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Exploring large vessel occlusion and ASPECT scores in hypertensive stroke: a retrospective study using pre-contrast computed tomography brain scan findings

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In the fulfilment of the requirements for the degree of Master of Medicine in the Clinical Disciplines.

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Declaration by Candidate

I, Dr Tumelo Jacqueline Tshamano, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

I have acknowledged all sources and cited these in the reference section. There are no conflicts of interest in creating the research paper.

This paper was prepared in a "submissible" format in line with the guidelines of the South African Journal of Radiology.

Signed on this day 7th September 2024



Dr Tumelo Jacqueline Tshamano

Declaration by Supervisors

The following individuals contributed as supervisors to the work undertaken by the candidate, Tumelo Jacqueline Tshamano, student number 2295858, as part of their research paper entitled "Exploring large vessel occlusion and ASPECT scores in hypertensive stroke: a retrospective study using pre-contrast computed tomography brain scan findings" in the fulfilment of the requirements for the degree of FC Rad Diag (SA) MMed.

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Details of Candidate and Supervisors (including percentage contributions):

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Co-supervisor 3: Prof. Dibuseng Ramaema 10%

Contribution of work by supervisors and candidate for the above-mentioned research paper:

The research paper is the original work of the candidate, Dr Tumelo Jacqueline Tshamano, who drafted the protocol and final research paper for this study.

Supervisors reviewed draft manuscripts of the protocol and the final research paper

and provided guidance regarding research methodology, improvements to content, general conduct, and conceptual ideas.

This proposal and the research paper were submitted to Turnitin concerning plagiarism.

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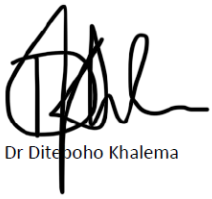
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Authors Guideline for the intended Journal

These guidelines are taken from the South African Journal of Radiology (SAJR)

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Acknowledgements structure

Acknowledgements

The acknowledgement section follows the conclusions section and addresses formal, required statements of gratitude and required disclosures. It includes listing those who contributed to the work but did not meet authorship criteria, with the corresponding description of the contribution. Acknowledge anyone who provided intellectual assistance, technical help (including with writing and editing), or special equipment and/or materials. Authors are responsible for ensuring that anyone named in the Acknowledgements agrees to be named.

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List of Abbreviations and Terminology

ASPECTS	Alberta Stroke Program Early CT Score
CEO	Chief Executive Officer
CHBAH	Chris Hani Baragwanath Academic Hospital
COVID-19	Corona Virus Disease of 2019
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTB	Computed Tomography Brain
DMSA	Data Management and Statistical Analysis
DSA	Digital Subtraction Angiography
HDP	Hypertensive Disorders of Pregnancy
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HREC	Human Research Ethics Committee
HS	Haemorrhagic Stroke
IS	Ischaemic Stroke
LI	Lacunar Infarction
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MVD	Microvascular Disease
PACS	Picture Archiving and Communication System
PML	Progressive Multifocal Leukoencephalopathy
PRES	Posterior Reversible Encephalopathy Syndrome
SAS	Statistical Analysis System
SD	Standard Deviation

Abstract

Background: Hypertension is one of the most common causes of stroke in Africa, including in sub-Saharan Africa. There is a lack of epidemiological and radiological information on hypertensive strokes.

Objectives: We aimed to describe, classify and grade the pre-contrasted computed tomography brain (CTB) scan findings occurring in hypertensive stroke patients and to determine the inter-reader variability between three qualified radiologists.

Method: This was a retrospective chart review of 205 pre-contrasted CTB scans in adult hypertensive patients presenting with a stroke at the Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa, between 01 June 2019 and 31 March 2020.

Results: There were 205 scans eligible to be included in this study. There were 67 (32.7%) normal and 138 (67.3%) abnormal scans. Ischaemic strokes were the most prevalent (43.5%), followed by lacunar infarctions (17.4%) and haemorrhagic strokes (13%). Stroke mimickers (n=32; 23.2%) were more common than lacunar infarctions and haemorrhagic strokes.

Eight out of 19 patients with acute and hyperacute anterior circulation stroke (42.2%) presented with a favorable Alberta Stroke Program Early CT Score (ASPECTS) of 6 and above. Anterior circulation large vessel occlusion (LVO) was significant and occurred in six patients (31.6%) of the hyperacute and acute ischaemic strokes.

The middle cerebral vascular territory was the most affected site for ischaemic strokes, haemorrhagic strokes and lacunar infarctions. Chronic ischaemic infarctions were the most common stage of presentation (n=25; 18.1%). In general, the interrater reliability for the three raters was substantial and there was almost perfect agreement.

Conclusion: The pre-contrast CTB scan is essential in assessing hypertensive strokes because it risk stratifies, which aids in management and prognostication.

Contribution: Detailed analysis of the pre-contrast computed tomography brain scan findings in hypertensive stroke patients, including interpretation of ASPECT scoring, LVO status, stage of ischaemic strokes and highlighting stroke mimickers.

Keywords: Hypertension, hypertensive encephalopathy, ischaemia, stroke, neuroimaging

Introduction

Literature review

Epidemiology

In Asia and Africa, and South Africa in particular, there is paucity of radiological and epidemiological data on hypertension and hypertensive stroke patients.[1-3] In sub-Saharan Africa, hypertension is the most common contributor to heart disease, stroke and heart failure.[4] The Alberta Stroke Program Early CT Score (ASPECTS) is used in conjunction with the pre-contrast CTB scan to characterise ischaemic stroke findings.[5-7] Data regarding the ASPECT score and large vessel occlusion (LVO) status in Southern Africa is deficient, more research is needed in order to guide stroke care.

Imaging findings

Performing a pre-contrast CTB scan characterizes the stroke and determines associated stroke complications.[2, 7] In addition, imaging enables exclusion of stroke mimickers such as tumours and haemorrhages.[7-9]

Ischaemic stroke

An hyperacute infarct occurs between 0 and 24 hours and is characterised by the hyperdense middle cerebral artery sign, outline loss of the basal ganglia, focal hypoattenuation, cortical sulcal effacement and the loss of grey white matter interface which is seen on CT scan. The hyperdense vessel sign indicates the intraluminal thrombus demonstrated on a pre-contrasted CTB scan as a focal hyperdensity. It is commonly seen in the setting of a hyperacute ischaemic stroke. It occurs in the middle cerebral artery, though any other vessels in the circle of Willis can be affected.[5, 10]

The ischaemic penumbra is the ‘tissue-at-risk’ and it represents the hypoperfused brain parenchyma.[11] This functional damage occurring in the penumbra can be reversed if the patient receives timely reperfusion therapy.[11] Approximately 25% of all ischaemic strokes do

qualify to receive medical thrombolysis, provided the pre-contrast CTB has excluded intracranial haemorrhages, and 10-12% are eligible to receive endovascular treatment.[12]

A hyperacute stroke may not display the above signs and the scan may appear falsely normal.[13, 14] An acute infarct is one that is in between the time frame of 24 hours to 1-week period. On CT imaging there is focal hypoattenuation. A subacute infarct is one that is between 1- and 3-weeks' time, during this time swelling is markedly reduced and the cortex may appear normal. A chronic infarct is one that is more than 3 weeks old and has undergone gliosis and appears low density.[5]

Intraparenchymal haemorrhage

Intraparenchymal haemorrhage is identified on pre-contrast CT scan. It is identified as an intra-axial haemorrhage, commonly affecting the basal ganglia, brainstem, thalamus, and the cerebellum. The pathophysiology of an intraparenchymal haemorrhage is due to a tear of the vessels that have been affected by hypertensive related degenerative changes.[15, 16]

Haemorrhagic transformation

Occurs in up to 43% of patients and ranges from petechial haemorrhage adjacent to the infarcted tissue margin to intraparenchymal haematoma>30% of the infarcted tissue exerting marked mass effect.[16]

Lacunar stroke

Lacunes are small cavities that are between 2 and 17mm in diameter best depicted on Magnetic Resonance Imaging. Lacunes are common in the internal capsule and basal ganglia. Lacunar strokes can be silent and multiple lacunar infarcts are associated with leukoaraiosis.[8]

Alberta Stroke Program Early CT Score

The Alberta Stroke Program Early CT Score (ASPECTS), is used in conjunction with the pre-contrast CT brain to characterize the ischaemic findings. It minuses a point for each region of parenchymal hypoattenuation within the anterior circulation, that is present.[5]

Anterior circulation ASPECTS

An ASPECT score of 10-points is given to a CT brain that is normal. To calculate the ASPECTS, one point is subtracted from the total of ten.[5]

The 10 points that are analysed are the:

- Caudate
- Insular cortex
- Internal capsule
- Putamen
- M1: the anterior middle cerebral artery cortex in the frontal operculum.
- M2: corresponding to the middle cerebral artery cortex lateral to insular ribbon.
- M3: corresponding to the middle cerebral artery posterior cortex which is in the temporal lobe posteriorly.
- M4: which is the anterior middle cerebral artery territory that is immediately above M1.
- M5: corresponding to the area superior to M2 which is of the middle cerebral artery lateral territory.
- M6: corresponding to the area immediately superior to M3 of the posterior middle cerebral artery territory

Lower scores of less than 5, predict that there will be a poor functional outcome. The lower scores are also associated with the complications of haemorrhagic transformation after thrombolytic agent has been administered. A normal pre-contrast CT brain does not exclude an acute infarction. Pre-contrast CT brain has a low negative predictive value for detecting small ischaemic volumes. ASPECTS scores between the range 8-10 are linked to experiencing a greater benefit from intravenous thrombolysis.[5, 10]

Posterior circulation ASPECTS

The posterior circulation ASPECT score (pc-ASPECTS) has been developed to assess vertebrobasilar ischaemia. The posterior circulation ASPECTS also implores a 10-point scaling system. Thereafter, points are subtracted of the regions that have undergone ischaemia. In contrast to the anterior circulation ASPECTS, the midbrain and pons are both worth 2 points each respectively, irrespective of whether ischaemia has occurred bilaterally or unilaterally. The thalami, occipital lobes and cerebellar hemispheres are worth 1 point each. Locations that cause mortality are infarctions that occur in the pons and midbrain.[17]

Large Vessel Occlusion

LVO is identified by the presence of a hyperdense vessel sign, indicating that the infarction is in the hyperacute stage and that the patient can benefit from performing a thrombectomy.[5, 18] Identifying the LVO is important, however limited on pre-contrast CTB but, when present, has a high specificity of 95%.[18]

Endovascular therapy treats large LVO in the indicated setting provided contraindications are excluded.[10, 19-21] Magnetic resonance imaging (MRI) is beneficial in the assessment of the hyperacute stage of ischaemic. The limitation, however, is that it is more time-consuming than computed tomography (CT), which is readily available in the acute setting.[10]

This study aimed to assess the imaging findings of hypertensive strokes on pre-contrast CTB scans. Furthermore, to provide data on ASPECTS and LVO status as these have management and prognostication implications. The inter-reader variability between three qualified radiologists was also analysed.

Research methods and design

A retrospective chart review was assessed on 205 adult hypertensive stroke patients. Their pre-contrast CTB scans were interpreted. The study period occurred between 01 June 2019 and 31 March 2020.

The inclusion criteria were all patients above the age of 18 years with neurological symptoms related to hypertensive stroke. In patients having both pre-contrast and post-contrast CT brain scans done, for this study only the pre-contrast study was assessed. The exclusion criteria were incomplete, lost, or illegible CTB scan request forms.

The demographic information such as age, sex, race and clinical data such as comorbidities were obtained retrospectively from the hospital's Picture Archiving and Communication System (PACS) and was only accessible to the primary investigator. All the patients' scans were allocated a research number to maintain anonymity and read once by the three qualified radiologists, who have more than four years of experience and further training in neuroradiology. All the three readers were blinded to the patient's clinical information.

Equipment

The CTB scans that were utilised during the study period were

- Canon Acquilon Prime (TSX-303A/AC). Multislice helical scan - 0.5mm per slice.
- Philips Ingenuity CT - iDose technique. Multislice helical scan - 0.625mm per slice.
- Toshibas Aquilion 64 and CXL: Multislice helical scan - - 0.5mm per slice.

Patients were scanned on one of the above listed machines.

Sample size

The sample size estimation was based on critical research questions, namely (1) the descriptive analysis of the different stroke types, etc., and (2) the estimation of interrater reliability.

For (1): Based on the worst-case (for sample size) estimates of 50%, 5% precision and a 95% confidence level, a sample size of 385 would be required. The sample size of 205 reduces the precision from 5.0% to 6.7%, which is deemed acceptable for a study of this nature.

The sample size for prevalence was analysed using the formula[22]

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = sample size,

Z = Z-statistic for the chosen level of confidence,

P = expected prevalence or proportion

d = precision

For (2): For all kappa-like agreement coefficients, the required number of subjects (n) depends on the relative error (r), the number of subjects in the entire population (N) and the difference p_a-p_e between the overall agreement probability p_a and the chance agreement probability p_e as follows[23]:

$$n = \frac{n^*}{1 + \frac{n^*}{N}}, where\ n^* = \frac{1}{r^2(p_a - p_e)^2}$$

Assuming that N is very large and that the chance-agreement probability is 0, the overall agreement probability is at least 0.7 (0.8), and a relative error of 20%, the required n is 51 (39).[23] The actual sample size of 205 is thus more than adequate.

Methodology

Interrater reliability for categorical CT brain scan finding for all the three raters and each pair was estimated using the Brennan-Prediger coefficient of agreement. The interrater reliability for the ASPECT scores for all of the three raters and pairs of raters was assessed using the intraclass correlation coefficient.[23] The magnitude of the interrater reliability statistics was interpreted according to the classification by Landis and Koch.[24] Having established that there was good inter-rater reliability, the results of any one reviewers was analysed since this is much more likely to have logical consistency. We proceed with the results for reviewer TB. The data analysis was performed using SAS (Statistical Analysis System) version 9.4 for Windows. A 5% significance level was used.

Ethical considerations

Permission to conduct this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (HREC), the CHBAH CEO (Chief Executive Officer) office and the CHBAH Department of Diagnostic Radiology. Ethics Clearance Certificate Number M2011114 (Appendix A). Written consent from participants was not a pre-requisite as this was a retrospective study.

Results

Table 1 depicts the demographic and clinical data. The mean age of the patients in the study was 61, with a range of 21-92 and an SD (Standard Deviation) of 15. There were 105 (51.2%) females and 100 (48.8%) males. Black patients were the most common (n = 187; 91.2%). A significant number of patients (n = 42; 20.5%) had seizures, followed by diabetes (n = 39; 19%). There were 34 female patients of childbearing age, and seven (20.6%) had hypertensive disorders of pregnancy. Known HIV/AIDS status comprised only of 7.8% of the patients; the status of the remaining patients was unknown. A minority of patients were known to being smokers (2.4%); the status of the remainder was also unknown.

The total number of scans eligible for reporting was 205. Most scans were abnormal (n = 138; 67.3%); a significant number of scans (n = 67; 32.7%) were normal, as demonstrated in **Table 2.** Abnormal scan findings comprised of the varying stroke types, stroke mimickers, associations and complications.

Table 3 reveals that ischaemic stroke was the most prevalent pathology (43.5%), followed by lacunar infarctions (17.4%). Haemorrhagic strokes were the least prevalent (13%). It is of note that some patients did present with more than one stroke type, occurring in various vascular territories and stages.

Table 4 demonstrates that majority of the patients presented with chronic ischaemic infarction and that acute ischaemic stroke (including hyperacute ischaemic stroke) were prevalent but to a lesser extent, as compared to chronic ischaemic strokes. The most common stage of presentation for lacunar infarctions was in the chronic stage.

The ASPECTS and LVO status assessments were assessed as a collective for hyperacute and acute stages of ischaemia (n=21), as demonstrated in **Table 5**. Eight out of 19 patients (42.2%) presented with a favorable ASPECTS of 6 and above, in the anterior circulation. LVO in the anterior circulation occurred in six out of 19 patients (31.6%) of the hyperacute and acute ischaemia. LVO in the posterior circulation was found to not be statistically significant (n=0).

One patient had ischaemic strokes in both the anterior and posterior circulations with no associated LVO to account for the strokes.

Table 6 demonstrates that the frontal, parietal and temporal lobes were the anatomical lobes predominantly affected by ischaemic strokes. The basal ganglia were the site most affected by lacunar infarctions and haemorrhagic strokes. The middle cerebral vascular territory was the predominant site of involvement for ischaemic strokes, lacunar infarcts and haemorrhagic strokes, respectively.

Table 7 shows that stroke mimickers were found in 32 patients (23.2%). The most prevalent lesions on the pre-contrast CT brains were intra-axial lesions, seen in seven patients (21.8%), with their differential diagnosis including brain neoplasms, abscesses and metastases. Meningiomas, gliosis and subdural haematomas were also commonly discovered.

The assessment of the associations and the complications revealed that microvascular disease (MVD) was the most common finding (31.2%), followed by brain atrophy and hydrocephalus (7.2% each). Some were co-existent. Intraventricular haemorrhage extension was the least common finding (2.2%). The associations and complications are depicted in **Table 8.**

Inter-reader variability

Interrater reliability was assessed for anatomical regions, vascular territory, staging, ASPECTS, LVO and complications and associations for all three raters and each pair. The interrater reliability metrics between all of the three reviewers and between each pair of reviewers was assessed. In general, the interrater reliability for the three raters together was >0.8. This indicates that there was substantial and almost perfect agreement amongst the reviewers (Appendix B).

Discussion

In this study, we aimed to describe, classify and grade the pre-contrasted CTB scan findings in hypertensive stroke patients. We also determined the inter-reader variability between three qualified radiologists.

Demographics

The mean patient age was 61 (range 21 – 92; SD 15), supporting the fact that hypertension and hypertensive stroke are more prevalent in the elderly population.[2, 3, 8, 25-27] There were 100 males (48.8%) and 105 females (51.2%). The majority of the patients were black (n=187; 91.2%).[2] This is most likely due to the location of the hospital and the demographics of the surrounding communities.

Clinical data

This study's aim did not primarily focus on analysing the patient's clinical data or risk factor profiling. The referring clinicians provided the clinical data on the CTB scan request forms and it was assessed. A significant number of hypertensive stroke patients presented with seizures which occurred in (n=42; 20.5%). Seizures are a common co-occurring symptom in hypertensive stroke patients, and this is also found by studies done by Mabaso et al. (2022) and Hersdorffer et al. (1996).[7, 28] HIV increases the stroke risk through various mechanisms such as vasculopathy and coagulopathy.[29] Feris et al. (2020) reported an HIV infection prevalence rate of 20.58%.[27] In our study, there were 16 patients with known HIV infection (7.8%); this is likely an underestimation but is slightly higher than the 6.1% prevalence demonstrated by Tipping et al. (2007).[18]

Diabetic patients are up to three times more likely to suffer from a stroke than in the general population, and in this study, known diabetic patients had a high prevalence rate of 19% (n=39).[2, 3, 12, 25] The prevalence of known smoking was very low, at 2.4% (n=5), also due to underreporting. Avula et al. (2020) reported that COVID-19 (Corona Virus Disease of 2019) is potentially neurotropic and can cause strokes, although the exact mechanisms are not entirely understood.[30] None of the patients included in this study had a positive diagnosis of COVID-19.

Hypertensive disorders of pregnancy (HDP) have a high morbidity and mortality rate and a five-fold increased stroke incidence.[31-33] Out of the 35 patients who were within childbearing age in this study, seven (20%) were diagnosed with HDP. The average age of HDP in this study was 29 years, and the age range was 21-36 years. HDP age risk factor varies; some studies have found that advanced maternal age is a risk factor. Conversely, other studies found that younger aged patients are at risk for HDP.[34]

Normal vs Abnormal scans

A significant number of hypertensive stroke patients were found to have normal scans (n=67; 32.7%) despite having neurological symptoms. In the setting of a hyperacute ischaemic infarct, the scan may appear falsely normal.[5] In addition, fogging is a phenomenon occurring in the setting of subacute ischaemic infarctions, whereby the CT scan also deceptively appears normal.[13, 14] Fogging phenomenon is a concept that radiologists need to be cognisant of in daily clinical practice.[13, 14] There is deficiency of data in settings where a CTB scan is reported as normal in hypertensive stroke patients. Mabaso et al. performed a study assessing new onset seizures and CT brain findings, they found that normal scans were significant at (n=274; 51.6%).[7] Of note is that their study co-hort was more heterogeneous and not only inclusive of hypertensive stroke patients.[7] Where there is a mismatch between radiological and clinical findings the role of MRI is beneficial.[10] However, MRI is more time-consuming as compared to computed tomography (CT), which is readily accessible in the acute setting.[10]

Imaging aims to differentiate the less common haemorrhagic stroke (15% of cases) from the more common ischaemic stroke (85% of cases).[2, 3, 5, 7, 10, 25, 30] Ischaemic strokes in this study were the most common (n=60; 43.5%) and lacunar infarctions were (n=24; 17.4%). The total number of ischaemic strokes in this study was less than that found in other studies. Daffue et al. demonstrated that the incidence of ischaemic strokes in their study was 67.8%, significantly higher than in this study.[3] Haemorrhagic strokes made up 40% of cases in a study done by Tribelthorn et al.[2] and in the research done by Daffue et al., they found haemorrhagic strokes to be 32.2%.[3] In our study haemorrhagic strokes were significantly less prevalent at (n=18; 13%).

In this study, stroke mimickers were significant at (n=32; 23.2%), making them more common than lacunar infarctions and haemorrhagic strokes. Common stroke mimickers were meningiomas, intracranial masses, subdural haematomas and lobar haemorrhages. Stroke mimickers are essential to be aware about as they alter the management pathway as supported by multiple authors.[5, 7, 10, 25]

Staging

Chronic ischaemic infarctions were the most common stage of presentation and occurred in 25 patients (18.1%). Patients presenting with chronic ischaemia are already outside the opportunity of intervention. Hyperacute and acute ischaemic infarctions were assessed collectively and were (n=21;15.2%). Subacute ischaemic infarctions were the least common and occurred in 14 (10.1%) cases. This contrasts with the research conducted by Tribelhorn, where they found that subacute ischaemic stroke were the most common at 55%, acute ischaemic stroke occurred in 41%, and subacute-chronic stage ischaemia were the least common 4%.[2]

Pre-contrast CTB plays a pivotal role in excluding intracranial haemorrhages, as that is a contraindication to administer thrombolysis.[25] Intravenous thrombolysis is administered in the hyperacute stroke stage. In addition, patients must qualify for the inclusion criteria and present within the therapeutic window of 3 - 4.5 hours.[19, 25] Studies have shown that many patients present outside the time sensitive therapeutic window, therefore not qualifying for intravenous thrombolysis.[2, 3, 25] Robust patient education, pre-hospital and hospital stroke protocols and guidelines are needed to expedite the care of patients, particularly those within the thrombolysis window and intervention period.[2, 19, 25, 35]

ASPECTS

Patients presenting with an acute and hyperacute ischaemic stroke do benefit from analyzing their ASPECT score, as it has management and treatment implications.[6] Studies have depicted that lower scores of five and below predict a poor functional outcome.[10] ASPECT scores of six and above are linked to a more significant benefit from intravenous thrombolysis.[5, 6] A local study depicted that patients with an ASPECTS of greater than 7 was found in a significant

proportion at (n=33; 52.4%).[3] In a similar manner, in this study, a favorable ASPECT score of six and above was demonstrated in 42.2% of patients (n=8), in the anterior circulation. A sizeable number of patients in this study (n=4; 21.1%) presented with a very low ASPECT score of 0, in the anterior circulation.

LVO

LVO in the anterior circulation was significant at 31.6% (n=6). Similarly other researchers, have found that 25 - 35% of strokes have LVO.[11] In this study, the findings of LVO in the posterior circulation were not statistically significant (n=0). One patient had an ischaemic stroke in both the anterior and posterior circulations but with no LVO was found to account for the strokes. LVO is identified by the presence of a hyperdense vessel sign on the pre-contrast CTB.[5] LVO identification is important however limited on pre-contrast CTB but, when present, has a high specificity of 95%.[18] The hyperdense vessel sign indicates an early hyperacute ischaemic finding, typically requiring thrombectomy.[18] Computed tomography angiography (CTA), MRI and magnetic resonance angiography (MRA), or perfusion studies are also recommended to further characterise the nature of the LVO and core-penumbra mismatch, especially in the later presenters.[20] The gold standard for the diagnosis of an LVO is conventional digital subtraction angiography (DSA).[20]

Neuro-intervention has an essential role in the performance of mechanical thrombectomy and these services are deficient in the South African setting. The inclusion criteria for mechanical thrombectomy include more proximal thrombi and patients presenting within 24 hours of stroke symptomatology. In contrast, medical thrombolysis has been found to be more beneficial in treating more distant thrombi than larger proximal ones.[19, 21] LVO's greater than eight millimetres are often not responsive to intravenous thrombolysis alone.[20, 36] In such cases, mechanical thrombectomy procedures should be considered and offered to qualifying candidates.[20]

Anatomical site and vascular territory

Ischaemic strokes were more common in the frontal (n=27; 19.6%) and parietal lobes (n=26; 18.8%). Lacunar infarctions had the highest prevalence in the basal ganglia (n=16; 11.6%), which is supported by Arboix et al. (2009).[8] Haemorrhagic strokes were also more commonly detected in the basal ganglia (n=9; 6.5%), the same predilection site is demonstrated in a local study.[2]

In our study, ischaemic strokes, lacunar infarctions and haemorrhagic strokes mainly occurred in the middle cerebral artery distribution. This reaffirms the finding that strokes have a preponderance for the middle cerebral artery territory as found in studies done locally and internationally.[2, 3, 36]

Associations and complications

Microvascular ischaemic disease occurred significantly at a prevalence of 31.2% (n=43). Arboix et al. (2009) found that periventricular diffuse white matter hypodensity is caused by microangiopathy and is associated with dementia and cognitive impairment.[8]

Interrater reliability assessment

The interrater reliability for the three raters was generally >0.8. This indicates substantial and almost perfect agreement amongst the reviewers (Appendix B). Interrater reliability for anatomical regions, vascular territory, staging, ASPECTS, LVO and complications and associations for all three raters and each pair was estimated using the Brennan-Prediger coefficient of agreement. Interrater reliability for the ASPECTS scores for all three raters and pairs of raters was determined using the intraclass correlation coefficient.[23] The magnitude of the interrater reliability statistics was interpreted according to the classification by Landis and Koch.[24]

Strengths and limitations of the study

This study has demonstrated the important role that a pre-contrast CTB has when characterizing and managing hypertensive stroke patients, particularly as it pertains to determining their ASPECT score and LVO status to expedite urgent stroke care. The study highlighted that most patients present in the chronic stage of ischaemic stroke, when they are already outside the window for acute stroke care. With the implementation of a multidisciplinary 24-hour acute stroke care centers, including increasing neurointerventional training, more acute and hyperacute patients can be treated at an earlier stage thereby decreasing morbidity and mortality.

It is important to note that the original patient CTB scan request forms at the records department were not available upon the time of request, and the patient's clinical information were obtained from the report on PACS. Illegible and inadequate histories on the request forms were a limitation in conducting this research. Additional limitations include that this was a retrospective study, incomplete clinical data was made available, including – HIV status and smoking status of all patients was not known.

Conclusions and recommendations

In conclusion, in a hypertensive stroke patient an expedited pre-contrasted CT brain scan is essential to characterize the scan findings, exclude intracranial haemorrhages, look for associations, complications and to rule out stroke mimickers. Determining the ASPECT score and LVO status is imperative as it has management and prognostication implications.

Future studies should investigate and compare the pre-contrasted CTB scan findings of patients who undergo medical thrombolysis and or mechanical thrombectomy, in the pre-and post-treatment phases. There should be further investigation into using CT perfusion studies as a standard protocol in this population, where the onset of symptoms is not that clear and for those patients outside the early window period (6-24 hours).

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Authors contributions

TJT takes responsibility for the paper as a whole. TJT and TB formulated the topic. TB conceptualised the data collection tool. TJT is the principal investigator responsible for the literature review, data collection and preparation of the manuscript. TB, DK, DR, and AM were responsible for supervisory roles.

Data availability

Data to support the findings of this study are available from the corresponding author.

Disclaimer

Views and opinions expressed in this article belong to the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.[8]

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Appendices

Appendix A: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Tumelo Jacqueline Tshamano

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M2011114

NAME: (Principal Investigator)	Dr Tumelo Jacqueline Tshamano
DEPARTMENT:	Radiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Hypertensive stroke and Pre-contrast Computed Tomography Brain findings
DATE CONSIDERED:	27/11/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr T. Buthelezi, Dr C. Do Vale and Dr D. Khalema
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/12/2020

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 Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

7/12/23
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Inter reader variability

	Reviewer				Coefficient of interrater agreement			
Characteristic	B	K	R	n (scans)	All 3 raters	B & K	B & R	K& R
n (total number of scans)	215	215	215					
Scan qualifies for analysis	205	209	200	215	0.86	0.89	0.82	0.88
Scan abnormal	138	124	135	191	0.69	0.66	0.68	0.65
R_IS	35	34	38	191	0.80	0.82	0.76	0.80
R_LI	13	3	19	191	0.83	0.88	0.89	0.88
R_HS	5	3	7	191	0.97	0.98	0.98	0.98
R_IOP	0	0	0	191	1.00	1.00	1.00	1.00
L_IS	34	33	35	191	0.77	0.80	0.75	0.76
L_LI	21	4	22	191	0.79	0.81	0.76	0.76
L_HS	12	8	10	191	0.95	0.97	0.94	0.93
L_IOP	0	0	0	191	1.00	1.00	1.00	1.00
RT_FRONTAL_IS	15	18	7	191	0.83	0.86	0.79	0.86
RT_FRONTAL_LI	2	0	0	191	0.99	0.98	0.98	1.00
RT_FRONTAL_HS	1	0	0	191	0.99	0.99	0.99	1.00
RT_FRONTAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
LT_FRONTAL_IS	17	15	2	191	0.87	0.89	0.84	0.87
LT_FRONTAL_LI	4	0	0	191	0.97	0.96	0.96	1.00
LT_FRONTAL_HS	3	2	1	191	0.98	0.99	0.98	0.99
LT_FRONTAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
RT_TEMPORAL_IS	12	8	6	191	0.90	0.86	0.93	0.92
RT_TEMPORAL_LI	0	0	1	191	0.99	1.00	0.99	0.99
RT_TEMPORAL_HS	2	0	2	191	0.98	0.98	0.98	0.98
RT_TEMPORAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
LT_TEMPORAL_IS	17	14	10	191	0.89	0.91	0.84	0.94
LT_TEMPORAL_LI	0	0	0	191	1.00	1.00	1.00	1.00
LT_TEMPORAL_HS	5	2	8	191	0.95	0.97	0.95	0.95
LT_TEMPORAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
RT_PARIETAL_IS	16	13	20	191	0.87	0.88	0.85	0.87
RT_PARIETAL_LI	0	0	7	191	0.95	1.00	0.94	0.93
RT_PARIETAL_HS	2	0	5	191	0.97	0.98	0.97	0.95
RT_PARIETAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
LT_PARIETAL_IS	15	8	22	191	0.86	0.92	0.81	0.82
LT_PARIETAL_LI	0	0	7	191	0.95	1.00	0.94	0.93
LT_PARIETAL_HS	4	1	5	191	0.96	0.98	0.95	0.96
LT_PARIETAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
RT_OCCIPITAL_IS	13	6	7	191	0.91	0.89	0.90	0.96
RT_OCCIPITAL_LI	0	0	1	191	0.99	1.00	0.99	0.99
RT_OCCIPITAL_HS	1	0	1	191	0.99	0.99	1.00	0.99
RT_OCCIPITAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
LT_OCCIPITAL_IS	7	4	4	191	0.94	0.95	0.94	0.94
LT_OCCIPITAL_LI	0	0	1	191	0.99	1.00	0.99	0.99
LT_OCCIPITAL_HS	0	0	1	191	0.99	1.00	0.99	0.99
LT_OCCIPITAL_OIP	0	0	0	191	1.00	1.00	1.00	1.00
RT_BASAL_GANGLIA_IS	4	6	7	191	0.96	0.96	0.97	0.96
RT_BASAL_GANGLIA_LI	11	3	10	191	0.93	0.90	0.84	0.87
RT_BASAL_GANGLIA_HS	2	2	3	191	0.98	0.98	0.97	0.99
RT_BASAL_GANGLIA_OIP	1	0	0	191	0.99	0.99	0.99	1.00
LT_BASAL_GANGLIA_IS	8	6	7	191	0.98	0.98	0.97	0.99
LT_BASAL_GANGLIA_LI	12	4	15	191	0.83	0.88	0.76	0.83
LT_BASAL_GANGLIA_HS	7	4	3	191	0.96	0.97	0.94	0.97
LT_BASAL_GANGLIA_OIP	0	0	0	191	1.00	1.00	1.00	1.00
RT_THALAMUS_IS	0	1	1	191	0.99	0.99	0.99	1.00
RT_THALAMUS_LI	2	1	1	191	0.98	0.99	0.97	0.98
RT_THALAMUS_HS	1	0	1	191	0.99	0.99	1.00	0.99

Interpretation of Kappa

	Poor	Slight	Fair	Moderate	Substantial	Almost perfect
Kappa	0.0	.20	.40	.60	.80	1.0

Kappa	Agreement
< 0	Less than chance agreement
0.01–0.20	Slight agreement
0.21– 0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Almost perfect agreement

NOTE: Study initially started with 215 scans. Having established good inter-rater reliability, the results of any one reviewer were analysed since this is much more likely to have logical consistency. We proceed with the results for reviewer TB. Due to technical limitations of the scans the reviewers were not able to report on all 215 scans.

RT_THALAMUS_OIP	0	0	0	191	1.00	1.00	1.00	1.00
LT_THALAMUS_IS	0	0	1	191	0.99	1.00	0.99	0.99
LT_THALAMUS_LI	3	1	1	191	0.97	0.98	0.96	0.98
LT_THALAMUS_HS	1	2	0	191	0.99	0.99	0.99	0.98
LT_THALAMUS_OIP	0	0	0	191	1.00	1.00	1.00	1.00
BRAINSTEM_IS	0	0	1	191	0.99	1.00	0.99	0.99
BRAINSTEM_LI	0	1	1	191	0.99	0.99	0.99	1.00
BRAINSTEM_HS	2	2	2	191	1.00	1.00	1.00	1.00
BRAINSTEM_OIP	0	0	0	191	1.00	1.00	1.00	1.00
RT_CEREBELLUM_IS	7	5	7	191	0.93	0.93	0.94	0.92
RT_CEREBELLUM_LI	1	0	0	191	0.99	0.99	0.99	1.00
RT_CEREBELLUM_HS	1	1	1	191	1.00	1.00	1.00	1.00
RT_CEREBELLUM_OIP	0	0	0	191	1.00	1.00	1.00	1.00
LT_CEREBELLUM_IS	11	4	5	191	0.91	0.90	0.87	0.95
LT_CEREBELLUM_LI	3	0	0	191	0.98	0.97	0.97	1.00
LT_CEREBELLUM_HS	0	0	1	191	0.99	1.00	0.99	0.99
LT_CEREBELLUM_OIP	0	0	0	191	1.00	1.00	1.00	1.00
OTHER_SPECIFY	0	0	0	191	1.00	1.00	1.00	1.00
RT_ANTERIOR_VASC_TERR_IS	4	3	8	191	0.94	0.90	0.95	0.95
RT_ANTERIOR_VASC_TERR_LI	2	0	0	191	0.99	0.98	0.98	1.00
RT_ANTERIOR_VASC_TERR_HS	1	0	0	191	0.99	0.99	0.99	1.00
LT_ANTERIOR_VASC_TERR_IS	2	1	2	191	0.97	0.97	0.96	0.97
LT_ANTERIOR_VASC_TERR_LI	3	0	0	191	0.98	0.97	0.97	1.00
LT_ANTERIOR_VASC_TERR_HS	0	0	1	191	0.99	1.00	0.99	0.99
RT_MIDDLE_VASC_TERR_IS	22	26	26	191	0.84	0.83	0.83	0.86
RT_MIDDLE_VASC_TERR_LI	8	3	17	191	0.84	0.91	0.84	0.80
RT_MIDDLE_VASC_TERR_HS	5	2	5	191	0.97	0.95	0.98	0.97
LT_MIDDLE_VASC_TERR_IS	28	26	31	191	0.81	0.83	0.76	0.81
LT_MIDDLE_VASC_TERR_LI	12	4	21	191	0.82	0.86	0.78	0.77
LT_MIDDLE_VASC_TERR_HS	11	6	10	191	0.95	0.96	0.95	0.93
RT_POSTERIOR_VASC_TERR_IS	15	9	14	191	0.88	0.87	0.86	0.90
RT_POSTERIOR_VASC_TERR_LI	1	0	2	191	0.98	0.99	0.98	0.97
RTPOSTERIOR_VASC_TERR_HS	3	0	2	191	0.98	0.97	0.99	0.99
LT_POSTERIOR_VASC_TERR_IS	12	6	7	191	0.89	0.89	0.88	0.91
LT_POSTERIOR_VASC_TERR_LI	3	0	2	191	0.97	0.97	0.95	0.98
LT_POSTERIOR_VASC_TERR_HS	1	2	1	191	0.98	0.99	0.98	0.97
BRAINSTEM_IS_POSTERIOR_VASC_TERR	0	0	1	191	0.99	1.00	0.99	0.99
BRAINSTEM_LI_POSTERIOR_VASC_TERR	0	1	1	191	0.99	0.99	0.99	1.00
BRAINSTEM_HS_POSTERIOR_VASC_TERR	2	2	2	191	1.00	1.00	1.00	1.00
RT_HYPERACUTE_IS	0	0	0	191	1.00	1.00	1.00	1.00
RT_HYPERACUTE_LI	0	0	0	191	1.00	1.00	1.00	1.00
LT_HYPERACUTE_IS	1	1	2	191	0.98	0.98	0.97	0.99
LT_HYPERACUTE_LI	0	0	0	191	1.00	1.00	1.00	1.00
RT_ACUTE_IS	8	16	3	191	0.88	0.88	0.91	0.86
RT_ACUTE_LI	0	0	1	191	0.99	1.00	0.99	0.99
LT_ACUTE_IS	14	17	8	191	0.84	0.85	0.86	0.81
LT_ACUTE_LI	1	0	0	191	0.99	0.99	0.99	1.00
RT_SUBACUTE_IS	8	2	14	191	0.88	0.99	0.83	0.88
RT_SUBACUTE_LI	0	0	1	191	0.99	1.00	0.99	0.99
LT_SUBACUTE_IS	8	3	12	191	0.90	0.93	0.88	0.87
LT_SUBACUTE_LI	2	1	1	191	0.99	0.99	0.99	1.00
RT_CHRONIC_IS	20	17	19	191	0.82	0.84	0.76	0.83
RT_CHRONIC_LI	13	2	16	191	0.85	0.89	0.83	0.82
LT_CHRONIC_IS	13	11	13	191	0.83	0.88	0.79	0.84
LT_CHRONIC_LI	16	4	22	191	0.80	0.85	0.77	0.76
BRAINSTEM_HYPERACUTE_IS	0	0	0	191	1.00	1.00	1.00	1.00

BRAINSTEM_ACUTE_IS	0	0	1	191	0.99	1.00	0.99	0.99
BRAINSTEM_SUB_ACUTE_IS	0	0	0	191	1.00	1.00	1.00	1.00
BRAINSTEM_CHRONIC_IS	0	0	0	191	1.00	1.00	1.00	1.00
BRAINSTEM_HYPERACUTE_LI	0	0	0	191	1.00	1.00	1.00	1.00
BRAINSTEM_ACUTE_LI	0	0	0	191	1.00	1.00	1.00	1.00
BRAINSTEM_SUBACUTE_LI	0	0	0	191	1.00	1.00	1.00	1.00
BRAINSTEM_CHRONIC_LI	0	1	1	191	0.99	0.99	0.99	1.00
ANTERIOR_ASPECTS				23	0.82	0.80	0.86	0.82
0	4	3	4					
1	2	1	1					
2	1	0	0					
4	0	0	2					
5	6	0	2					
6	1	4	2					
7	3	5	7					
8	8	6	7					
9	2	15	9					
not applicable	172	174	165					
missing	6	1	1					
POSTERIOR_ASPECTS				13	0.92	1.00	0.96	1.00
0	0	0	1					
8	4	0	0					
9	1	4	7					
not applicable	193	203	192					
missing	6	1	1					
ANTERIOR_LVO				184	0.83	0.88	0.82	0.80
no	21	33	22					
yes	6	2	12					
not applicable	172	174	165					
missing	6	1	1					
POSTERIOR_LVO				183	0.93	0.94	0.93	0.91
no	5	5	6					
yes	0	0	2					
not applicable	193	203	192					
missing	2	1	0					
RIGHT_MIDLINE_SHIFT	2	3	3	191	0.96	0.97	0.97	0.93
LEFT_MIDLINE_SHIFT	5	1	9	191	0.95	0.96	0.97	0.92
MASS_EFFECT_ON_RT_LATERAL_VENTRI	0	4	8	191	0.92	0.96	0.93	0.88
MASS_EFFECT_ON_LEFT_LATERAL_VENT	0	3	5	191	0.96	0.97	0.95	0.96
CEREBRAL_OEDEMA	6	3	3	191	0.94	0.95	0.91	0.93
HYDROCEPHALUS	10	8	7	191	0.91	0.93	0.91	0.89
INTRAVENTRICULAR_HAEMORRHAGE_EXT	3	6	9	191	0.96	0.97	0.94	0.97
SUBFALCINE_HERNIATION	0	3	6	191	0.96	0.97	0.94	0.95
MVD	44	39	37	191	0.73	0.78	0.72	0.71
BRAIN_ATROPHY	14	4	45	191	0.66	0.86	0.59	0.57

Appendix C: Figures

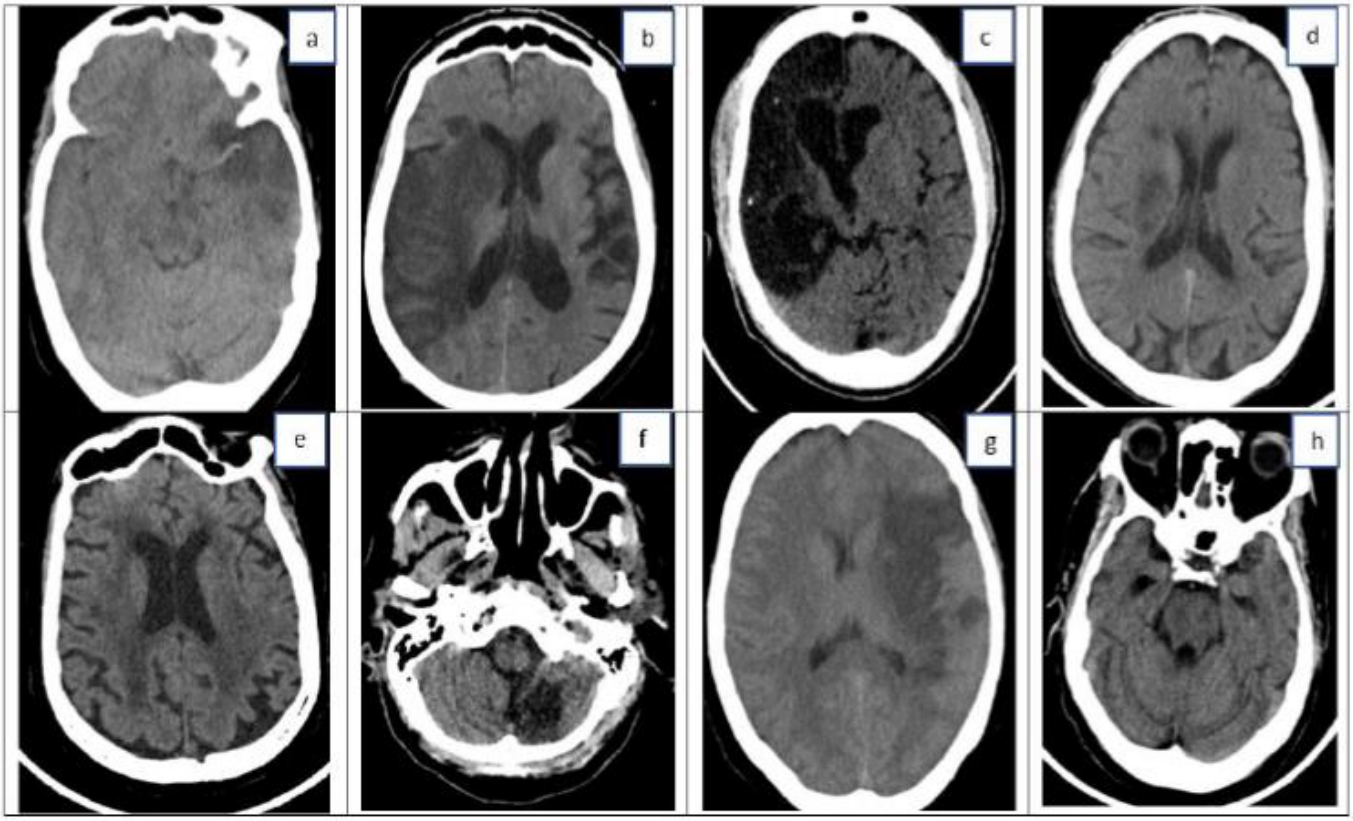


Figure 1: Left dense MCA (Middle Cerebral Artery) sign indicating LVO in the middle cerebral artery and acute left fronto temporal lobe ischaemic stroke (a). Right frontotemporal subacute ischaemic stroke with mass effect on right lateral ventricles (b). Right frontotemporal chronic ischaemic stroke (c). Right frontal and basal ganglia subacute ischaemic strokes (d). Microvascular ischaemic disease and moderate global brain atrophy (e). Left cerebellum chronic ischaemic stroke (f). Left frontotemporal acute ischaemic stroke with mass effect on the left lateral ventricles (g). Acute pontine lacunar infarcts (h).

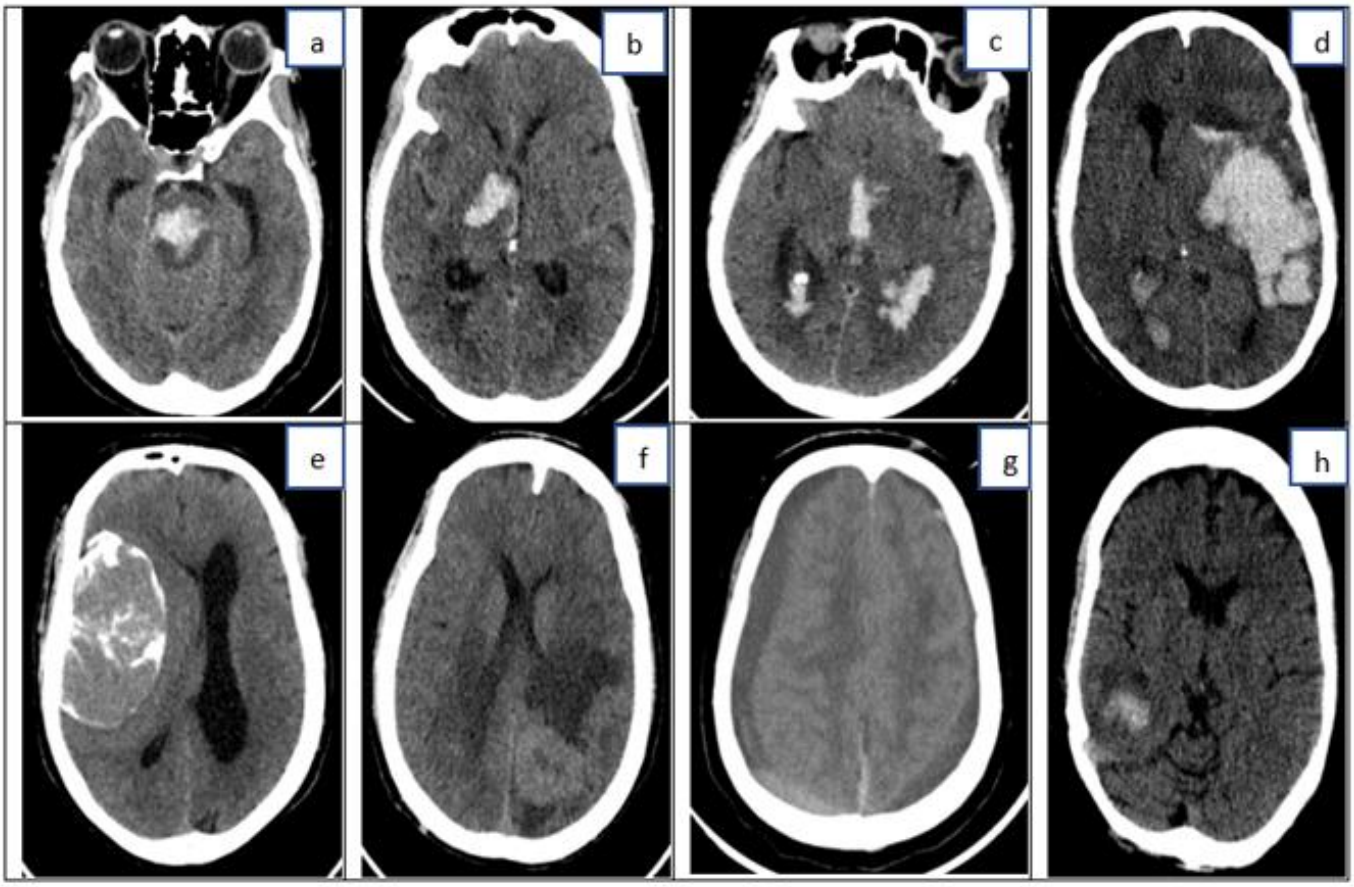


Figure 2: Pontine haemorrhagic stroke complicated by entrapment hydrocephalus (a). Haemorrhagic right basal ganglia stroke with intraventricular extension (b). Intraventricular extension from an intraparenchymal haemorrhagic stroke (not shown) and associated hydrocephalus (c). Large left fronto-temporal intracerebral haemorrhage with intraventricular extension, right-ward midline shift and entrapment hydrocephalus (d). Right fronto-temporal meningioma, complicated by subfalcine herniation (e). Left parietal lobe hyperdense mass, with central hypoattenuation, marked vasogenic oedema and mass effect; the differential diagnosis includes metastases or primary brain tumour (f). Acute on chronic bilateral subdural haemorrhages complicated by cerebral oedema (g). Right temporal haemorrhagic lobar lesion with perilesional oedema, differential diagnosis includes haemorrhagic metastases or complicated arteriovenous malformation (h).

Appendix D: Tables

Table 1: Age distribution and overall description of patient characteristics

Characteristic	Category	n (%)
Scans reported		**205**
Age (years)	Mean (SD); range	61(15) 21-92
Sex	Female	105 (51.2)
	Male	100 (48.8)
Ethnicity	Black	187 (91.2)
	Coloured	10 (4.9)
	White	5 (2.4)
	Asian	3 (1.5)
Comorbidities	Hypertension	205 (100)
	Seizures	42 (20.5)
	Diabetes	39 (19)
	Previous stroke	14 (6.8)
	Dyslipidaemia	13 (6.3)
	Heart disease	6 (2.9)
	*HIV/AIDS (the rest unknown)	16 (7.8)
	HDP (n=34*)	7 (20.6)
	Smoker (the rest unknown)	5 (2.4)
	Other****	29 (14.1)

Table 1: Age distribution and overall description of patient characteristics

* Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

**Hypertensive disorders of pregnancy

***All females of child bearing age; average age = 29 years; age range 21-36 years.

**** Other comorbidities included pulmonary oedema, acromegaly, Parkinson's disease, pneumonia, meningitis, intracranial aneurysms and renal disease.

Table 2: Normal vs abnormal

Total number of scans (n=205)	Normal vs abnormal scans	n (%)
	Normal scans	67 (32.7)
	Abnormal scans*	138 (67.3)

*Comprising of the stroke types, stroke mimickers, associations and complications

Table 3: Overall prevalence of stroke types

Findings	n (%)
Ischaemic stroke (IS)	60 (43.5)
Lacunar infarction (LI)	24 (17.4)
Haemorrhagic stroke (HS)	18 (13)

Table 4: Stage of infarction (IS – ischaemic stroke, LI – lacunar infarction)

		IS	LI
		n (%)	n (%)
Stage	Acute (including hyperacute)	21 (15.2)	1 (0.7)
	Subacute	14 (10.1)	2 (1.4)
	Chronic	25 (18.1)	21 (15.2)

Table 5: ASPECT Score and LVO

	Score	n (%)
ASPECT score – anterior circulation (hyperacute and acute only) (n=19)	0	4 (21.1)
	1	2 (10.5)
	2	1 (5.3)
	3	0 (0)
	4	0 (0)
	5	4 (21.1)
	6	1 (5.3)
	7	1 (5.3)
	8	5 (26.3)
	9	1 (5.3)
	10	0 (0)
ASPECT score – posterior circulation (hyperacute and acute only) (n=3)	0	0 (0)
	1	0 (0)
	2	0 (0)
	3	0 (0)
	4	0 (0)
	5	0 (0)
	6	0 (0)
	7	0 (0)
	8	2
	9	1
	10	0 (0)
LVO (hyperacute and acute only)	Anterior (n=19)	6 (31.6)
	Posterior (n=0)	0

Table 6: Stroke anatomical region and vascular territory (IS – ischaemic stroke, LI – lacunar infarction, HS – haemorrhagic stroke)

Stroke type:		**IS**	**LI**	**HS**
		n (%)	n (%)	n (%)
Anatomical region	Frontal	27 (19.6)	4 (2.9)	4 (2.9)
	Parietal	26 (18.8)	0 (0)	6 (4.3)
	Temporal	24 (17.4)	0 (0)	7 (5.1)
	Occipital	15 (10.9)	0 (0)	1 (0.7)
	Basal ganglia	12 (8.7)	16 (11.6)	9 (6.5)
	Cerebellum	11 (8)	2 (1.4)	1 (0.7)
	Thalamus	0 (0)	3 (2.2)	2 (1.4)
	Brainstem	0 (0)	0 (0)	1 (0.7)
Vascular territory	Anterior	4 (2.9)	3 (2.2)	1 (0.7)
	Middle	45 (32.6)	15 (10.9)	15 (10.9)
	Posterior (including brainstem)	18 (13)	2 (1.4)	5 (3.6)

Table 7: Stroke mimickers

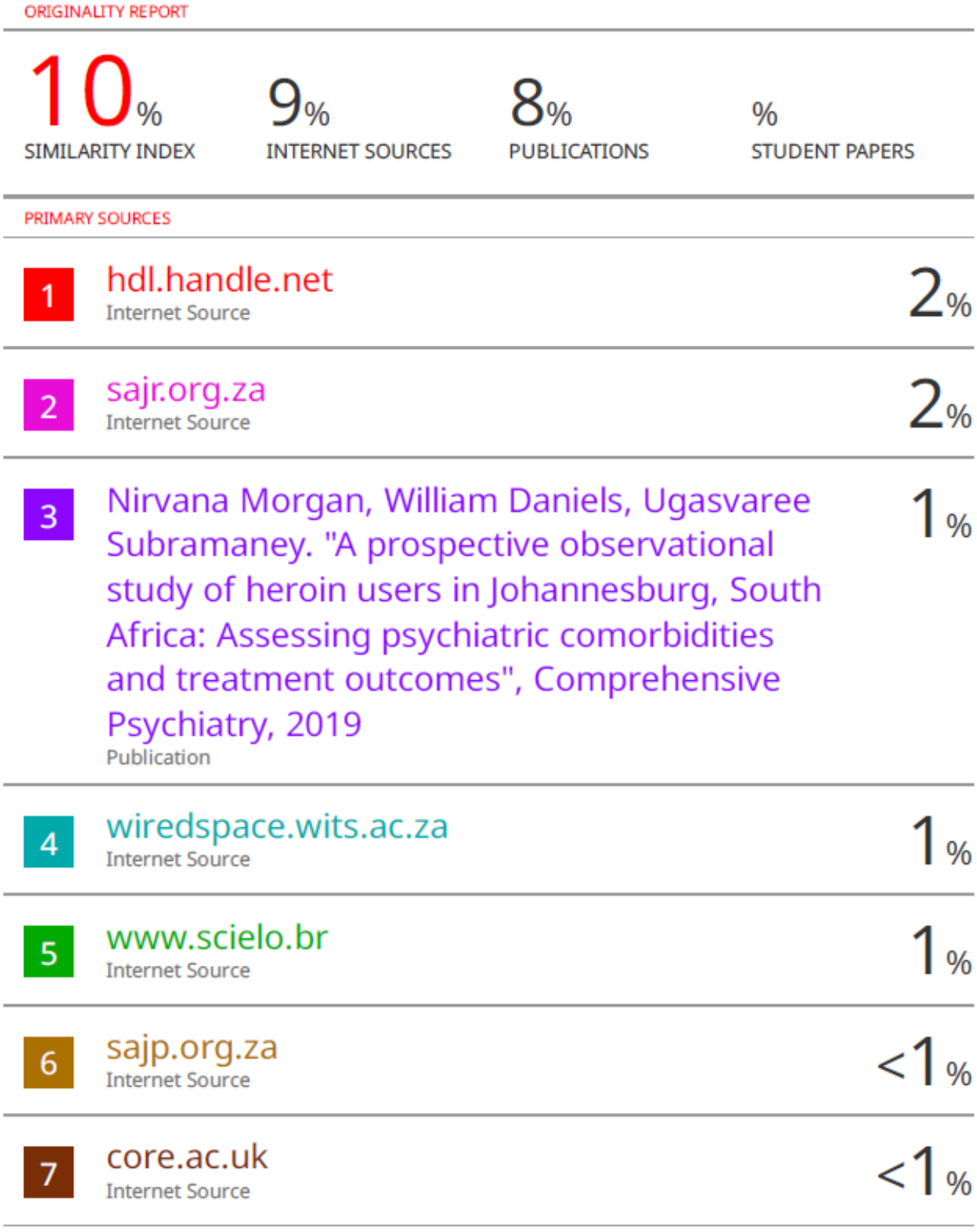
Stroke mimickers (n=32)	n	%
Intra-axial lesions: Differential Diagnoses including brain abscess/metastases/neoplasm	7	21.8
Gliosis	6	18.7
Meningioma	5	15.6
Subdural haematoma	5	15.6
Intra-axial calcifications, i.e. granulomas/Farhs disease	3	9.3
Vascular malformation	2	6.2
Progressive multifocal leukoencephalopathy (PML)	1	3.1
Chronic calvarium fracture	1	3.1
Posterior reversible encephalopathy syndrome (PRES)	1	3.1
Dural venous sinus thrombosis	1	3.1

Table 8: Associations and complications

Associations and complications	n (%)
MVD	43 (31.2)
Hydrocephalus	10 (7.2)
Brain atrophy	10 (7.2)
Midline shift	7 (5.1)
Cerebral oedema	6 (4.3)
Intraventricular haemorrhage extension	3 (2.2)

Some of the above associations and complications were co-existent

Appendix E: Turnit in Report



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Appendix F: Protocol

Hypertensive stroke and pre-contrast Computed Tomography Brain findings

Dr TJ Tshamano

2295858

Masters in Medicine Diagnostic Radiology

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1. Rationale

This studies purpose is to scrutinize the imaging findings on pre-contrasted Computed Tomography (CT) brain scans in patients with hypertensive stroke at Chris Hani Baragwanath Academic Hospital.

2. Introduction

2.1. Epidemiology

In Asia and Africa and in particular South Africa, there is a lack of epidemiological information to determine the full extent of hypertension and hypertensive stroke. There are studies reporting rudimentary prevalence rates of stroke survivors ranging from 15/100,000 in Ethiopia in 1988 to 963/100,000 in 2010 (1). The inconsistencies in the findings of these studies indicate that an uneven methodological rigour was used (1, 2).

Stroke is determined to be the second/third leading cause of mortality in Asian countries such as Hong Kong, Taiwan, South Korea and Singapore and it is proven to be the leading cause of death in China (1).

The prevalence of high blood pressure in South Africa is 35.1% (3). In sub-Saharan Africa, hypertension is the commonest contributory cause of heart disease, stroke and heart failure (4). Hypertension contributes to 13% of deaths overall and over 40% of deaths in those with diabetes in sub- Saharan Africa (4).

2.2. Risk factors

Risk factors that can be modified for stroke include hypertension, dyslipidaemia, atrial fibrillation, diabetes, smoking, hormone replacement therapy, drugs (i.e. cocaine) and alcohol abuse (5). Non modifiable risk factors are age, sex, race or ethnicity (5). Potentially modifiable factors are poor nutrition, obesity, inactivity, hypercoagulability, hyperhomocystinaemia as well as an increase in the inflammation and oxidative stress (5). Out of all the risk factors, hypertension and diabetes are on a rapid incline worldwide and contribute significantly to the rise in the incidence of stroke (5).

2.3. Hypertension guidelines

In South Africa, the universal hypertension target is a systolic blood pressure of less than 140mmHg and a diastolic blood pressure of less than 90mmHg for all categories of hypertension (3).

The current South African Hypertension Society (SAHS) definition of hypertension is classified as follows, normal is less than 120mmHg/80mmHg. Optimal is 120-129mmHg/<80mmHg. High normal is 130-139mmHg/80-89mmHg. High blood pressure Grade 1 is 140-159mmHg/90-99mmHg. High blood pressure Grade 2 is 160-179mmHg/100-109mmHg. High blood pressure Grade 3 is ≥180mmHg/≥110mmHg. Isolated systolic hypertension is ≥140mmHg/≤90mmHg (3).

2.4. Hypertension and stroke

Ischaemic stroke is caused by the blockade of an intracranial or an extracranial artery. The vessel blockade occurs because of a variety of mechanisms such as cardio-embolism, occlusive arterial disease and small vessel disease (6). Modifications in the constitution of cerebral blood vessels such as atherosclerotic changes, neural mechanical and the humoral factors contribute to the alteration in morphology of the cerebrovascular wall which predisposes to autoregulatory dysfunction (7, 8).

2.5. Hypertension manifestations

Hypertensive crisis is a term used to encompass both hypertensive emergency and hypertensive urgency (9).

2.6. Clinical manifestations

2.6.1 Hypertensive stroke

There are varied clinical presentations that a patient may experience, the spectrum being rapid-onset focal neurological signs/symptoms, low level of consciousness, and signs of brainstem malfunction. The size and location of the intra-parenchymal haematoma or infarct influences the symptomatology (10).

2.6.2. Hypertensive crisis

In the clinical practice it is important to differentiate between hypertensive emergency and urgency as there are different treatment methods between the two entities. Hypertensive emergency manifests itself as acute target organ damage (9, 11).

Target organ damage causes dysfunction of multiple organ systems such as in the eyes, brain, heart, and kidneys. The mortality rate is higher in hypertensive emergency compared to hypertensive urgency (9, 12).

The commonest signs and symptoms in hypertensive urgency are headache (22%), chest pain (27%) and difficulty in breathing (22%) (11).

2.6.3. Lacunar stroke

Clinical manifestations may either be an asymptomatic lacunar infarct, which are common in hypertensive patients, transient cerebral ischaemia and clinical lacunar syndromes which can also occur.

2.7. Imaging findings

2.7.1. Pre-contrast Computed Tomography

The aim of imaging is to differentiate a haemorrhagic stroke (15% of cases) from an ischaemic stroke (85% of cases) (6, 13). Pre-contrast CT brain scans enable exclusion of causes such as tumours, extra-axial collections, infectious causes, cerebral angioma, demyelinating disease and other stroke mimickers, which have caused neurological symptoms (14).

2.7.2. Ischaemic stroke

An hyperacute infarct occurs between 0 and 24 hours and is characterised by the hyperdense middle cerebral artery sign, outline loss of the basal ganglia, focal hypoattenuation, cortical sulcal effacement and the loss of grey white matter interface which is seen on CT scan (13). A hyperacute stroke may not display the above signs and the scan may appear falsely normal. An acute infarct is one that is in between the time frame of 24 hours to 1-week period. On CT imaging there is focal hypoattenuation (13). A subacute infarct is one that is between 1- and 3-weeks' time, during this time.

swelling is markedly reduced and the cortex may appear normal. A chronic infarct is one that is more than 3 weeks old and has undergone gliosis and appears low density.

2.7.3. Intraparenchymal haemorrhage

Intraparenchymal haemorrhage is identified on pre-contrast CT scan. It is identified as an intra-axial haemorrhage, commonly affecting the basal ganglia, brainstem, thalamus, and the cerebellum. The pathophysiology of an intraparenchymal haemorrhage is due to a tear of the vessels that have been affected by hypertensive related degenerative changes (10, 15).

2.7.4. Haemorrhagic transformation

Occurs in up to 43% of patients and ranges from petechial haemorrhage adjacent to the infarcted tissue margin to intraparenchymal haematoma>30% of the infarcted tissue exerting marked mass effect (15).

2.7.5. Lacunar stroke

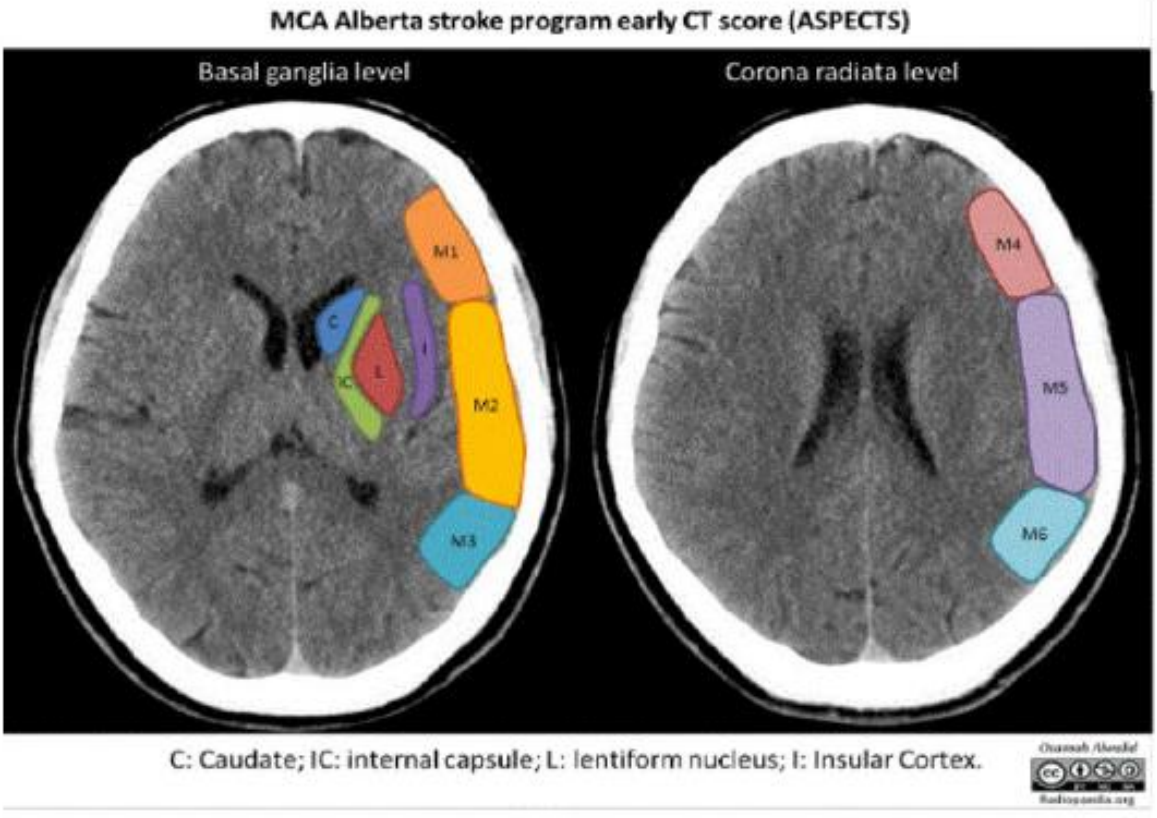
Lacunes are small cavities that are between 2 and 17mm in diameter best depicted on Magnetic Resonance Imaging. Lacunes are common in the internal capsule and basal ganglia. Lacunar strokes can be silent and multiple lacunar infarcts are associated with leukoaraiosis (14).

2.7.6. Review of ASPECT score

2.7.6.1. Anterior circulation ASPECTS

The Alberta Stroke Program Early CT Score, abbreviated as the ASPECTS, is used in conjunction with the pre-contrast CT brain to characterize the ischaemic findings. It minuses a point for each region of parenchymal hypoattenuation within the anterior circulation, that is present.

An ASPECT score of 10-points is given to a CT brain that is normal. To calculate the ASPECTS, one point is subtracted from the total of ten (13).



C: Caudate; IC: internal capsule; L: lentiform nucleus; I: Insular Cortex.

The 10 points that are analyzed are the:

- Caudate
- Insular cortex
- Internal capsule
- Putamen
- M1: the anterior middle cerebral artery cortex in the frontal operculum.
- M2: corresponding to the middle cerebral artery cortex lateral to insular ribbon.
- M3: corresponding to the middle cerebral artery posterior cortex which is in the temporal lobe posteriorly.
- M4: which is the anterior middle cerebral artery territory that is immediately above M1.
- M5: corresponding to the area superior to M2 which is of the middle cerebral artery lateral territory.
- M6: corresponding to the area immediately superior to M3 of the posterior middle cerebral artery territory (6, 13).

Lower scores of less than 5, predict that there will be a poor functional outcome (6). The lower scores are also associated with the complications of haemorrhagic transformation after thrombolytic agent has been administered (6). A normal pre-contrast CT brain does not exclude an acute infarction. Pre-contrast CT brain has a low negative predictive value for detecting small ischaemic volumes (6). ASPECTS scores between the range 8-10 are linked to experiencing a greater benefit from intravenous thrombolysis (13).

2.7.6.2. Posterior circulation ASPECTS

The posterior circulation ASPECT score (pc-ASPECTS) has been developed to assess vertebrobasilar ischaemia. Areas of hypoattenuation on CT angiogram and areas of ischaemia on the pre-contrast CT scan are assessed using the pc-ASPECT score. Compared to pre-contrast CT scan, CT angiogram has a higher sensitivity to detect ischaemia, however the specificity and positive predictive value were the same in both modalities (16). Diffusion-weighted imaging (DWI) sequences are the best modality to characterise posterior circulation stroke (16).

The posterior circulation ASPECTS also implores a 10-point scaling system. Thereafter, points are subtracted of the regions that have undergone ischaemia. In contrast to the anterior circulation ASPECTS, the midbrain and pons are both worth 2 points each respectively, irrespective of whether ischaemia has occured bilaterally or unilaterally. The thalami, occipital lobes and cerebellar hemispheres are worth 1 point each. Locations that cause mortality are infarctions that occur in the pons and midbrain (16).

Patients with a CT angiogram pc-ASPECTS score ≥8 were less likely to die and have a better prognosis (16). In patients with basilar artery occlusion and pc-ASPECT score <8, identified patients have poor functional outcome despite recanalization of the basilar artery (16). There are currently no definitive criteria to determine which patients will likely benefit from thrombolysis (16).

2.8. Treatment options of hypertensive strokes

2.8.1 Ischaemic stroke

Alteplase is a single chain recombinant tissue plasminogen activator and is the agent of choice for thrombolysis in ischaemic strokes. It works best when administered between 3 - 4 ½ from stroke symptom onset (6).

If the infarct extends for over 33% of the territory of the middle cerebral artery, it increases the risk of an intracranial haemorrhage. These patients are deemed not appropriate candidates for thrombolytic therapy and are disqualified from this treatment option (13).

2.8.2 Haemorrhagic stroke

Overall management principles of intracerebral haemorrhage include aggressive medical and or surgical management with specialist care (10). Patients with ASPECTS ranging between 5 and 10 do benefit from mechanical thrombectomy (17) especially if instituted timeously.

2.9. The project in context: Comparison to literature

The study in context of the literature, will determine the findings of hypertensive stroke on pre-contrast Computed Tomography brain scans in the cohort of patients.

3. Aim

The study aims to assess imaging presentation of hypertensive stokes on pre-contrast Computed Tomography brain (CTB) scans.

4. Study Objectives

Primary objectives:

1. To describe the pre-contrasted Computed Tomography brain (CTB) scan findings.
2. To classify the pre-contrasted Computed Tomography brain (CTB) scan findings.
3. To grade the pre-contrasted Computed Tomography brain (CTB) scan findings.

Secondary objectives:

1. To determine the inter-reader variability between three qualified Radiologists.

5. Methods

5.1. Setting

Chris Hani Baragwanath Academic Hospital (CHBAH).

5.2. Research paradigm

Retrospective cross-sectional study.

5.3. Sample size

The aim of imaging is to differentiate a haemorrhagic stroke (15% of cases) from an ischaemic stroke (85% of cases). We calculated the minimum sample size required in order to conduct a multi-rater kappa-statistic with three unique raters with a binary outcome (haemorrhagic stroke or not). Assuming that 15% of patients imaged will have a haemorrhagic stroke, a minimum acceptable Kappa (ƙ0) of 0.6, an expected Kappa difference (half width of confidence interval) of 0.15 and a significance level (α) of 5%, the minimum

sample size required is 159 patients. We used the *kapssi* command in Stata (https://fmwww.bc.edu/repec/bocode/k/kapssi.html) to estimate the sample size. The study population will be pre-contrast CT brain studies of adult hypertensive stroke patients at Chris Hani Baragwanath Academic Hospital done between the period of 1st June 2019 to 31st March 2020.

We will include all patients in this study period to increase the power of the study. On average, the radiology department at CHBAH does two CT scans of the brain for hypertensive stroke per day. Assuming 20 working days per month over the 9-month study period, the potential number of scans conducted in the study period is 360. Therefore, our minimum sample size of 159 is both achievable and realistic for the study period and can be comfortably exceeded.

5.3.1. Inclusion criteria

Hypertensive stroke patients with neurological symptoms, scanned at Chris Hani Baragwanath Academic Hospital CT scan machines between 1st June 2019 until 31st of March 2020.

- Female and male patients above the age of 18 years.
- Pregnant patients.
- In a patient having both precontract CT brain and post contrast CTB only the precontrast CT brain will be assessed.

5.3.2. Exclusion criteria

- Incomplete, lost, or illegible CT brain request forms.

5.4. Materials and methods

5.4.1. Reporters

Pre-contrast CT brains will be reported by qualified Radiologists following a data collection sheet, Appendix A. A qualified radiologist is defined as a person who has passed the Diagnostic Radiology Fellowship Final examination from the College of Medicine of South Africa (CMSA) or equivalent qualification approved by Health Professionals Council of South Africa (HPCSA). We will have three readers, the third reader will act as a tiebreaker, to achieve consensus in the event that there is disagreement between the two readers.

5.4.2. Equipment

Canon Acquilon Prime (TSX-303A/AC). Multislice helical scan.

Head protocol: 120 KV, mAs automatically adjusted according to per patient.

Installed August 2019 until present.

Philips Ingenuity CT

iDose technique. Multislice helical scan.

Head protocol: 120 KV, 30mA.

Installed March 2017 until present.

Toshibas Aquilion 64 and CXL: Multislice helical scan.

Both 120 KV and 100mA for the head protocol.

Installed 2011 and de-installed August 2019

Pre-contrast CT brain protocol.

Three readers who are qualified radiologists.

5.5. Data collection

No informed consent is necessary nor feasible because this is a retrospective analysis. All data will be collected retrospectively from the clinical records and PACS system at the study site. All patients will be assigned a research number to maintain anonymity and study information will be collected on a data collection sheet. No identifiable information will be collected, anonymized. Pre-contrast CTB scans will be read once by three qualified radiologists. All three readers will be blinded to patient's clinical information. Inter-reader variability will be calculated. The findings will be recorded on part b of the data collection sheet (Appendix A) under the assigned research number for each patient and will be analyzed by the primary investigator.

Only the primary investigator will have access to the patient's details during the allocation of the random study identity number. Patient records will always stay in the hospital premise sas data capturing will be conducted at the study site. Anonymised CT Brain scans will be saved on a password-protected hard drive and on primary site PACS system.

5.6. Reliability and validity

The pre-contrast CT brain reports will be reported by qualified radiologists.

5.7. Bias

Unavoidable selection bias when selecting scans for assessment based on the history supplied on the request form by a referring clinician.

6. Data analysis and statistics

An electronic data collection sheet (based on the Data Collection Tool - Appendix A) will be created in EpiData software, with value labels and check codes to minimize data entry errors. Data will be exported into Stata version 15 for data cleaning and analysis. Categorical variables (such as sex, race, side, anatomical site and stage) will be presented as frequencies and percentages. Continuous variables (such as age and ASPECTS score) will be tested for normality using histograms and quantile-quantile (q-q) plots. Normally distributed variables will be described in terms of means and the standard deviation. Non-normal data will be presented as medians and interquartile range. Free text fields (such as clinical findings, comorbidities, secondary complications, other findings etc) will be classified into broad categories based on the main themes that come up in the reports.

We will use three reviewers, allowing the third reviewer to be a tiebreaker and for a consensus to be achieved. To compare the agreement between the three reviewers, we will use the free-marginal inter-rater Kappa statistic which is described by Brennan and Prediger (Brennan et al, 1981), its multi-rater counterpart as described by Randolph (Randolph et al, 2005). The free marginal Kappa statistics is recommended when reviewers are at liberty to allocate observations to categories in any way that they select (Gebresillasie S et al, 2015). To compare agreement for numerical outcomes (such as the ASPECTS score) we will use the intraclass correlation coefficient. We will also categorise the ASPECTS score into binary prognostic groups (<8 vs ≥ 8), and compare inter-rater agreement using the free-marginal inter-rater Kappa statistic for the three reviewers.

7. Ethics

Permission and ethics clearance for the study was acquired from the University of Witwatersrand Human Research Ethics committee (HREC), CHBAH CEO Office and the Department of Diagnostic Radiology. Ethics Clearance Certificate Number M2011114.

7.1. Data safety

Patient details obtained during the research project will not be shared with any other parties that are not involved with the project. There will be no publishing of patient personal details to any other parties. Only the primary investigator will have access to the patient's details during the allocation of the random study identity number. Patient records will always stay on the hospital premises as data capturing will be conducted at the study site. Anonymised CT Brain scans will be saved on a password-protected hard drive and on primary site PACS system. All data will be anonymized prior to analyses.

8. Timing

Month of the Year	1 April 2020	2 May 2020	3 June 2020	4 July 2020	5-7 Aug 2020-Oct 2020	8-10 Nov 2020-Jan 2021	11-15 Feb 2021-June 2021	16 July 2021	17,18 Aug 2021, Sept 2021
Literature search	x								
Reading literature	x	x							
Summarising literature		x							
Protocol Preparation			x	x	x				
Protocol Assessment					x				
Application to ethics					x				
Collection of data						x			
Data analysis							x		
Writing up thesis							x	x	
Submit: marking									x
Writing up paper									x

9. Budget

Petrol	R1000
Stationary	R500
Hard drive	R800
Total	**R2300**

10.Anticipated problems

AGFA PACS problems leading to loss of patient data.

Access to patient request forms at the records department.

Illegibility or inadequate history provided on the request forms.

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Appendix A

Data Collection Tool: Hypertensive stroke and pre-contrast Computed Tomography brain (CTB) findings.

Patient research number: _____

Part A: Demographics

Age								
Sex	**Male**		**Female**					
Race	**Black**		**White**		**Coloured**		**Asian**	
Clinical findings								
Comorbidities and other risk factors:								

Part B: Pre - Contrast CTB Findings:

Findings		**Ischaemic Stroke**	**Lacunar Infarction**	**Haemorrhagic Stroke**	**Other Intracranial Pathology**
Abnormality on CT					
Side:	Right				
	Left				
Anatomical Site:	Frontal lobe				
	Temporal lobe				
	Parietal lobe				
	Occipital lobe				
	Basal ganglia				
	Thalamus				
	Brainstem				
	Cerebellum				
	Other-Specify				
Vascular Territory	Anterior				
	Middle				
	Posterior				
Stage:	Hyperacute				
	Acute				
	Sub-acute				
	Chronic				
ASPECTS Score	Anterior				
	Posterior				
Secondary Complications - Specify:					

Other Findings -Specify:	
Comment	
Normal /abnormal Study:	