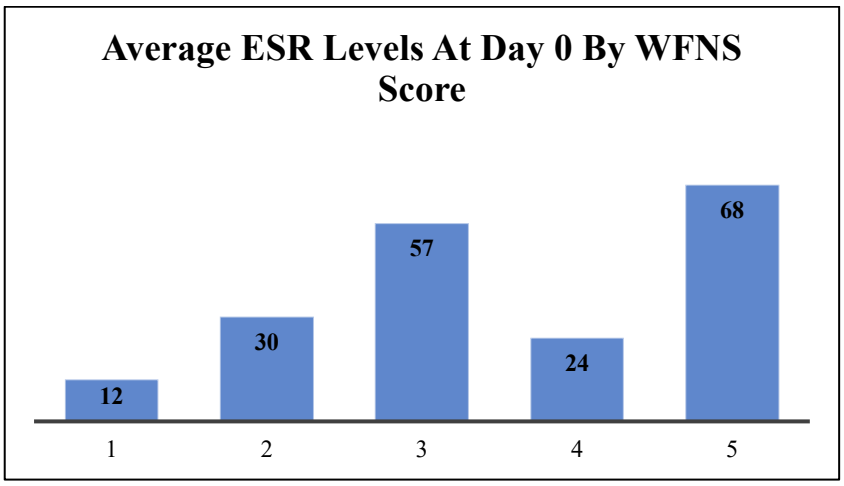


Figure 4.28: Chart Illustrating the Average ESR Levels in the Blood at Day 0 by the WFNS Scores.

Notwithstanding these findings, the biomarkers and their trends in accordance to the respective scores were considered and are contained in Appendix 14. These trends offer some potential insights that could be considered in future studies of a similar nature given adequate sample size and more robust data collection.

CHAPTER FIVE

DISCUSSION

5.1 Study Sample

The sample size (n = 49) for this study was not a large one by global standards, yet is comparable to other studies found in the literature when adjusting for similar study periods.[52,80,111-113] Furthermore, when reviewing the admission registers from the respective hospitals where the study was conducted, the sample size was consistent with the general trend of numbers of aSAH patients who are admitted into the three respective neurosurgical units at any given time. A one-year review – 1 November 2018 to 31 October 2019 – of the admission records from the three neurosurgical units identified a total of 170 aSAH admissions. Apart from time constraints, an added limitation to the sample size was due to incomplete data, particularly the obtaining of all sets of blood investigations that were central to the study.

The composition of the study sample included 45% of the recruits from Chris Hani Baragwanath Academic Hospital (CHBAH), 39% from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and 16% from Helen Joseph Hospital (HJH). This trend was not surprising given the different capacities of the respective hospitals and neurosurgical units – *see Methods section 3.1.1*. While the CMJAH neurosurgical unit bed capacity (n = 20) is only slightly more than a quarter of that of the CHBAH unit (n = 72), and double that of the HJH unit (n = 10), in the current study CMJAH accounted for numbers that are narrowly close to those from CHBAH. This is explained by the fact that CMJAH neurosurgery runs a uniquely high turn-over, fluid system which is designed to allow for the exchange of patients with each

referral from satellite hospitals to make space for new admissions. The CMJAH neurosurgical unit also has an in-house fully capacitated ICU, which the other two units do not have, the operation of which it has full autonomy over. Therefore CHBAH, and in particular HJH, have greater limitations with regards to patient admission turnover.

5.2 Demographic Profiles

5.2.1 Age

The age demographics of the current study population (age range, overall mean age, and the highest absolute number affected by age group) were consistent with what is reported in other studies globally.[13,62,80,82,83,90,93,111] De Rooij et al., however, cited 20 studies reporting aSAH incidence per age category which did not taper after the ages of 45-65 but continued to rise albeit in a plateauing fashion.[83] The lower mean age for males compared to females is also supported in literature.[62,83,93,114] Rubbert et al. reported the mean age for males to not only be lower than that for females, but also lower than the overall mean age.[115] The age distribution of aSAH in this study population showed the most affected age group to be between 41 – 60, followed by those 61 years and older, with those 40 years and younger being the least affected. This is similar to findings by Lieshout et al.[80]

5.2.2 Gender

There was a gender preponderance consistent with previous studies, with females being 1.86 times more affected than males.[62,86,91,93,116-119,123] This is much higher than that reported by Connolly et al. (1.24) but approximates the gender bias reported by Linn et al., Brinjikji et al

and Inagawa et al.[62,81,93] Gender bias within the respective ethnic groups showed African females to be affected 2,31 times more than African males. There was an equal distribution in the Caucasian group and the Indian group had only males. The numbers in the Indian and Caucasian groups were, however, too small to derive any significance regarding gender bias within these ethnic groups.

5.2.3 Ethnicity

The composition of the current study sample by ethnic grouping strongly reflected the socioeconomic realities and ethnic composition of our country.[23-28] Given that the study was conducted at units in the public health sector, it was not surprising that Africans made up the majority of the study population to such a vast extent (88%), with the white population making up only 8% and Indians 4%. Without suggesting that this trend would be much different in the private health sector when considering the general population trends of our country by ethnic grouping, access to private health care may strongly influence it. In their study Brinjikji et al. reported affordability to private health care (by medical aid or self-pay) as a significant factor between patients being treated for aSAH vs unruptured aneurysms; and also found the aSAH group to be from poorer socioeconomic background.[93] Furthermore, Blacks and other non-Caucasian groups in other parts of the world have been shown to be more affected than Caucasians.[62,85,93,121,122] Some authors have attributed the increased risk in Blacks to suboptimal management of hypertension and smoking.[124,125]

The presenting (Day 0) Mean Modified Fisher scores according to age and gender showed an equal gender distribution at age less than 20 and favoured males between ages 21–40. From age 41 and above, however, females had more favourable scores than males. Lai et al. studied

328 consecutive aSAH patients over a period of 7 years and found that presentation Modified Fisher (and Hunt and Hess) scores had no significant gender bias. They, however, did not report on the scores for different age groups as done in this study.[114] Examining data from Fisher et al., notwithstanding their scale being different from the modified one, 37 (out of 47) of their patients were selected for analysis and comparison to the mean Modified Fisher Scores by gender and age of the current study.[68] The 37 were selected strictly to ensure compatibility to the current study regarding the time limits (Day 2 post-ictal) in which the CT-scans were done. Their data revealed no changes in the mean Fisher score (3) by age in the female gender; a change from a score of 2 in everyone below the age 61; and 3 for those 61 and above. Thus, their findings suggest that females at presentation scored worse than the males in the age groups up to 60. This contradicts the findings of the current study. The contradiction, however, cannot be counted as absolute when one considers modifications to the score as well as technological improvements in assessing aSAH. In the early 2000s several authors identified the shortcomings of the original score and produced the modified version which added value in the prediction of DCI.[69,126] They, however, did not highlight associations of age and gender to the Modified Fisher Score.

When pairing gender and ethnicity in assessing the mean Modified Fisher scores, the Indian and Caucasian groups did not have adequate numbers to reveal much of a trend; the Indian group only having two patients and both of them male, and the Caucasian group only having four patients and an equal gender distribution. The African group showed a higher mean Modified Fisher score for males. African females overall had the lowest mean Modified Fisher score. Ayala et al. reported that Black men and women had the highest death rates among patients with aSAH, with Black women having a higher death rate.[94] Howard et al. showed that Black women suffered less fatal strokes compared to their male counterparts for age less than

75years, and that case fatalities increased with age in this population group, whereas for Black males the same occurred, only for the mortality rate to plateau and taper between ages 60-74years.[127] While the current study did not focus on death rates, it is interesting that the presenting mean Modified Fisher scores favoured the patient group (Black Females) which was found in the previous studies as having the highest mortality rate. It is worth noting that the Modified Fisher score is an independent predictor of mortality.

5.3 Risk Factors Associated with Aneurysm Development and Rupture

Given the patient profile of the disease entity (aSAH), and in the current study in particular, history taking and recording of comorbidities (hypertension, smoking, HIV/AIDS) as well as potential family history pertinent to the study were significantly challenged. This was due to various factors including the patients' reduced levels of consciousness at presentation and beyond; poor collateral in terms of availability and quality thereof when available; stigma where habits and comorbidities perceived as negatively affecting one's health are concerned (smoking, HIV/AIDS); and general as well as health education levels. Much of the current study population and their next-of-kin had not even heard of aSAH as a stroke subtype, let alone understanding its pathophysiology.

5.3.1 Hypertension and Smoking

Hypertension and smoking are well known risk factors for all stroke subtypes including aSAH, the control and reversal of which is recommended in an effort to prevent not only aSAH ultimately but primarily aneurysm development.[94,127-133] According to Shinohara et al. coexisting hypertension, and other chronic health problems including those of the respiratory

system, place one at a higher and less favourable clinical aSAH grade.[134] Building on their previous work Feigin et al. reported that hypertension conferred an approximate 2.5x increased risk of aSAH in longitudinal and case-control studies, with a 30% added risk in females.[135] They also reported tobacco smokers (current or former) to be at a two-to-three-fold increased risk of aSAH compared to non-smokers.

Considering the challenges of history taking and data recording alluded to above, it is not surprising that smoking was reported as positive in the minority (24,5%) of the patients. On the other hand, hypertension was reported in more than half of our study population and was a leading risk factor in all the smoking categories ("Yes, "No" and "Unknown").

5.3.2 Family History and Hypertension

Several authors have reported aSAH family history to be a risk factor,[136,137] and one study mentioned that as much as 4% first-degree relatives of cerebral aneurysm patients had aneurysms themselves.[138]

The family history of stroke was negative in a little more than half of our study population and the rest (including by collateral from their next-of-kin) reported having an unknown family history of stroke. It is interesting that none of the current study population reported a positive family history of stroke. This could be sheer lack of knowledge about the health profiles in their families, among other challenges, as alluded to before regarding history taking in our setting. There was also a curious relationship between the family history of stroke and hypertension. Firstly, an almost equal number of patients reported not having family members previously suffer a stroke in both the hypertensive and non-hypertensive groups. Yet, the non-

hypertensive group predominantly reported a negative family history of stroke, whilst the opposite was true in the hypertensive group. It is also interesting that in the hypertension "Unknown" group there was a proportionately higher percentage of a negative family history of stroke. Without making any presumptions in accounting for the "Unknown" factor, it is curious as to whether this could have masked the presence of a family history of stroke in our study population, and therefore its relationship to hypertension.

5.3.3 Risk Factors in Relation to the Modified Fisher Score

A history of hypertension (together with age and clinical grade on presentation) was reported by Rosen et al. to correlate with aSAH volume.[139] They found this correlation significant using data from studies conducted on tirilazad,[140-143] while their own database yielded no significant relationship. The history of hypertension was found in 33% of their study population; it was present in 55,1% in the current study population. While not directly studied against the Modified Fisher score, smoking was reported by Krishnamurthy et al. as significantly associated with delayed neurological deterioration (DND) post aSAH.[144] A history of smoking was found in 67% of their study population (hypertension in 52%); it was only 24,5% in the current study population. Their study yielded a median Fisher grade of 3, whereas it was 4 for this study (with a much smaller sample size). Hammer et al., however, also not looking at direct relations of smoking and hypertension to the Modified Fisher score, reported these comorbidities as being protective against poor outcomes post aSAH, and also suggest that they may alleviate cerebral vasospasm, albeit unclear, of which the radiological score is a strong predictor.[145]

The mean Modified Fisher score in the current study population was not affected by hypertension (when viewed alone); save to say that it tended towards the higher end and was highest in the patients whose history of hypertension was "Unknown" – Figure 4.10(a). It was also highest in the groups in which both hypertension and smoking history were "Unknown"; non-smokers whose history of hypertension was "Unknown"; smokers who had a negative history of hypertension; and in those whose history of hypertension and family history of stroke were both "Unknown" – Figures 4.10(b) and (c). The "Unknown" contributing factor to this observation cannot be explained. The lowest mean Modified Fisher scores were observed in smokers with an "Unknown" history of hypertension; those who had a positive history of hypertension but an "Unknown" history of smoking; and non-hypertensives whose family history of stroke was "Unknown" – Figures 4.10(b) and (c). Apart from the inference that smoking and hypertension seem to have an equal impact on the mean Modified Fisher scores in the current study population, these findings do not have much significance.

When looking at hypertension paired with smoking history and family history of stroke the following observations were made. For hypertensives, a smoking history did not impact on their mean Modified Fisher scores (3) between those with a positive and negative smoking history, whilst hypertensives with an "Unknown" history of smoking had a better score by a point. However, for the non-hypertensives, those with a positive history of smoking had a higher score compared to those with a negative or "Unknown" smoking history. When hypertension was paired with family history, those who had a negative family history of stroke had the same mean Modified Fisher scores (3) whether they were hypertensive or not; and when the family history of stroke was "Unknown" those who had an "Unknown" history of hypertension had a worse score.

5.3.4 HIV/AIDS: A Special Consideration

HIV/AIDS was included opportunely in this study as this disease is prevalent in our community, country and worldwide. Cerebrovascular complications secondary to HIV/AIDS, both ischaemic and haemorrhagic, the latter which is otherwise known as HIV-associated cerebral aneurysmal arteriopathy (HACAA), are also well documented.[145-149] It was thus of reasonable interest to study the relationship between HIV/AIDS and aSAH. Firstly, the well-known challenge in getting HIV/AIDS VCT consent, stigma first and foremost, remains significant.[150-153] This challenge was further compounded by the patient profile for this study, the great majority (if not all) of whom were essentially vulnerable when it come to their ability to consent, due to the very nature of aSAH mostly affecting their level of consciousness, whether briefly or for a period which extended beyond the study period. As such obtaining consent from their next-of-kin was considered an extremely sensitive matter: this route was not pursued.

Notwithstanding the above, approximately a 3rd of the study population consented to HIV/AIDS VCT, with a little more than half refusing (including via next-of-kin), and 12,2% falling into the "Unknown" category. Although not as many as hoped for, a 3rd is a decent sample to make some observations. Firstly, the majority of those who consented were HIV-negative. It could be argued that a (previously known) negative HIV status gives one confidence in consenting VCT. Secondly, when looking at the mean Modified Fisher score by HIV status, the HIV-negative, HIV-unknown, and VCT-refusing groups all had a score of 3, which tends towards severe. Thirdly, the HIV-positive group had the highest (most severe) score of 4. When looking at the different groups in detail 70% of the HIV-negative group had a score ≥3, whilst this was the case in 83,3% of the HIV-positive group. In the HIV-unknown

group 83,3% had a score ≥3. In the VCT-refusing group 77,7% had a score ≥3. Although these findings were not statistically significant, they do point towards the tendency of HIV perhaps negatively impacting on the Modified Fisher score, something to probe further. Data regarding CD4 count, retrieved in only 8,2% of the sample, was too little to derive any observation.

There is not much reported in the literature on the relationship between HIV/AIDS status and the Modified Fisher score. A systemic review by Baaesa et al. which included all cases of HACAA, of which only adults are highlighted herein, revealed a 35,7% mortality rate amongst the adult population, 50% of which was secondary to neurologic complications.[149] They reported a median age of 36,5years, with males accounting for 56,3% of the cases, and a mean period of 4,6 years from time of HIV infection to aneurysm diagnosis.[149] They also reported that 93,8% of the patients had multiple aneurysms, 75% of which were fusiform, 12,5% saccular and 12,5% both; 37,5% cases had coexisting cerebral ischaemic infarction at time of aneurysm diagnosis, and 25% had aneurysms without infarction nor SAH.[149] The median CD4 count was 76 cells/mm^3 with only 18,5% cases having CD4 >200; CD4 was not much different between those who died and those who survived (137,2 vs 126,9).[149] From the existing literature, although no direct correlations have been made of HIV and the Modified Fisher score, it is apparent that a positive HIV status has a negative prognosis in aSAH.

5.4 Subarachnoid Presentation

5.4.1 Presentation: History Taking

A sentinel bleed (headache), which may be a prelude to aSAH proper, and is said to raise the likelihood of early rebleeding 10-fold, is found in 10 – 43% cases.[154-156] In the current study

22,4% experienced a sentinel bleed, within the timeline described elsewhere in literature,[62,157,158] while the majority was equally made up of those who did not experience the headache (affirmative) and those categorised as "Unknown". Of those in whom a sentinel headache was reported, the majority were compos mentis and therefore recounted the history themselves; whereas the no headache and "Unknown" groups showed the direct opposite. This potentially points to the reliability of the symptom when reported by a fully conscious person who suffers aSAH,[159] as well as the lack of certainty that comes with collateral history taking regarding this and any other emergency presentation in general. Furthermore, the majority of the patients remained the same clinically (using Hunt & Hess score), while those reporting a sentinel headache improved the least and those in the "Unknown" category worsened the most.

Time from occurrence of a "thunderclap" headache and seizures to presenting at the emergency department ranged from days 0 – 7 (mean of 0,6) and from days 0 – 1 (mean of 0,25) respectively. This is consistent with findings in literature.[160] Almost two thirds (65,3%) presented on the same day at the aSAH ictus, a fifth (20,4%) a day after, and the rest presenting two days after. Again, the majority remained the same clinically (using Hunt & Hess score), while those who presented on Day 1 post aSAH improved the most, and those who presented on Day 0 worsened the most. Seizures were reported in only 4 cases (8,2%) of the study sample, with three quarters of those presenting within the day of aSAH ictus. This also reflects what has been found in previous studies.[161-166] Half of those in whom seizures were reported remained the same and the other half improved and worsened equally. Ohman cited hypertension as a risk for seizure occurrence in aSAH;[161] in the current study this was not the case as 75% (n = 3) were non-hypertensive and 25% (n = 1) had an "Unknown" hypertension history.

5.4.2 aSAH Presentation and the Modified Fisher Score

The mean Modified Fisher score in relation to sentinel headache was 3 for all categories – "Yes", "No", and "Unknown". Of those who reported a sentinel bleed (22,4%; n = 11), 81,8% (n = 9) had a score of 4, the other two having low scores (0 and 1). Of those who reported having no sentinel bleed (38,8%; n = 19), 78,9% (n = 15) had a score of 3 and higher. Of those in the sentinel headache "Unknown" category (38,8; n = 19), 73,7% (n = 14) had a score of 3 and higher. Therefore, while the group who reported a positive history had a higher occurrence of worst scores, a sentinel bleed was not significantly associated with an improved score in this study.

No seizures were reported for admission Day 5. The mean Modified Fisher score was higher in those who were reported to have had seizures at presentation compared to those who did not (4 vs 3). Rhoney et al. reported that seizure occurrence was associated with cisternal clot thickness; seizures had no negative impact on prognosis regardless of timing; seizures mostly occurred prior to presentation, rarely in-hospital and mostly after 7days post aSAH ictus.[163] In a different study, Butzkueven et al. confirmed that the volume of blood on initial CT scan correlated with seizure onset, but in contrast to Rhoney et al. they reported that seizures negatively impacted on outcome and were a risk factor for late seizures.[164] Lin et al. reported that Modified Fisher scores of and above strongly related to seizures post aSAH, and their findings supported those of Butzkueven et al. regarding late onset seizures as well as long term outcomes (neurological deficits).[165]

5.5 Clinical Parameters for Measuring aSAH Severity

Clinical status at presentation post aSAH (defined by Hunt and Hess and WNFS scores) has been reported as a predictor of early rebleeding.[64-67,167,168] Van Donkelaar et al. highlighted that clinical status is also predictive of the Modified Fisher score.[169] This echoes findings by Rosen et al. that aSAH volume is higher in those presenting with worse clinical grading.[139] Furthermore, they postulate the blood volume to be a surrogate marker of the ruptured aneurysm wall defect size as well as stability, regardless of the clinical status. Last but not least, the other well-established predictors of mortality at presentation are age, loss of consciousness (LOC) at ictus, and admission Glasgow Coma Scale (GCS).[67]

In the current study 73,5% had Hunt and Hess scores ≤3 with mean Modified Fisher scores ≤3; 57,2% had WFNS ≤3 with mean Modified Fisher scores ≤3; 55,1% had GCS ≥13 with mean Modified Fisher scores ≤3. Those who had higher scores (and GCS ≤13) also had the worst Modified Fisher scores (4). A good clinical status is associated with favourable radiological findings (Modified Fisher score) and plays a pivotal role in the decision to treat aSAH urgently.[170] A review by Inagawa, however, reported variable findings with regard to clinical status and its association to angiographic (AV) or symptomatic vasospasm (SV) and DCI.[171] Both the Hunt and Hess and WFNS grades (scores) are reported by many to have "positive" associations with AV, SV and DCI; while only 2 studies have contradicted this thus far and the majority studies showing the associations to be inconsistent.[171] It is interesting that while the clinical grades correlate with the Modified Fisher score, which in turn is a significant independent predictor of AV and DCI, the clinical grades themselves have an inconsistent association with these aSAH sequelae. Nonetheless, both clinical scores remain a significant part of the management protocol(s) for aSAH, together with the radiological score.

The death rate in the current study was 14,3% (n = 7); and the average time to demise was Day 3 from (of) admission. The highest death rate was 20%, 100% and 75% in the GCS≤8, Hunt and Hess 5 and WFNS 5 groups respectively; all of whom had Modified Fishers scores of 4. The rate of hydrocephalus with respect to the clinical grades was highest in the GCS 9-13, Hunt and Hess 5 and WFNS 5 groups (68,8%, 75% and 76,5% respectively); all of whom had Modified Fisher scores of 4. Poor clinical grades, along with delayed hospital management, are said to be risk factors for hydrocephalus post aSAH.[170] Hydrocephalus is discussed again later.

5.6 Radiological Findings

A baseline CT brain scan without contrast continues to be the gold standard in diagnosing aSAH; with the benefits of evaluating the volume and pattern of aSAH and elucidating sequelae such as features of raised ICP as well as hydrocephalus.[62,68,69,172] The sensitivity of CT within the first 72hours post aSAH is reported to approximate 100%, with a steady decline thereafter.[172,173] CTA and DSA are used to demonstrate or exclude aneurysm(s) as causal, with a decent yield of positive results.[134,170,174-183]

5.6.1 The Modified Fisher Score

The Modified Fisher score, an aSAH grading system, is an independent predictor of cerebral vasospasm (CV), delayed cerebral infarction (DCI) and delayed ischaemic neurological deficit (DIND).[68,69] A high (severe) score of 3 or 4 on index CT scan, denoting thick aSAH with or without lateral ventricular haemorrhage, was identified by van Donkelaar et al. as a significant and independent predictor for rebleeding ≤24 hours.[169] In this study the

majority (55,1%) of cases had Modified Fisher scores of 4 (the most severe); followed by those with scores of 3 (23%). Those with Modified Fisher scores of 2 and better made up the rest and were almost equally distributed between scores (grades). It would have been interesting to follow up these patients for a longer period as to determine their long-term outcomes; the current study, however, was purely focused on observations made and data recorded on Days 0 and 5 for the purposes of drawing a relationship between inflammatory markers and the radiological grading.

5.6.2 Hydrocephalus

Hydrocephalus was present in 51% of the cases; and the mean Modified Fisher score was most severe (4) in those who had hydrocephalus compared to those who did not (3). Using the grades of presenting clinical status hydrocephalus was most frequent those with WFNS 4, Hunt and Hess 4 and GCS 9-13. Previous studies have reported a 15-87% presence of acute hydrocephalus post aSAH;[185-191] with shunt-dependency occurring in 8,9-48%.[185-189,191-195] These studies established that hydrocephalus occurred with the more severe Modified Fisher score (between 3 and 4). Poor clinical grades, along with delayed hospital presentation and management, as aforementioned, are also said to be risk factors for hydrocephalus post aSAH.[170] While most authors agree that hydrocephalus is not a risk factor for CV, DCI or DIND post aSAH, a few suggest that it could be a predictor, including Black, who postulates that the relationship between hydrocephalus and CV could be as a result of the CSF-and-vessel-obstructive clot load in the basal cisterns.[171,184] Hydrocephalus is also said to be a risk factor for rebleeding.[134]

5.6.3 Aneurysm Characteristics

5.6.3.1 Aneurysm Location and Implications

Aneurysm location was reported in all cases for this study. A total of 59 singular aneurysms were reported, including each of those that were reported as "multiple" in a single patient. From these eleven aneurysm locations were derived – see *Results section 4.6* above. These were further grouped for comparison with other studies and in descending order of frequency were ICA (29%), MCA (23%), ACoA (22%), ACA (19%) and VBA (5%). Inagawa's 2010 study on ruptured aneurysm location spread, including a review of other studies, reported a community-based aneurysm location spread as ACoA (35%), MCA (26%), ICA (24%), ACA (8%) and VBA (7%).[196-200] Since the current study is a hospital-based one, it is also worth highlighting frequencies from other hospital-based studies, and they also showed similar trends as reported by Inagawa.[196,201-207] Vivancos et al. quoted the following aneurysm location frequencies: ACoA (36%), MCA (26%), Pcom (18%), and ICA (10%); with posterior circulation aneurysms accounting for 9% of all cases, and multiple aneurysms found in 20%.[170] Thus ICA aneurysms were the most frequent in the current study; VBA (vertebrobasilar) aneurysms the least as found in other studies; and ACoA, ACA and MCA aneurysms were in between. ACoA and ACA aneurysms grouped together (41%), as in the study by Inagawa, eclipse those from the ICA and MCA.[196] Multiple aneurysms (those that were properly defined) were found in 17% of the cases.

Aneurysm location is said to have implications on aSAH clinical and radiological scores (WFNS and Modified Fisher scores). Inagawa reported that the percentage of Modified Fisher grade 4 was higher in patients with ICA and ACoA aneurysms than in those with other

aneurysms; grade 3 was higher in patients with MCA and VBA aneurysms; grade 2 was higher in patients with ACA and VBA; and percentage of WFNS grade 5 was highest in those with posterior circulation aneurysms.[196]

Added to that, 5-15% of aSAH patients demise before presenting to hospital,[18,46,88,89,170,208] and the reported rate of sudden death secondary to anterior and posterior circulation aneurysms is 12% and 44% respectively.[209]

The mean WFNS score for the current study was the same for anterior as for the posterior circulation aneurysms (3). It was higher for left sided aneurysms compared to the right sided ones (3 vs 2). Multiple aneurysms yielded a mean WFNS score of 2. The mean Modified Fisher score was higher for the aneurysms of the anterior circulation compared to those in the posterior circulation (3 vs 2). Laterality of aneurysm location had no impact on the mean Modified Fisher score in this study. Aneurysms of multiple location also had a mean Modified Fisher score of 3. Thus, aneurysm location in the current study did not mirror the trends reported in literature. This could potentially be owed to the small study sample.

5.6.3.2 Aneurysm Size and Implications

A large aneurysm size is known to increase aSAH mortality and risk of rebleeding.[95,126,168,169,210-215] A study by Lantigua et al. showed mean aneurysm size related to mortality was 10mm (range: 6 – 15mm); with the highest percentage of mortality (45%) in those with Modified Fisher 4.[95] There has been much debate regarding aneurysm size and the resultant SAH on CT, as well as whether size is a predictor of CV, DCI and DIND.[171] Some authors have postulated that smaller sized aneurysms yielded more severe SAH,[217-220] while

others demonstrated the opposite,[216] added yet to findings that rupture of larger sized aneurysms produced a poorer clinical status.[217,218,221]

Aneurysm size was reported in 57,1% of the current study population. When categorised according to size the majority (53,6%) were between 2,5 – 5,0mm; followed by 35,7% that were between size 5,1 – 10,0mm; and those <2,5mm and >10mm were the least frequent. The mean Hunt and Hess and WFNS scores were highest for aneurysms >10mm; followed by those of aneurysms between 2,5 – 5,0mm. Mean WFNS was lowest for aneurysms <2,5mm. The mean Modified Fisher scores were highest (4) for aneurysms <5,0mm, followed by those of aneurysms >10mm (3). They were lowest (2) for aneurysms between 5,1 – 10mm in size. The presence of hydrocephalus was highest (50%) in those with aneurysms >10mm, followed by those with aneurysm size 2,5 – 5,0mm, and then 5,1 – 10,0mm. Aneurysms <2,5mm had no hydrocephalus. The Day 5 death rate was highest (50%) for aneurysms >10mm, followed by those between 2,5 – 5,0mm (20%). The rest had zero mortality.

The findings in this study were contradictory as patients with larger sized aneurysms presented with the most severe clinical condition (Hunt and Hess; WFNS Scores) yet did not have the worst SAH (Modified Fisher Score). In contrast, those who had smaller sized aneurysms presented with the worst radiological score and the best clinical scores.

5.7 Inflammatory Markers and the Hunt and Hess, WFNS and Modified Fisher Scores

Inflammation (neuroinflammation) has been demonstrated to play a vital role in the pathophysiology and prognosis post aSAH.[98-101] Previous studies have considered various inflammatory processes and cascades that ensue as a result of aneurysmal rupture, including

how inflammatory markers could provide insights into the pathophysiology of aSAH;[50-55,97] none had looked at inflammatory markers in relation to clot volume as assessed on the CT scan. The current study sought to investigate whether a relationship existed between the level(s) of inflammatory markers in the blood and aSAH as graded clinically by Hunt and Hess and WFNS Scores; and particularly whether a relationship existed between these markers and the radiological Modified Fisher Score assessed on a CT scan done on presentation.

C-reactive protein (CRP) was the central inflammatory marker of interest for the current study; ESR, PCT, WCC, Platelets, Albumin were intended for use as surrogate markers so as to provide potential added information and aid in resolving or excluding other contributory factors such as concomitant systemic inflammation. CRP, along with other inflammatory markers, has been associated to outcome after SAH.[70-79] Several authors have reported on CRP levels (both in blood and CSF) and their associations to CV, DCI, DIND, and outcomes at patient discharge.[103-108] The direct role of CRP in SAH, however, remains largely undefined: whether CRP invades the central nervous tissue causing direct insult or is merely a systemic marker of SAH severity is unknown. Moreover, it is not clear if CRP reliability in predicting SAH outcomes is impacted by confounding complications such as lower respiratory infections, cardiac and other complications.

Also associated with inflammation in SAH, but not outcome, is procalcitonin (PCT).[102] More recently, Kapoor et al. prospectively investigated the value of nutritional biomarkers including albumin in SAH prognosis. They reported that albumin decreased in the first week post aSAH and that lower serum albumin values at presentation were predictive of poor outcome as defined by neurological deficits (52% vs 20%), infarction (35% vs 23%), mortality (28% vs 16%) and unfavourable Glasgow Outcome Score (GOS) (38% vs 25%).[109]

All biomarkers – CRP, ESR, PCT, WCC, Platelets, Albumin - were retrieved and captured from 49 patients for Days 0 and 5 as they presented and aSAH was proven on CT and CTA. These were then tested for correlation to the Hunt and Hess, WFNS and Modified Fisher scores as described in *section 4.7.2* of the Results. Firstly, despite protocols being distributed at the Emergency Departments as well as among other relevant departments (including ICU, High Care and general wards) and colleagues from the three recruiting sites, it was very challenging to obtain all blood investigations needed for the study. To this end, blood samples for Day 5 were less successfully obtained; ESR and PCR were the least successfully obtained. The challenges encountered began with the drawing of blood (appropriate time as per study protocol, sampling tubes, adequate volumes, specimen labelling) and spanned to the challenges on the side of the NHLS (logging of correct details, specimen reported as lost, inadequate volumes, and gate keeping, among others).

According to statistical regression performed with the Hunt and Hess, WFNS and Modified Fisher Scores as dependent variables, testing for an association between the biomarkers (independent variables) and these showed that in the current study there was insufficient evidence to prove that an association existed between the biomarkers and the clinical and radiological scores. There were findings, however, of significant relationships, albeit in the context of high misclassification errors, rendering these relationships somewhat questionable. Albumin levels at Day 0 proved to have a significant relationship with the Modified Fisher Score; while ESR and platelet levels at Day 0 proved to have a significant relationship with the Hunt and Hess Score at Day 0; and ESR levels at Day 0 proved to have a significant relationship with the WFNS Score at Day 0.

Low serum albumin levels (alone and when used with the Modified Fisher Score) have been reported to be predictive of poor outcome post aSAH.[109] Although Day 0 albumin proved to have a significant relationship with the Modified Fisher Score in this study, there was no clear distribution of albumin-level thresholds between the different scores (see *Figure 4.26* in Results section).

High levels of ESR in the blood have been reported to associate with DCI post aSAH; this implicating systemic inflammation as a contributor to DCI.[226] In this study increased levels of Day 0 ESR in the blood were associated with increased Day 0 Hunt and Hess Scores. There seems to be a threshold change in the levels of ESR between the low (1 and 2), moderate (3) and severe (4 and 5) scores (see *Figure 4.27* in Results section). A similar trend of a directly proportional relationship between Day 0 ESR and Day 0 WFNS Scores was observed, although it was also not perfectly linear (see *Figure 4.28* in Results section).

The significance of platelets, both as a consequence of aSAH and the role they play in contributing to worse outcomes in stroke, CV and DCI, has been reported by several authors.[99,222-225] In this study the level of platelets at Day 0 demonstrated an indirectly proportional relationship with the Hunt and Hess Scores at Day 0.

5.8 Limitations of The Study

i. Time constraint was a major limitation for this study. A longer time period would have yielded a greater number of recruits, resulting in a larger sample size and a much-improved statistical analysis.

ii. Record keeping remains a significant constraint towards realisation of better health care by way of both service delivery and research. Despite the study protocol being issued to different and strategic departments (Emergency Medicine, Internal Medicine, Neurology, and Neurosurgery), recording of pertinent information, particularly coming to the history taking, was not optimal.

iii. Although standardised clinical grading tools for aSAH were employed – namely the GCS, Hunt and Hess and WFNS Scores – the application of these across the different disciplines involved in patient care and referral was subject to interobserver error.

iv. Patient records (bed letters and radiographs) were also lost between the hospital wards, registries as well as mortuaries where relevant, this resulted in a significant number of patients being excluded from the study due to lack of complete information.

v. Data capturing, and recording, also had limitations where the National Health Laboratory Services was concerned. Patient names and/or hospital codes would often be misspelled (or have numbers missing) leading to incomplete or missing blood/serological results, and otherwise a great difficulty in retrieving them. A number of blood results were also not obtained due to samples being reported by the NHLS to be "clotted", "inadequate/insufficient" or rejected for "gatekeeping" and other obscure reasons.

vi. The most limiting challenge was that of successfully obtaining blood results for both Day 0 and Day 5 in all patients. The most lacking biomarkers to obtain in the study were ESR and PCT.

vii. Capturing data from the three different centres was difficult as they work in a non-standardised fashion, each with its own challenges when it comes to patient referrals, screening and admission. The three centres also function on an individual basis, not connected to each other by way of any electronic gateway/portal system(s). This would have greatly assisted towards a more centralised data pool as well as a more standardised

manner of screening and recruiting participants for the study, and therefore a simpler manner of ensuring that the objectives detailed by the study protocol were achieved with greater efficacy.

viii. Location was also a significant limitation as the index hospitals for the study are all located in Johannesburg, which is often a good distance away from the lower level (district) hospitals that need to refer patients with aSAH. This often resulted in delayed referrals and therefore exclusion of patients from the study.

ix. Limiting the study to these specialised centres also may have limited generalisability and conferred some sampling bias. It also meant that the vast majority of patients being recruited were more severely affected than may be found in the general population; this also limited the scope of observing a sample more representative of the local population in general.

x. The scarcity of resources was also a great limitation from various aspects: the departments of radiology in each of the hospitals where the study was conducted face a paucity of properly functioning CT scan machines, not to mention the extra burden of having to provide CT scan services for patients referred by peripheral hospitals which lack these. The CT scan services have to be shared with a great number of other patients including those from general medicine and trauma. This resulted in delayed scanning of patients which meant exclusion from the study.

xi. Initial CT scans of some of the patients were done at the referring (peripheral) hospital(s) and this may have impacted on the quality of interpretation of the Modified Fisher Scores.

xii. The author reviewed all of the files, which had information pertaining to the study, and this could potentially confer bias in the capturing and recording of data.

xiii. Although the author enlisted two neutral contributors in the interpretation of CT scans (one from Neurosurgery and another from Radiology), there remains potential bias in reporting

and interpretation thereof. Interobserver variation, or convergence, could have resulted from conflicting interpretations where contributors were from different disciplines or from the same discipline respectively, leading in reporting bias somewhat.

xiv. Literacy and language barrier were significant limitations, not only regarding the basic elements of history taking, but also understanding of the disease entity that the participants (and/or their next-of-kin) were admitted and treated for, and also due to the complexities of aSAH and how this study sought to contribute.

xv. HIV/AIDS remains a stigma in our country and community. This significantly limited the attainment of potential gains not only towards better care for HIV positive patients, but better care for patients with HACAA.

xvi. Last but not least, the socioeconomic demographics of our country confer a racial bias in our study, as a great majority of patients who seek health care in the public sector (where the study was conducted) are the poor and previously disadvantaged who are invariably black.

CHAPTER SIX

CONCLUSION

Stroke, and aSAH in particular, remains a significant contributor to the global burden of disease; despite the large body of work that has gone into improving the prevention, exigent diagnosis and management thereof, including rehabilitation programs post hospital discharge. It has now been positioned as a separate category as a major non-communicable disease, with significant impact on global health as well as economic development, unlike previously being included within the 'cardiovascular diseases' group. It is particularly impacting as it affects persons at their peak age of productivity.

This study sought to investigate – and contribute towards – the events that occur in the acute phase of aSAH by probing the trend of acute inflammatory markers in the blood and whether they would be associated with the severity of aSAH. There was insufficient evidence in this study to prove an association between the level(s) of inflammatory markers in the blood and the severity of aSAH as graded clinically by the Hunt and Hess and WFNS Scores; and radiologically by the Modified Fisher Score. In particular, there was insufficient evidence to prove the relationship of CRP levels in the blood to aSAH severity as assessed by the Modified Fisher, Hunt and Hess and WFNS Scores. The inflammatory marker that proved to be associated with aSAH severity by Modified Fisher Score was Albumin; with ESR and Platelets together having an association with the Hunt and Hess Score; and ESR alone having an association with the WFNS Score.

The findings in this study make a case for the potential of albumin, ESR and platelets to be included in the admission and treatment protocols for patients presenting with aSAH. This information can be used synergistically to reinforce urgent referral and/or transfer of persons suffering a "thunderclap" headache (with potential aSAH) to specialised centres that have facilities to urgently diagnose and treat aSAH – particularly from peripheral centres that lack adequate facilities such as a CT scan machine.

The age and gender demographics in this study were consistent with those found in literature internationally. Racial and ethnic demographics were skewed by the nature of health care organisation and administration in our country – South Africa – as well as availability and access thereof. As such the racial demographics were skewed towards the black population.

As with the analysis concerning the inflammatory markers, there was not sufficient evidence to significantly probe the risk factors involved in aSAH: hypertension, smoking, family history of stroke and HIV/AIDS. These were reported nonetheless as they constituted the descriptive part of the study and their presence ranged from approximately a quarter to just over half of the study population (smoking and hypertension respectively). In the local context health education remains minimal, including knowledge of one's family history of disease. This made family history of stroke near impossible to probe, with no positive findings.

HIV/AIDS and its complications, as well as how it intersects with other comorbidities, should always be considered in the local setting. This, however, comes at a great cost of first having to overcome the stigma attached to the condition. Addressing this will always yield greater benefit not only to those found positive, but to society at large. In this study a higher percentage

of the HIV-positive group had worse Modified Fisher Scores compared to those in the HIV-negative group.

aSAH presentation – sentinel headache, seizures and time to presenting to hospital post ictus – was largely acute and consistent with what is reported internationally. Sentinel headache (or knowledge thereof) was not associated with the Modified Fisher Score in this study; while those who reported seizures at presentation had worse scores compared to those who did not. These findings were, however, not statistically significant.

Radiological investigations and their findings were of optimum reliability in this study. The grading of aSAH and the reporting of aneurysms were precise and the general findings (trend) mirrored that which is reported internationally.

Given more time and resources a more robust and collaborative, interdisciplinary, study of this nature would yield invaluable information that could be used to formulate protocols in urgently diagnosing and treating aSAH patients, including expedient referral from the peripheral centres to the more capable neurological and neurosurgical units.

RECOMMENDATIONS

i. A longer (continued) study period in order to achieve a larger sample size, with specifically CRP, WCC, PCT and albumin as biomarkers of interest.
ii. An extended study period that incorporates mid to long-term outcomes, including withdrawing blood samples at more intervals per patient in order to attain a trend that is more than two occasions, and also comparing these to clinical and radiological outcomes at 6-12 months.

iii. A pilot study would be a good start in order to give the referring departments more time to become more consistent in implementing the study protocol.

iv. The respective departments and hospitals involved in treating stroke patients should develop a sustainable electronic registry of neurovascular conditions, particularly aSAH, that would log and keep records pertinent to stroke and its subtypes.

v. A national register of cerebrovascular diseases should become of our priority goals in order to induce research that actively seeks to solve these conditions in our country.

vi. Sustainable and secure electronic networks/gateways between the tertiary (academic) and referring (peripheral) hospitals for better streamlining of patient information such as clerking notes as well as investigations completed at the referral facilities.

vii. Improved arrangements with the NHLS regarding blood sample reporting and "gate keeping" protocols, particularly for investigations that are close to one another timewise.

viii. Enlisting at least one private health care facility in an attempt to introduce broader socioeconomic representation in the study, both from the patient as well as from a health care facility point of view, thus gaining broader understanding of the general population. This would also enable the study to probe socioeconomic issues including those of resources and logistics, education, literacy and health care affordability.

ix. Usage of different media in availing and creating better access to education and information about stroke subtypes, their prevention and treatment; catering for the different official languages in South Africa.

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APPENDICES

Appendix 1: The Hunt and Hess Score (Scale)

		% DIND (Clinical Vasospasm) Associated with each Grade
Grade 1	Asymptomatic, or minimal headache; slight nuchal rigidity	22%
Grade 2	Moderate to severe headache, nuchal rigidity; no neurological deficit (apart from cranial nerve palsy)	33%
Grade 3	Drowsiness, confusion, or mild focal deficit	52%
Grade 4	Stupor, moderate to severe hemiparesis, possible early decerebrate posturing	53%
Grade 5	Deep coma, decerebrate posturing, moribund	74%

Appendix 2: The WFNS (World Federation of Neurosurgeons Score)

Grade	**GCS Score**	**Motor Deficit**
I	15	Absent
II	13 or 14	Absent
III	13 or 14	Present
IV	7-12	Present or absent
V	3-6	Present or Absent

Appendix 3: The Fisher Score

Grade	Blood on Non-contrast CT scan
1	No subarachnoid blood detected
2	Diffuse or vertical layers < 1mm thick*
3	Localised clot or vertical layers ≥ 1mm thick
4	Intracerebral or Intraventricular clot with diffuse or no subarachnoid haemorrhage

* "Vertical" cisterns: interhemispheric, insular, ambient

Appendix 4: The Modified Fisher Score (Scale)

Modified Fisher Grade	Blood on CT	Symptomatic Vasospasm Associated with each Grade
0	No SAH or IVH	
1	Focal or diffuse thin SAH, no IVH	24%
2	Focal or diffuse thin SAH, with IVH	33%
3	Focal or diffuse thick SAH, no IVH	33%
4	Focal or diffuse thick SAH, with IVH	40%

Appendix 5: Study Protocol

Attention Emergency Unit Doctors!!!

For all patients presenting with and proven to have aneurysmal subarachnoid haemorrhage on CT brain scan as well as CT angiography, please do the following at the time of presentation:

1. Note clearly the patient's presenting GCS
2. Note clearly the patient's presenting neurological deficit(s)
3. The following bloods:
    a. U&E
    b. FBC
    c. Albumin
    d. CRP
    e. ESR
    f. PCT
    g. INR & PTT

Dept of Neurosurgery

Appendix 6: Information Sheet (Participant)

STUDY INFORMATION DOCUMENT

Study title:

In the context of aneurysmal subarachnoid haemorrhage (aSAH), increased level of serum inflammatory markers is associated with a higher modified Fisher score and a worse WFNS and Hunt and Hess Score.

Greeting

Good day sir, madam. Thank you for taking the time to consider this invitation.

Introduction:

I, Dr Morena Nthuse Mpanza, am conducting research on cerebral aneurysmal bleeding, otherwise known as a bleeding stroke, and in the event of which, am investigating the relationship between the volume of blood that leaks into the brain, as interpreted from the brain scan, and the level of inflammation marker in the blood called CRP. Research is a process used in seeking new knowledge.

In this study we want to learn whether there is a relationship between the two above-mentioned, as well as the strength of the relationship. If the relationship is proven to exist and is strong, it could assist in selecting and prioritizing patients, including at the peripheral hospitals, for more urgent transfer towards our specialized centers of care. It will also help in predicting outcome. It will do so by enabling the attending doctors to undertake blood tests measuring the inflammation marker (CRP), which is easier to do and less harmful to the patient. Blood tests are also more accessible whereas CT-scan machines may not be available at the peripheral hospitals. Thus, the blood results will guide urgency of transfer in the absence of the scans, particularly in the early period of suffering the bleed (as manifest by a specific type of – “thunderclap” – headache).

These blood tests and scans already form part of the treatment of patients with bleeding stroke. By consenting to participate in this study, you will not be subjected to anything that is not already done for a patient who suffers a bleeding stroke.

Invitation to Participate:

We are inviting you to take part in this research study.

What is involved in the study.

1. When the patient (you) arrives and is admitted at our institution for a suspected bleeding stroke, s/he will undergo the regular tests as mentioned above, namely:
    a. basic screening blood tests as well as tests for the inflammation marker CRP; these blood samples will be a tablespoon or two full, taken on the day of admission and on Day5 of admission;
    b. a CT-brain scan to prove / or disprove a bleeding stroke; and
    c. a CT-brain angiogram which studies the vessels to prove / or disprove the presence of a cerebral aneurysm (abnormal stretching of a blood vessel).

    Notwithstanding the results of these tests, nor the decision to participate in this study, you, the patient will be treated according to standard international protocol(s) for the management of bleeding stroke.

    The results of the above, together with information from the patient bed letter (file), will be collected and collated for the purposes of this research. Information from the bed letter will only include the following:
    - ✓ Age, Gender, and Ethnicity;
    - ✓ History of smoking and / or hypertension;
    - ✓ HIV status where you have been informed and voluntarily consented to HIV testing; refusal for HIV testing does not disqualify you from the study, nor does it from proper and standard health care;
    - ✓ History of a ("thunderclap") headache
    - ✓ History of seizures
    - ✓ The status of the patient's wakefulness on examination, as well as whether they have suffered any neurological deficits (weakness)

    Once collected, all this information and results will be statistically tested to investigate the relationship we seek to investigate as stated above.

2. The study will be conducted over a period of three to six months, or until a sufficient patient group size (30-40 persons) is recruited.

Risks of being involved in the study:

There is no added risk in participating in the study, as it has been detailed above that the procedures to be undertaken, should you agree to participate, are standard and only observational in nature, and will not affect your care in any negative manner.

Benefits of being in the study:

There is no direct benefit to you from this study. The long-term objective is the possibility of better treatment for subsequent patients, as stated above.

While involved in the project and after the results are available, you will be given pertinent information on the study.

Your Participation is voluntary

Refusal to participate will involve no penalty or loss of benefits to which you are entitled. You may choose to discontinue participation at any time without penalty, or loss of benefits to which you are otherwise entitled. There is no requirement for you to provide a reason for withdrawing and any data collected in such an instance will in default be destroyed, unless you specifically consent to its retention.

Confidentiality:

Normally, all personal information will be treated in the strictest confidence and will only be available to me, the Principal Investigator (PI), and my Supervisor. The only exceptions - and all of them are rare - would normally be:

1. personal information may be disclosed if required by law
2. the Human Research Ethics Committees of the University may exceptionally require personal data to respond to a formal complaint, or for a compliance audit
3. the South African Health Products Regulatory Authority (SAHPRA), which is the successor body to the South African Medicines Control Council (SAMCC), might conceivably require access to personal data, if conducting an investigation into a drug trial

All data collected in the course of the study will be securely retained for two (2) years if a scientific publication arises from the study and six (6) years if there is no publication. Thereafter it will be destroyed accordingly.

Anonymity

Your anonymity in the study will be safeguarded by usage of codes that de-link your identification information from the information we wish to collect and use as stated above.

Contact details of researcher/s:

Principal Investigator: Dr MN Mpanza
Cell: 0637747195
Email: n2se@yahoo.com

Supervisor: Dr C Profyris
Cell: 0739032114
Email: c.profyris@gmail.com

Outputs

The envisaged outcome of this study will be the knowledge of whether a relationship exists between the blood volume that leaks into the brain in the event of a bleeding stroke, and the blood inflammation marker CRP. These results will be shared with you upon completion of this research.

Contact details of HREC administrator and chair – for reporting of complaints / problems.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

Date: January 2020

Appendix 7: Information Sheet (Next-Of-Kin)

STUDY INFORMATION DOCUMENT

Study title:

In the context of aneurysmal subarachnoid haemorrhage (aSAH), increased level of serum inflammatory markers is associated with a higher modified Fisher score and a worse WFNS and Hunt and Hess Score.

Greeting

Good day sir, madam. Thank you for taking the time to consider this invitation on behalf of your next-of-kin, the patient.

Introduction:

I, Dr Morena Nthuse Mpanza, am conducting research on cerebral aneurysmal bleeding, otherwise known as a bleeding stroke, and in the event of which, am investigating the relationship between the volume of blood that leaks into the brain, as interpreted from the brain scan, and the level of inflammation marker in the blood called CRP. Research is a process used in seeking new knowledge.

In this study we want to learn whether there is a relationship between the two above-mentioned, as well as the strength of the relationship. If the relationship is proven to exist and is strong, it could assist in selecting and prioritizing patients, including at the peripheral hospitals, for more urgent transfer towards our specialized centers of care. It will also help in predicting outcome. It will do so by enabling the attending doctors to undertake blood tests measuring the inflammation marker (CRP), which is easier to do and less harmful to the patient. Blood tests are also more accessible whereas CT-scan machines may not be available at the peripheral hospitals. Thus, the blood results will guide urgency of transfer in the absence of the scans, particularly in the early period of suffering the bleed (as manifest by a specific type of – “thunderclap” – headache).

These blood tests and scans already form part of the treatment of patients with bleeding stroke. By consenting that your next-of-kin, the patient, participate in this study, know that s/he will not be subjected to anything that is not already done for a patient who suffers a bleeding stroke. By consenting, know that you’re not giving legal consent but you’re advising that the patient, your next-of-kin, would have most likely consented if they were corpus mentis.

Invitation to Participate:

We are inviting you as legally appointed guardian to represent your next-of-kin in taking part in this research study. Once they recover and are able to consent for themselves, we will undertake a process of informing them about the study in the similar manner, and invite them to consent.

What is involved in the study.

1. When the patient (your next-of-kin) arrives and is admitted at our institution for a suspected bleeding, s/he will undergo the regular tests as stipulated above, namely:
    a. basic screening blood tests as well as tests for the inflammatory marker CRP; these blood samples will be a tablespoon or two full, taken on the day of admission and on Day5 of admission;
    b. a CT-brain scan to prove / or disprove a bleeding stroke; and
    c. a CT-brain angiogram which studies the vessels to prove / or disprove the presence of a cerebral aneurysm (abnormal stretching of a blood vessel).

    Notwithstanding the results of these tests, nor the decision to participate in this study, the patient will be treated according to standard international protocol(s) for the management of aneurysmal bleeds.

    The results of the above, together with information from the patient bed letter (file), will be collected and collated for the purposes of this research. Information from the bed letter will only include the following:
    - ✓ Age, Gender, and Ethnicity;
    - ✓ History of smoking and / or hypertension;
    - ✓ HIV status where you / or the patient have been informed and voluntarily consented to HIV testing; refusal for HIV testing does not disqualify the patient from the study, nor does it from proper and standard health care;
    - ✓ History of a ("thunderclap") headache
    - ✓ History of seizures
    - ✓ The status of the patient's wakefulness on examination, as well as whether they have suffered any neurological deficits (weakness)

    Once collected, all this information and results will be statistically tested to investigate the relationship we seek to investigate as stated above.

2. The study will be conducted over a period of three to six months, or until a sufficient patient group size (30-40 persons) is recruited.

Risks of being involved in the study:

There is no added risk in participating in the study, as it has been detailed above that the procedures to be undertaken, should you agree to participate on behalf of the patient, are standard and only observational in nature, and will not affect the patient's care in any negative manner.

Benefits of being in the study:

There is no direct benefit to you / or the Participant (your next-of-kin) from this study. The long-term objective is the possibility of better treatment for subsequent patients, as stated above.

While involved in the project and after the results are available, you / or The Participant (your next-of-kin) will be given pertinent information on the study.

Your next-of-kin's Participation is voluntary

Refusal to participate will involve no penalty or loss of benefits to which your next-of-kin (the Participant) is otherwise entitled. You may choose to discontinue participation at any time without penalty, or loss of benefits to which your next-of-kin (the Participant) is otherwise entitled. There is no requirement for you / or the Participant to provide a reason for withdrawing and any data collected in such an instance will in default be destroyed, unless you / or the Participant specifically consent to its retention.

Confidentiality:

Normally, all personal information will be treated in the strictest confidence and will only be available to me, the Principal Investigator (PI), and my Supervisor. The only exceptions - and all of them are rare - would normally be:

1. personal information may be disclosed if required by law
2. the Human Research Ethics Committees of the University may exceptionally require personal data to respond to a formal complaint, or for a compliance audit
3. the South African Health Products Regulatory Authority (SAHPRA), which is the successor body to the South African Medicines Control Council (SAMCC), might conceivably require access to personal data, if conducting an investigation into a drug trial

All data collected in the course of the study will be securely retained for two (2) years if a scientific publication arises from the study and six (6) years if there is no publication. Thereafter it will be destroyed accordingly.

Anonymity

Your next-of-kin's anonymity in the study will be safeguarded by usage of codes that de-link his/her identification information from the information we wish to collect and use as stated above.

Contact details of researcher/s:

Principal Investigator: Dr MN Mpanza
Cell: 0637747195
Email: n2se@yahoo.com

Supervisor: Dr C Profyris
Cell: 0739032114
Email: c.profyris@gmail.com

Outputs

The envisaged outcome of this study will be the knowledge of whether a relationship exists between the blood volume that leaks into the brain in the event of a bleeding stroke, and the blood inflammation marker CRP. These results will be shared with you / or the participant upon completion of this research.

Contact details of HREC administrator and chair – for reporting of complaints / problems.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

Date: October 2019

Appendix 8: Consent Form (Participant)

PARTICIPANT CONSENT SHEET

Project Title

In the context of aneurysmal subarachnoid haemorrhage (aSAH), increased level of serum inflammatory markers is associated with a higher modified Fisher score and a worse WFNS and Hunt and Hess Score.

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained;
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Principal Investigator: Dr MN Mpanza, telephone no. 0637747195, or by e-mail at n2se@yahoo.com,

Supervisor: Dr C Profyris, telephone no. 0739032114, or by e-mail at c.profyris@gmail.com

Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.

Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:

Name of Witness: _____
Signature: _____
Date: _____

Appendix 9: Consent Form (Next-Of-Kin)

PARTICIPANT CONSENT SHEET

Project Title

In the context of aneurysmal subarachnoid haemorrhage (aSAH), increased level of serum inflammatory markers is associated with a higher modified Fisher score and a worse WFNS and Hunt and Hess Score.

1. I have been given a Participant Next-Of-Kin Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to my Next-of-Kin, should I agree for him/her to participate, nor will s/he receive any payment; conversely, participation will not cost him/her anything but his/her time;
6. I understand that, even if I initially consent for him/her to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about him/her for the purposes of the study would immediately be destroyed, unless I, s/he give consent for it to be retained;
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Principal Investigator: Dr MN Mpanza, telephone no. 0637747195, or by e-mail at n2se@yahoo.com

Supervisor: Dr C Profyris, telephone no. 0739032114, or by e-mail at c.profyris@gmail.com

Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.

Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:

Name of Witness: _____
Signature: _____
Date: _____

Appendix 10: Data Collection Sheet

History of Hypertension	
History of Smoking	
Family History of aSAH	
HIV status (VCT)	
CD4 count	
History of Sentinel bleed	
Day of Sentinel bleed to presentation	
Day of SAH ictus	
GCS on admission day 0	
GCS on admission day 5	
Hunt and Hess Scale on admission day 0	
Hunt and Hess Scale on admission day 5	
WFNS score on admission day 0	
WFNS score on admission day 5	
Seizures on admission day 0	
Seizures on admission day 5	
CRP level on admission day 0	
CRP level on admission day 5	
ESR level on admission day 0	
ESR level on admission day 5	
PCT level on admission day 0	
PCT level on admission day 5	
WCC level on admission day 0	
WCC level on admission day 5	
Platelets level on admission day 0	
Platelets level on admission day 5	
Albumin level on admission day 0	
Albumin level on admission day 5	
Fisher score on admission day 0	
Presence of hydrocephalus on day 0	
Aneurysm location	
Aneurysm size	

Appendix 11: Link data Sheet

	Pt	HSP	HSP_Code	Age	Gender	Ethnic_ Group
1						
2						
3						
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Appendix 12: Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr MN Mpanza

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1911168

NAME: (Principal Investigator)	Dr MN Mpanza
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Neurosurgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	In the context of aneurysmal subarachnoid haemorrhage (aSAH), increased level of serum inflammatory markers is associated with a higher modified Fisher score and a worse WFNS and Hunt and Hess Score
DATE CONSIDERED:	2019/11/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr C Profyris
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/02/21

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

23/02/2020
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix 13: Microsoft Excel Spreadsheet Showing All the Raw Data Captured

Pt	HSP	Age	Gender	Ethnic	HPT	Smoking	FamHx	HIV	CD4	SentHA	Sent_Day	Ictus
1	HJH	69	M	A	U	U	U	U		U		0
2	HJH	77	F	A	Y	N	N	N		N		0
3	HJH	27	M	A	N	Y	N	U		N		1
4	HJH	56	F	A	Y	N	U	R		U		0
5	HJH	49	F	A	U	U	U	U		N		0
6	HJH	40	F	A	U	N	N	Y		U		2
7	CMJAH	72	M	W	U	U	N	U		Y	5	0
8	CMJAH	33	F	A	N	N	N	R		U		0
9	CMJAH	29	M	A	N	U	N	Y	597	Y	22	7
10	CMJAH	18	F	W	N	U	N	N		Y	4	2
11	CMJAH	46	F	A	U	U	U	R		N		0
12	CMJAH	62	F	A	Y	U	U	U		N		0
13	CMJAH	49	F	A	Y	U	U	R		U		0
14	CMJAH	33	F	A	Y	Y	N	R		Y	14	1
15	CHBAH	60	M	A	Y	Y	U	R		Y	14	0
16	CHBAH	50	F	A	Y	N	U	Y	634	N		1
17	CHBAH	39	M	A	U	U	U	N		U		1
18	CHBAH	42	F	A	N	U	U	R		N		1
19	CHBAH	49	F	A	Y	N	N	N		N		2
20	CHBAH	71	M	I	Y	Y	U	R		U		0
21	CHBAH	49	F	A	Y	N	U	R		U		0
22	CHBAH	56	M	A	Y	U	U	N		Y	14	1
23	CHBAH	56	M	W	U	U	U	R		U		2
24	CHBAH	66	F	A	Y	N	U	R		U		0
25	CHBAH	33	M	A	N	U	U	Y	596	U		1
26	CHBAH	58	F	A	Y	U	U	R		U		0
27	CHBAH	56	F	A	U	U	U	R		U		0
28	CHBAH	50	F	A	Y	N	N	N		U		1
29	CHBAH	59	F	A	Y	N	U	R		U		2
30	CHBAH	27	F	A	Y	Y	N	N		Y	7	0
31	CHBAH	72	F	A	Y	N	N	R		U		0
32	CHBAH	55	F	A	Y	Y	U	R		U		0
33	CHBAH	68	F	A	Y	N	U	R		N		1
34	CHBAH	19	M	A	N	Y	N	U		N		0
35	CHBAH	69	M	I	Y	Y	U	R		U		0
36	CHBAH	69	F	A	Y	U	U	R		U		0
37	CMJAH	62	F	A	Y	Y	N	R		Y	5	0
38	CMJAH	51	M	A	N	Y	N	R		N		2
39	CMJAH	31	M	A	N	N	N	N		N		0
40	CMJAH	43	M	A	N	Y	N	R		N		0
41	CMJAH	70	F	A	Y	N	N	R		N		0
42	CMJAH	24	F	A	N	N	N	R		N		0
43	CMJAH	47	M	A	N	N	N	R		Y	7	0
44	CMJAH	63	F	A	U	N	U	R		N		0
45	CMJAH	50	F	A	U	N	U	R		N		0
46	CMJAH	51	F	A	Y	N	U	Y		N		0
47	CMJAH	36	F	W	Y	Y	N	N		N		0
48	HJH	45	F	A	Y	N	N	N		Y	5	1

Pt	HSP	Age	Gender	Ethnic	HPT	Smoking	FamHx	HIV	CD4	SentHA	Sent_Day	Ictus
49	HJH	44	M	A	Y	U	N	Y	157	Y	14	0

* Pt = Patient; HSP = Hospital; Ethnic = Ethnic Group; HPT = Hypertension; FamHx = Family History of Stroke; SentHA = Sentinel Headache; Sent_Day = Day of Sentinel Headache to Presentation; Ictus = Day Since aSAH Proper.

Pt	Seiz_D0	Seiz_D5	GCS_D0	GCS_D5	H&H_D0	H&H_D5	WFNS_D0	WFNS_D5	M_Fisher
1	N		6/15		4	0	5	0	4
2	N	N	10/15	6/10	4	4	4	5	4
3	Y	N	7/10	14/15	4	3	4	3	3
4	N		5/15	2/10	4	0	5	5	3
5	N	N	14/15	13/15	3	3	2	2	3
6	N	N	15/15	15/15	2	2	1	1	4
7	N		12/15	6/10	3	0	4	0	4
8	N	N	12/15	12/15	3	3	3	3	3
9	N	N	15/15	15/15	1	1	1	1	4
10	N		13/15	15/15	2	2	1	1	4
11	Y	N	6/15	6/10	4	4	5	5	3
12	N	N	15/15	15/15	2	2	1	1	0
13			13/15	15/15	3	2	2	1	3
14	N	N	15/15	15/15	2	2	1	1	4
15	N	N	10/15	11/15	4	4	4	4	4
16	N	N	8/15	12/15	3	2	4	2	4
17	N	N	14/15	14/15	3	3	3	3	3
18	N	N	15/15	15/15	2	2	1	1	3
19	N	N	15/15	15/15	2	2	1	1	2
20	N		11/15		3	0	4	0	3
21	N	N	13/15	12/15	3	3	3	4	4
22	N		14/15		3	0	2	0	4
23	N	N	12/15	13/15	3	3	4	2	4
24	N	N	7/15	5/15	4	4	4	5	3
25	N	N	14/15	15/15	3	2	2	1	1
26	N	N	13/15	14/15	3	3	3	2	2
27	N	N	9/15	5/15	4	4	4	5	4
28	N	N	15/15	15/15	2	2	1	1	4
29	N	N	14/15	14/15	2	2	2	2	1
30	N	N	15/15	15/15	2	1	1	1	1
31	N	N	14/15	14/15	3	2	2	2	2
32	N		10/15		3	0	4	0	4
33	N	N	15/15	15/15	1	1	1	1	0
34	Y	N	7/15	10/15	4	4	4	4	4
35	N	N	8/15	6/15	4	4	4	4	4
36	N		10/15		3	0	4	0	1
37	N	N	15/15	15/15	2	2	1	1	0
38	N	N	9/15	14/15	4	3	4	3	4
39	N	N	15/15	15/15	1	1	1	1	0
40	N	N	14/15	14/15	2	2	2	2	4
41	N	N	8/15	14/15	4	4	4	4	4
42	Y		2/10		5	0	5	0	4
43	N	N	15/15	15/15	2	2	1	1	4

Pt	Seiz_D0	Seiz_D5	GCS_D0	GCS_D5	H&H_D0	H&H_D5	WFNS_D0	WFNS_D5	M_Fisher
44	N	N	12/15	13/15	3	3	4	3	4
45	N	N	15/15	15/15	1	1	1	1	3
46	N	N	10/15	14/15	3	3	4	2	4
47	N	N	14/15	15/15	2	1	2	1	4
48	N	N	15/15	15/15	1	1	1	1	4
49	N	N	15/15	15/15	2	2	1	1	4

* Pt = Patient; Seiz = Seizures; GCS = Glasgow Coma Score; H&H = Hunt and Hess Score; WFNS = World Federation of Neurosurgeons Score; M_Fisher = Modified Fisher; D0 = Day 0; and D5 = Day 5.

Pt	CRP_D0	CRP_D5	ESR_D0	ESR_D5	PCT_D0	PCT_D5	WCC_D0	WCC_D5
1	197	0	104	0	0	0	13,78	0
2	12	0	22	0	0,07	0	11,54	14,5
3	2	0	59	0	0,28	0	7,77	5,63
4	13	35	55	0	1,65	0	13,69	0
5	16	28	0	0	0,18	0	12,5	23,04
6	6	25	0	0	0,02	0,01	13,03	6,14
7	9	28	0	4	0,23	0	15,74	13,5
8	139	164	57	0	0,16	0	8,89	9,44
9	24	14	21	0	0,08	0	7,7	9,04
10	23	60	6	0	0,57	1,57	12,5	7,3
11	334	351	0	0	0	0,56	13,06	10,05
12	9	9	0	0	0,11	0	21,15	23,89
13	11	9	0	24	0,03	0	7,7	5,5
14	9	0	8	0	0,03	0	11,24	7,6
15	3	45	0	0	0	0	25,43	19,95
16	4	48	0	16	0	0	6,25	7,45
17	79	83	0	0	0	0	9,46	13,66
18	55	115	0	0	0	0	5,87	5
19	8	23	0	0	0,02	0,02	14,03	7,93
20	27	0	0	0	0	0	17,61	0
21	218	300	0	0	0	0	14,85	14,28
22	54	0	0	0	0	0	13,04	0
23	4	0	0	0	0,03	0	9,19	8,16
24	315	0	0	0	0	0	3,65	14,3
25	1	1	0	25	0	0	2,71	9,44
26	10	0	0	0	0	0	7,09	5,37
27	32	0	46	50	0,13	0	0	22,22
28	13	25	0	0	0	0	15,08	0
29	4	13	0	0	0	0	4,37	0
30	10	5	0	0	0	0	8,33	0
31	5	0	20	0	0	0	5,65	0
32	2	0	22	0	0,14	0	16,8	0
33	0	0	0	0	0	0	6,99	0
34	2	0	1	0	0,08	0	14,83	0
35	1	0	0	0	0	0	9,14	0
36	9	0	1	0	0	0	4,86	0
37	0	9	0	6	0	0,14	7,03	13,79
38	0	123	0	28	0	0,16	18,68	13,71

Pt	CRP_D0	CRP_D5	ESR_D0	ESR_D5	PCT_D0	PCT_D5	WCC_D0	WCC_D5
39	9	9	0	9	0	0,02	2,95	5,65
40	9	15	0	32	0	0,05	10,24	5,71
41	18	105	26	0	0,1	0,07	15,15	18,21
42	41	0	45	0	0	0	2,79	0
43	28	340	0	121	0	0,14	5,97	9,84
44	30	9	0	43	0,18	0,06	10,51	5,94
45	9	22	0	31	0	0	5,07	4,44
46	15	18	13	18	0,08	0,09	6,7	5,9
47	61	13	40	0	0,1	0,79	16,77	6,5
48	72	99	14	19	0,1	0,12	11,45	10,23
49	167	282	0	0	0,86	0,89	21,68	11,4

* Pt = Patient; CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; PCT = Procalcitonin; WCC = White Cell Count; D0 = Day 0; and D5 = Day 5.

Pt	Plt_D0	Plt_D5	Alb_D0	Alb_D5	HCP	An_Location	An_Size
1	365	0	41	0	Y	R ICA	
2	377	340	42	44	Y	L ICA	
3	304	462	41	0	N	PCA	
4	252	0	39	0	Y	L MCA	
5	267	269	47	36	N	R MCA	3.50
6	746	507	37	0	Y	L MCA	
7	404	306	45	0	Y	ACoA	
8	234	260	39	0	N	R MCA	
9	182	311	41	0	N	L ACA	7.20
10	247	316	40	0	N	R MCA	10.00
11	219	177	32	26	N	L MCA	
12	437	384	0	0	N	R ICA	5.40
13	272	484	41	0	Y	R Pcom	
14	426	274	35	0	N	R ACA, L ACA	2.00x2.20
15	245	211	75	0	Y	L ACA	
16	349	323	37	0	Y	R Pcom	
17	404	652	0	35	N	ACoA	3.4x3.2x4.0
18	296	312	0	0	N	R ACA	3.2x3.4
19	233	254	44	34	Y	ACoA	6.7x4.8
20	233	0	40	0	N	Multiple	
21	189	173	37	31	Y	L ACA	5.00x5.00
22	271	0	52	0	Y	R ACA, ACoA	4.00, 4.60
23	183	221	46	46	Y	L ICA	
24	288	400	0	0	Y	L Pcom	
25	230	236	48	38	N	L Pcom	5.3x5.3
26	283	216	0	0	N	L MCA	
27	0	351	46	38	Y	ACoA	
28	226	0	45	41	Y	R MCA	
29	302	452	35	35	Y	R MCA	
30	261	0	0	0	N	L Pcom, R ICA	
31	257	0	0	0	N	L ACA, R MCA, ACoA	
32	385	0	45	0	Y	L ACA	4.3x3.2; 4.7x3.2
33	295	0	0	0	N	L ICA	5.00
34	203	0	44	0	N	L Pcom	2.7x3.6

Pt	Plt_D0	Plt_D5	Alb_D0	Alb_D5	HCP	An_Location	An_Size
35	322	0	41	0	Y	L ACA	5.00
36	189	0	38	0	N	L ICA	21x15
37	682	622	0	42	N	R MCA, ACoA, R ICA, L Pcom	6.6x5.5, 3.8x3.8, 4.0x3.5, 2.8x3.8
38	402	368	0	32	Y	ACoA	
39	277	290	40	41	N	PCA	6.9x7.5
40	212	0	41	34	Y	ACoA	3.0x3.3
41	365	329	39	33	Y	L Pcom	8.0x16.5
42	68	0	36	0	N	L ACA	4.5x3.0
43	316	209	0	32	N	ACoA	4.32
44	218	238	41	40	Y	ACoA	6.8
45	435	262	0	44	N	ACoA	3.3
46	306	442	47	42	Y	R MCA, R ICA	3.0, 2.2
47	292	472	30	19	Y	B/A; L MCA	7.4x5.8, 6x6, 8x7; 4x4.6
48	828	426	37	35	N	R MCA	4.2x4.0
49	252	166	38	29	Y	ACoA	5x6

* Pt = Patient; Plt = Platelets; Alb = Albumin; HCP = Hydrocephalus; An = Aneurysm; D0 = Day 0; and D5 = Day 5.

Appendix 14: Inflammatory Biomarkers and their trends in this study

C-reactive protein:

CRP Thresholds	Day0: N (%)	Day5: N (%)
≤10 (normal)	21 (45,7)	7 (21,9)
11 – 20	7 (15,2)	5 (15,6)
21 – 40	6 (13,0)	7 (21,9)
41 – 60	3 (6,5)	3 (9,4)
61 - 80	3 (6,5)	0
>80	6 (13,0)	10 (31,3)
Total	46	32

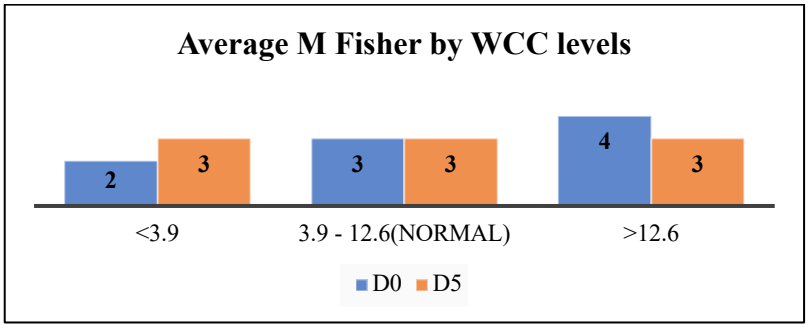
Erythrocyte sedimentation rate (ESR):

ESR Thresholds	Day 0: N (%)	Day 5: N (%)
0 – 10 (normal)	4 (22,2)	3 (21,4)
11 – 25	6 (33,3)	5 (35,7)
26 – 50	4 (22,2)	5 (35,7)
>50	4 (22,2)	1 (7,1)

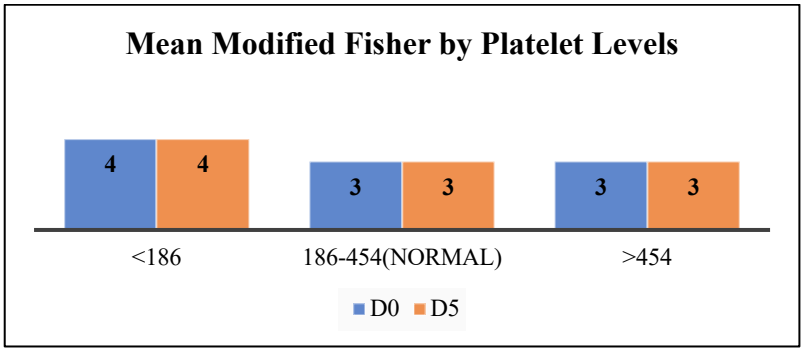
Procalcitonin (PCT):

ESR Thresholds:	Day 0: N (%)	Day 5: N (%)
Total No. collected from study population	23 (46,9)	15 (30,6)
< 0,25 (bacterial infection unlikely)	19 (82,6)	11 (73,3)
0,25 – 0,5 (systemic infection unlikely; localised bacterial infection possible, not excluded)	1 (4,3)	0
0,5 – 2,0 (suggestive of bacterial infection, systemic infection possible)	3 (13)	4 (26,7)
> 2,0 (suggestive of systemic infection)	0	0

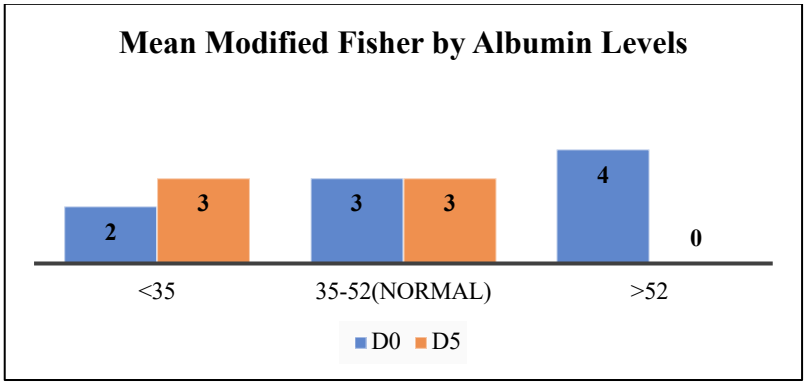
White cell count (WCC):



Platelets (Plts):



Albumin:



Hunt and Hess (H&H) Score Against CRP, ESR and Albumin:

H&H D0	CRP D0		CRP D5		Mean Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	9 – 72	29	9 – 99	36	7	0
2	4 – 167	31	5 – 340	72	41	0
3	1 – 218	37	1 – 300	69	32	23,5%
4	1 – 334	84	45 – 351	156	72	16,7%
5	41	41	0	0	-41	100%

H&H D5	CRP D0		CRP D5		Mean Delta
	Range (x-y)	Mean	Range (x-y)	Mean	
1	9 – 72	31	5 – 99	27	-4
2	1 – 167	23	1 – 340	70	47
3	2 – 218	57	9 - 300	104	47
4	1 – 334	90	45 – 351	167	77
5	0	0	0	0	0

H&H D0	ESR D0		ESR D5		Mean Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	14 – 21	7	9 – 31	20	13	0
2	6 – 40	18	6 – 121	53	35	0
3	1 – 57	23	4 – 43	22	-1	23,5%
4	1 – 104	45	28 – 50	39	-6	16,7%
5	45	45	0	0	-45	100%

H&H D5	ESR D0		ESR D5		Mean Delta
	Range (x-y)	Mean	Range (x-y)	Mean	
1	14 – 40	25	9 – 31	20	-5
2	6 – 20	11	6 – 121	37	26
3	13 – 59	43	4 – 43	23	-20
4	1 – 46	24	50	50	26
5	0	0	0	0	0

H&H D0	Alb D0		Alb D5		Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	37 – 41	39	35 – 44	40	1	0
2	30 – 45	38	19 – 42	33	-5	0
3	37 – 52	43	31 – 46	38	-5	23,5%
4	32 – 75	44	26 – 44	35	-9	16,7%
5	36	36	0	0	-36	100%

H&H D5	Alb D0		Alb D5		Delta
	Range (x-y)	Mean	Range (x-y)	Mean	
1	30 – 41	37	19 – 44	35	-2
2	35 – 48	40	29 – 42	36	-4
3	37 – 47	43	31 – 46	37	-6
4	32 – 75	46	26 – 44	35	-11
5	0	0	0	0	0

WFNS Score Against CRP, ESR and Albumin:

WFNS D0	CRP D0		CRP D5		Mean Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	6 – 167	32	5 – 340	74	42	0
2	1 – 61	20	1 – 28	13	-7	12,5%
3	10 – 218	112	83 – 300	182	70	0
4	1 – 315	30	9 – 123	54	24	17,6%
5	13 – 334	146	351	351	205	75%

WFNS D5	CRP D0		CRP D5		Mean Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	6 – 167	32	5 – 340	74	42	0
2	1 – 61	20	1 – 28	13	-7	12,5%
3	10 – 218	112	83 – 300	182	70	0
4	1 – 315	30	9 – 123	54	24	17,6%
5	13 – 334	146	351	351	205	75%

WFNS D0	ESR D0		ESR D5		Mean Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	6 – 21	12	6 – 121	37	25	0
2	20 – 40	30	24 – 32	27	-3	12,5%
3	57	57	0	0	-57	0
4	1 – 59	24	4 – 50	27	3	17,6%
5	45 – 104	68	0	0	-68	75%

WFNS D5	ESR D0		ESR D5		Mean Delta
	Range (x-y)	Mean	Range (x-y)	Mean	
1	6 – 40	18	6 – 121	34	16
2	13 – 20	17	16 – 32	22	5
3	57 – 59	58	28 – 43	36	-22
4	1 – 26	14	4	4	-10
5	22 – 46	34	50	50	16

WFNS D0	Alb D0		Alb D5		Mean Delta	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
1	35 – 45	40	29 – 44	37	-3	0
2	30 – 52	42	19 – 38	32	-10	12,5%
3	37 – 39	38	31 – 35	33	-5	0
4	37 – 75	44	32 – 46	39	-5	17,6%
5	32 - 41	37	26	26	-11	75%

WFNS D5	Alb D0		Alb D5		Mean Delta
	Range (x-y)	Mean	Range (x-y)	Mean	
1	30 – 48	40	19 – 44	36	-4
2	25 – 47	42	34 – 46	37	-5
3	39 – 41	40	32 – 40	36	-4
4	37 – 75	47	31 – 33	32	-15
5	32 – 46	40	26 – 44	36	-4

Inflammatory markers and radiological findings:

Modified Fisher Score Against CRP, ESR and Albumin:

Fisher	N (%)	CRP D0		CRP D5		Delta Mean	Death Rate
		Range (x-y)	Mean	Range (x-y)	Mean		
0	4 (8,7%)	9	9	9	9	0	0
1	4 (8,7%)	1 – 10	6	1 – 13	6	0	25%
2	3 (6,1%)	5 – 10	8	23	23	15	0
3	11 (22,4%)	2 - 334	91	9 – 351	110	19	18,2%
4	27 (55,1%)	1 – 218	41	9 – 340	91	50	14,8%

Fisher	N (%)	ESR D0		ESR D5		Delta Mean	Death Rate
		Range (x-y)	Mean	Range (x-y)	Mean		
0	4 (8,7%)	0	0	6 – 9	8	8	0
1	4 (8,7%)	1	1	25	25	24	25%
2	3 (6,1%)	20	20	0	0	-20	0
3	11 (22,4%)	55 – 59	57	24 – 31	28	-29	18,2%
4	27 (55,1%)	1 – 104	28	4 – 121	37	9	14,8%

Fisher	N (%)	Alb D0		Alb D5		Delta Mean	Death Rate
		Range (x-y)	Mean	Range (x-y)	Mean		
0	4 (8,7%)	40	40	41 – 42	42	2	0
1	4 (8,7%)	35 – 48	40	35 – 38	37	-3	25%
2	3 (6,1%)	44	44	34	34	-10	0
3	11 (22,4%)	32 – 47	40	26 – 44	35	-5	18,2%
4	27 (55,1%)	30 – 75	42	19 – 46	35	-7	14,8%

Hydrocephalus and aSAH severity:

Fisher	HCP (Count where the data was a Y)	HCP (Count where the data was a N)	% of Y from total
0	0	4	0%
1	1	3	25%
2	1	2	33,3%
3	3	8	27,3%
4	20	7	74,1%

H&H D0	HCP (Count where the data was a Y)	HCP (Count where the data was a N)	% of Y from total
1	0	5	0%
2	7	7	50%
3	9	8	52,9%
4	9	3	75%
5	0	1	0%
H&H D5	HCP (Count where the data was a Y)	HCP (Count where the data was a N)	% of Y from total
1	1	6	14%
2	8	8	50%
3	6	5	54,5%
4	6	2	75%
5	0	0	0

WFNS D0	HCP (Count where the data was a Y)	HCP (Count where the data was a N)	% of Y from total
1	4	12	25%
2	5	3	62,5%
3	1	3	25%
4	13	4	76,5%
5	2	2	50%

WFNS D5	HCP (Count where the data was a Y)	HCP (Count where the data was a N)	% of Y from total
1	6	13	31,6%
2	5	3	62,5%
3	2	3	40%
4	5	1	83,3%
5	3	1	75%

HCP and Inflammatory Markers CRP, ESR and Albumin:

HCP	CRP D0		CRP D5		Delta Mean	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
Yes	1 – 315	50	9 – 300	68	18	16%
No	1 – 334	42	1 – 351	87	45	12,5%

HCP	ESR D0		ESR D5		Delta Mean	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
Yes	13 – 104	41	4 – 50	27	-14	16%
No	1 – 59	23	6 – 121	35	12	12,5%

HCP	ALB D0		ALB D5		Delta Mean	Death Rate
	Range (x-y)	Mean	Range (x-y)	Mean		
Yes	30 – 75	43	19 – 46	36	-7	16%
No	32 – 48	40	26 – 44	37	-3	12,5%

Deaths and aSAH Severity Scores:

A total of 7 (14,3%) patients demised in the course of the study; before Day5

Death and scores:

- 4 (57,1%) had H&H3; 2 (28,6%) had H&H4; 1 (14,3%) had H&H5
- 1 (14,3%) had WFNS2; 3 (42,9%) had WFNS4; 3 (42,9%) had WFNS5
- 1 (14,3%) had MFS1; 2 (28,6%) had MFS2; 4 (57,1%) had MFS4

H&H		WFNS		Fisher		HCP	
Range (x-y)	Mean	Range (x-y)	Mean	Range (x-y)	Mean	Y	N
3 – 5	4	2 – 5	4	1 – 4	3	4 (57,1%)	3 (42,9%)

Deaths and Inflammatory Markers:

CRP collected in 85,7%; ESR in 71,4%; ALB in 100%

CRP		ESR		ALB	
Range (x-y)	Mean	Range (x-y)	Mean	Range (x-y)	Mean
2 – 197	49	1 – 104	45	36 – 52	42

Appendix 15: Turnitin (Plagiarism) Report

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ORIGINALITY REPORT

6%	3%	3%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	Sheng Chen, Hua Feng, Prativa Sherchan, Damon Klebe, Gang Zhao, Xiaochuan Sun, Jianmin Zhang, Jiping Tang, John H. Zhang. "Controversies and evolving new mechanisms in subarachnoid hemorrhage", Progress in Neurobiology, 2014 Publication	<1%
3	Caron M. Hong, Cigdem Tosun, David B. Kurland, Volodymyr Gerzanich, David Schreibman, J. Marc Simard. "Biomarkers as outcome predictors in subarachnoid hemorrhage – a systematic review", Biomarkers, 2014 Publication	<1%
4	Vera Zhiyuan Zheng, George Kwok Chu Wong. "Neuroinflammation responses after subarachnoid hemorrhage: A review", Journal of Clinical Neuroscience, 2017 Publication	<1%