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NONENHANCED COMPUTED TOMOGRAPHY EVALUATION OF ISCHEMIC STROKE PATIENTS PRESENTING AFTER 4.5 HOURS FROM ONSET OF SYMPTOMS USING ASPECTS, POSTERIOR CIRCULATION-ASPECTS AND X-RAY ATTENUATION RATIO: THE "TISSUE WINDOW"

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ABSTRACT

Background: Stroke is a major cause of disability and mortality world-wide. Ischemic stroke is reversible when patients present early. With the current treatment guideline in Nigeria, most ischemic stroke patients present after the 4.5 hours treatment "time window" and are ineligible for intravenous thrombolysis (IVT). However, studies with computed tomography and magnetic resonance imaging have shown variability in the duration of tissue viability, with some remaining viable up to 24 hours and beyond. These advanced imaging are not readily available in the sub-Saharan Africa but the X-ray attenuation ratio of hypoattenuating lesions on the easily accessible nonenhanced computed tomography (NECT), have recently shown to be a valuable alternative. In late presentation, IVT and endovascular thrombectomy (EVT) have proven to have reasonable degree of success in recanalization. Hence, the need for the study.
Materials and method: This was a retrospective cross-sectional study of ischemic stroke patients who presented between 4.5 and 24 hours for NECT. The extent of the ischemia was determined using the Alberta stroke programme early CT score (ASPECTS), while the Hounsfield unit ratio of the hypodense lesions was used to determine tissue viability.
Results: Fifty-five patients met the inclusion criteria and had a mean age of 58.8 years. Four (7.27%) patients clearly had ASPECTS and Hounsfield unit ratio (HUr) scores suggestive of salvageable penumbral tissue, while another four (7.27%) had the probability of being reversible.
Conclusion: Some patients were still eligible for treatment after the current guideline's 4.5 hours treatment "time window" using the ASPECTS and HUr scores on NECT.

KEYWORDS: Ischemic stroke, Nonenhanced CT, ASPECTS, X-ray attenuation ratio, tissue viability

INTRODUCTION

Stroke is a major cause of disability and mortality world-wide. The 2022 global stroke factsheet revealed an estimated number of one in four people having stroke during their lifetime (Feigin *et al.,* 2022).

Though, there is currently no accurate data on the nation-wide prevalence of stroke in Nigeria. A 2018 meta-analysis of eleven selected studies covering 1995 – 2016 reported prevalence of 27.4 per 100,000 from 2010 upwards (Adeloye *et al.,* 2019). In the sub-Saharan Africa, stroke has a very poor outcome and the 30-day case fatality range in

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Nigeria was quoted to be 21.2 – 40.0% (Arabambi *et al.,* 2022). Ischemic stroke is reversible with timely diagnosis and appropriate intervention. Eligibility for intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (Alteplase) is largely time dependent (treatment time window). This was initially set within 3 hours from onset of symptoms and later increased to 4.5 hours (Hacke *et al.,* 2008). Only 0 – 9.1% of ischemic stroke patients present before 4.5 hours and are thus eligible for treatment, with the current time window in Nigeria. Furthermore, wake-up and unwitnessed strokes which occur in 20 – 22.5% and 13.65% (Rubin and Barrett, 2015; Kim *et al.,* 2016) of patients respectively, are excluded from treatment because of the uncertainty of the time of onset. Recently, the treatment window in western countries was further expanded to be between six to twenty-four (6 – 24) hours, using either IVT or endovascular thrombectomy (EVT), based on findings during advanced imaging such as the computed tomography perfusion (CTP) and or magnetic resonance imaging (MRI) perfusion (Nogueira *et al.,* 2018; Mondelaers *et al.,* 2019; Nguyen *et al.,* 2022). This should be a welcomed relief in Nigeria, because it was observed that 25.0 – 51.7% of ischemic stroke patients present late but within 24 hours from onset of symptoms (Ogbole *et al.,* 2015; Arabambi *et al.,* 2021). Studies helped to differentiate the irreversibly damaged brain tissue (infarct core) from the tissue that could be salvaged (penumbra) (Powers *et al.,* 2019; Alzahrani *et al.,* 2023), and have led to a paradigm shift for treatment eligibility from “time window” to “tissue window” (Hill *et al.,* 2015; Wang *et al.,* 2019). However, these advanced imaging services are not readily rendered by most hospitals that manage stroke cases including well established stroke units (Kim *et al.,* 2021). Although, great strides have been made in the last two decades to correlate the findings (infarct core and penumbra) on CT and MRI with findings on the readily available nonenhanced CT (NECT) (Alzahrani *et al.,* 2023). The developed evaluation tools using NECT are, the Alberta stroke programme early CT score (ASPECTS) for anterior circulation (Barber *et al.,* 2000), posterior circulation acute stroke prognosis early computed tomography score (pc-ASPECTS) (Puetz et al., 2008) and X-ray attenuation (Hounsfield unit) ratio (Demeestene *et al.,* 2017; Zhu *et al.,* 2021; Wang *et al.,* 2021). These innovative quantitative assessments of acute ischemic stroke with nonenhanced computed tomography are poorly utilized in most Nigerian hospitals. Subsequently, 90.9 – 100% of ischemic stroke patients do not receive the appropriate treatment with resultant high rate of mortality and disability where majority of the patients become vulnerable to having secondary complications of the disease (stroke) including lobar atrophy, white matter lesions, cerebral infarct, in addition to structural changes/morphological patterns in the circle of Willis: the major arterial supply to the brain (Igiri *et al*., 2017; Paulinus *et al*., 2017; Udo-Affah *et al*., 2020; Paulinus *et al*., 2021; Paulinus *et al*., 2023). The study therefore, focused on patients who presented late (4.5 to 24 hours) for nonenhanced CT, were eligible for treatment with intravenous thrombolysis or endovascular thrombectomy based on ASPECTS, pc-ASPECTS and Hounsfield unit (HU) ratio.

MATERIALS AND METHODS

Study design

This was a retrospective cross-sectional observational study that involved evaluation of non-enhanced brain computed tomograms of acute ischemic stroke patients, performed between February 2021 and December 2022 in the Department of Radiology of a Nigerian tertiary healthcare facility. Approval was obtained from the institutional review board with protocol assigned number; UCTH/HREC/33/Vol.III/044. Patient confidentiality was maintained by assigning numbers in lieu of their names. The machine used was a 32 slice Siemens SOMATOM go.Now manufactured by Siemens Healthcare GmbH, Henkestr. 12791052 Erlangen, Germany in 2020. The Clinical information, patient management, relevant demographic data and CT images were extracted from the CT register, medical records and the Radiology information system (RIS) in the reporting work station.

Study protocol

The NECT images of all acute ischemic stroke patients were retrieved from the archive in the RIS and reviewed by a Radiologist with more than three years of experience in neuroradiology. The CT hypoattenuating (hypodense) lesions were evaluated quantitatively using ASPECTS, pc-ASPECTS and X-ray attenuation ratio (tissue window) to determine patients who presented late but within 24 hours that were eligible for intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT). The number of eligible patients based on the tissue window were then compared with the number that were considered eligible using the existing local treatment guideline of 4.5-hour time window from onset of symptoms. The number that actually received recanalization treatments were also retrieved from the medical records in the emergency department and neurology ward.

Inclusion criteria

Ischemic stroke patients who had a NECT between 4.5 – 24 hours from onset of symptoms, involvement of either the anterior or posterior cerebral circulations, brain parenchymal hypoattenuation > 20 HU, patients ≥ 18years, no IVT or EVT within the last three months.

Exclusion criteria

Patients with haemorrhagic stroke, haemorrhagic transformation, previous ischemic stroke, brain parenchyma hypoattenuation with HU < 20, intracranial masses or other structural abnormality, bilateral hypoattenuations involving the exact mirror locations on both sides.

NECT image analysis

The NECT images were viewed with the RadiAnt's Digital imaging and communication in medicine (DICOM) viewer (64-bit) software using the standard brain window (WL = 40, WW = 80) and a "stroke window" of: WL= 40, WW= 40 (Mullins *et al.,* 2006; Reidler *et al.,* 2019). These stroke window values were imputed through the customized option of the window settings. The images were evaluated in two ways;

i) Semi-quantitative assessment of anterior circulation with ASPECTS (Barber *et al.,* 2000), and the posterior circulation with pc-ASPECTS (Puetz *et al.,* 2008; Puetz *et al.,* 2011) representing the territories of middle cerebral artery and posterior cerebral circulation respectively**.** These involved the manual division of each cerebral hemisphere into ten (10) regions for the middle cerebral artery (MCA) territory and eight (8) regions in both hemispheres for the posterior cerebral circulation. Both have a 10-point scoring system from 0 – 10. ASPECTS regions/scores: These are ten (10) manually delineated topographic regions in each hemisphere, having equal scores of 1. Seven (7) of these are at the level of the caudate nucleus (figure 1a) correspond to the location of the head of caudate nucleus, internal capsule, lentiform nucleus, insular cortex, M1, M2 and M3**.** The remaining 3 regions (figure 1b) were just above the M1, M2 and M3 respectively at the level of the body of the lateral ventricles: M4, M5 and M6. A point is deducted from 10 for each region having the early signs of ischemic stroke, including parenchymal hypoattenuation. The pc-ASPECTS regions consisted of eight (8) regions demonstrated at three levels: thalamus, midbrain and pons (figure 2a – c). The thalamus, occipital lobe and cerebellar hemisphere on both sides had 1 point each, while the midbrain and pons had 2 points each. The corresponding point or points are subtracted from 10 for each affected pc-ASPECTS region.

ii) Quantitative assessment was done by measuring the X-ray attenuation (HU) of any site involved in parenchyma hypoattenuation. The region of interest (ROI) used for measurement was 0.1cm^2. The average of at least three measurements in each hypoattenuation was used, except if the lesion was less than 0.1cm^2 in which case, only one measurement was taken. The HU ratio is the HU value of the parenchymal hypoattenuation in the affected ASPECTS or pc-ASPECTS region divided by HU value of the exact (mirror) region of the contralateral cerebral and cerebellar hemispheres, and the thalamus (Alzahrani *et al*., 2023).

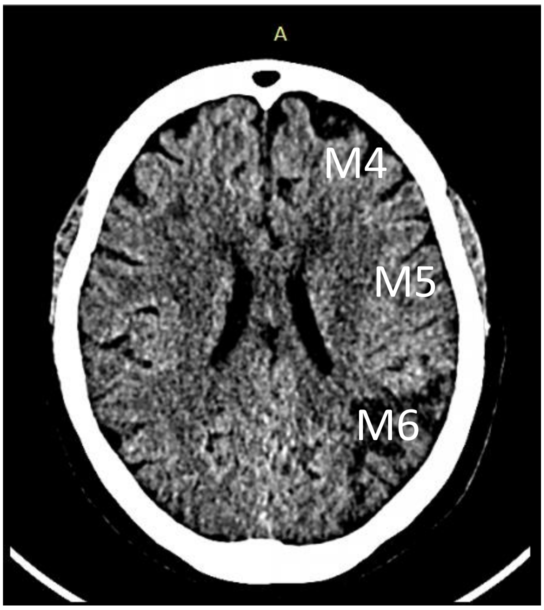

Figure 1a. Figure 1b.

Figure 1a and b showing the Alberta stroke programme early computed tomography score (ASPECTS) regions. Figure 1a. Nonenhanced axial CT at the level of the caudate nucleus. CN = Caudate nucleus, I = Insular cortex, LN = Lentiform nucleus, IC = Internal capsule.

Figure 1b. Nonenhanced axial CT at the level of the corona radiate and body of the lateral ventricles.

Figure 2a. Figure 2b. Figure 2c.

Figures 2a – c showing the Posterior circulation acute stroke prognosis early computed tomography score (pc-ASPECTS) regions.
Figure 2a. Nonenhanced axial CT at the level of the Thalamus. T = Thalamus, OL = Occipital lobe
Figure 2b. Nonenhanced axial CT at the level of the midbrain. MB = Midbrain
Figure 2c. Nonenhanced axial CT at the level of the pons. P = Pons, C = Cerebellum

Analysis

Microsoft Excel spread sheet was created for entry of the data: patients' demographics (age, gender), HU value of the parenchymal hypoattenuation in the ASPECTS and pc-ASPECTS regions of the affected hemisphere and the HU value of the exact mirror image in the contralateral hemisphere. The data obtained were analyzed using the simple statistical methods and appropriate descriptive data were presented as frequencies and percentages. Tables and bar chart were the means of displaying the result where applicable. Some continuous variables were also reported as means and standard deviation (mean ± SD).

RESULTS

Fifty-five (55) patients met the inclusion criteria. Parenchymal hypoattenuation was the only NECT ischemic stroke finding in all the patients. Majority (N=33, 60%) had single parenchymal hypoattenuation, while the remaining 40% had multiple hypoattenuations in the same vascular territory, with the exception of one. There were a total of 110 parenchymal hypoattenuations but in four of the patients, the HU of the hypoattenuations were less than 20, leaving us with 106 for evaluation.

The mean age of the patients in this study was 58.80 years. The males had a higher average of 60.64 years compared to 56.89 years for the females.

Table 1 shows the baseline characteristic of the fifty-five acute ischemic stroke patients who met the inclusion criteria and had nonenhanced computed tomogram (NECT) between 4.5 – 24 hours from onset of symptoms. There were marginally more males (50.9%) than females. Most (61.82%) of the patients were above 55 years old, with the 55–64-year-olds, constituting the largest group (32.73%) and those above 85 years, the smallest (1.82%). Unilateral involvement of the left hemispheres of the brain were the most common (50.91%) finding in ischemic stroke, while the right made up 30.91% of the cases. The brainstem was affected in 16.36% and there was bilateral involvement of the hemispheres in just one case (1.82%). Majority (67.27%) of the observed ischemia occurred in the anterior circulation and they also commonly (60%) present as single parenchymal hypoattenuations.

Figure 3 depicts the distribution of parenchymal X-ray attenuation of all the ASPECTS (anterior circulation) and pc-ASPECTS (posterior circulation) regions evaluated in the 55 patients. There was a total of 514 regions: 370 and 144 for ASPECTS and pc-ASPECTS respectively. In the anterior circulation, abnormal parenchymal hypoattenuation were observed in 80 (21.62%) of the regions. The hypoattenuations were seen in 26 (18.05%) regions in the posterior circulation.

Table 2 illustrates the distribution of the ASPECTS and pc-ASPECTS scores among the patients. Majority (N=27, 49.09%) of patients had an ASPECTS or pc-ASPECTS score of nine (9). Eighteen (37.73%) patients scored eight (8), four (7.27%) scored seven (7) and two (3.64%) scored six (6). One patient each scored five (5), three (3), two (2) and zero (0), while no one scored one (1) or four (4).

Table 3 outlines the frequency distribution of the hypoattenuations and patients based on HUr cut-off criteria for infarct core and penumbral lesions. It also shows the mean HU of all hypoattenuations in each HUr categories. Only one hypoattenuating lesion in a patient had a HUr ≥ 0.94 and this is highly suggestive of a penumbral lesion. For HUr equal or greater to 0.87, five hypoattenuating lesions observed in four patients made this score. The hypoattenuating lesions of forty-six patients had HUr of ≤ 0.79, with a very high probability of them being infarct cores. Only eleven hypoattenuations, in nine patients scored > 0.79 and therefore had very slim chances of being salvageable penumbral lesions**.** However, all the posterior circulation hypoattenuations HUr were < 0.79 inferring that HU increases as the HUr increases, from the group with the highest probability of infarct core to that with the highest probability of a penumbral lesion.

Table 4 outlines the HUr, ASPECTS and pc-ASPECTS of the nine patients that had hypoattenuating lesions with HUr score ≥ 0.79, thereby having a chance of being penumbra and ultimately qualifying for EVT or IVT. It shows the treatment eligibility of the patients based on the HU ratios of their hypoattenuating lesions and their corresponding ASPECTS or pc-ASPECTS scores. Four patients had HU ratios suggestive of both ischemic penumbra and core lesions. Their lowest scoring hypoattenuations, were HUr of 0.58, 0.6, 0.67 and 0.79. However, one of these four would be ineligible for EVT or IVT because of a corresponding very low ASPECTS score of three (3).

None of the patients in this study received intravenous thrombolysis or endovascular thrombectomy.

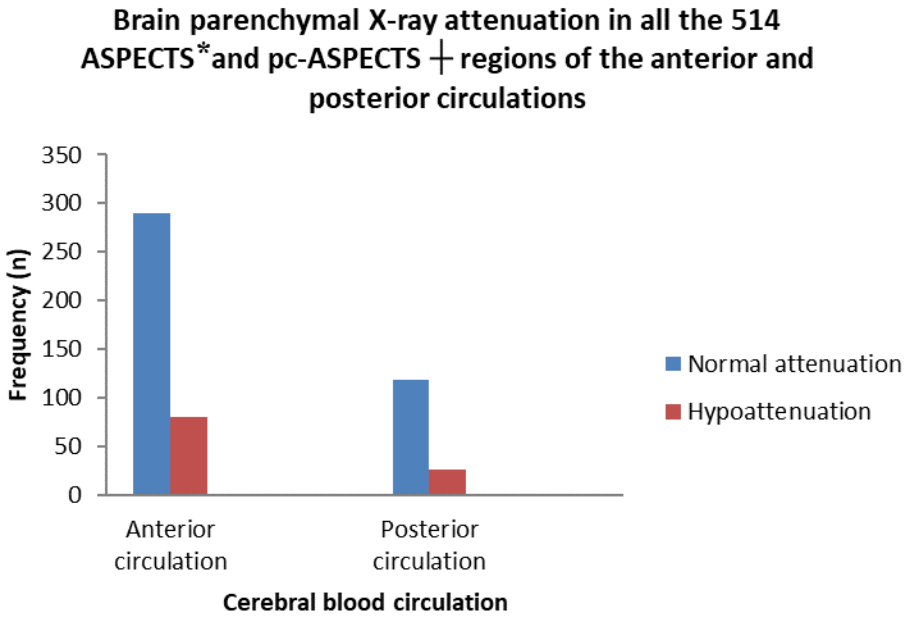

Figure 3. Distribution of X-ray attenuation in the ASPECTS and pc-ASPECTS regions evaluated in the major blood supply territories.

*ASPECTS = Alberta stroke programme early computed tomography score

┼ pc-ASPECTS = Posterior circulation acute stroke prognosis early computed tomography score.

Table 1: Baseline characteristics of acute ischemic stroke patients (n = 55)

Variables	Frequency (n)	Percentage (%)
Gender		
Male	28	50.90
Female	27	49.10
Age group (years)		
29 – 44	9	16.36
45 – 54	12	21.82
55 – 64	18	32.73
65 – 74	9	16.36
75 – 84	6	10.91
≥ 85	1	01.82
Hemisphere affected		
Right	17	30.91
Left	28	50.91
Brain stem	9	16.36
Bilateral	1	01.82
Blood circulation affected		
Anterior	37	67.27
Posterior	18	32.73
Hypoattenuation lesion		
Single	33	60.00
Multiple	22	40.00

Table 2: Topographic extent/size of brain tissue involved in ischemia (ASPECTS/pc-ASPECTS)

ASPECTS/pc-ASPECTS	Patients' frequency (n)	Percentage (n)
9	27	49.09
8	18	37.73
7	4	7.27
6	2	3.64
5	1	1.82
4	0	0
3	1	1.82
2	1	1.82
1	0	0
0	1	1.82
Total	55	100

ASPECTS = Alberta stroke programme early computed tomography score
pc-ASPECTS = Posterior circulation acute stroke prognosis early computed tomography score

Table 3: Distribution of patients and hypoattenuations based on the cut-off X-ray attenuation (HU ǂ) ratios of infarct core and penumbral lesions

HU ratio (HUr)	Number of patients (n)	Percentage of patients (%)	Number of hypoattenuating lesions (n)	Mean HU of hypoattenuating lesions in HUr category
Infarct core HUr				
≤ 0.79	46	83.64	95	24.79
> 0.79	9	16.36	11	29.40
Differentiating HUr (optimal)				
< 0.87	51	92.73	101	25.32
≥ 0.87	4	7.27	5	29.99
Penumbral lesion HUr				
< 0.94	54	98.18	105	25.48
≥ 0.94	1	1.82	1	36.29

ǂ HU = Hounsfield unit, § HUr = Hounsfield unit ratio

Table 4: Patients (n = 9) eligible for EVT based on their X-ray attenuation ratio (HUr) in correlation with ASPECTS

HUr/ HUr range of Parenchymal hypoattenuation	ASPECTS/ pc-ASPECTS	EVT Eligibility (+ / -)
0.79 – 0.82	7	+
0.58 – 0.80	8	+
0.80	9	+
0.6 – 0.87	3	-
0.67 – 088	6	+
0.86	9	+
0.89	9	+
0.91	9	+
0.95	8	+

HUr = Hounsfield unit ratio
ASPECTS = Alberta stroke programme early computed tomography score
pc-ASPECTS = Posterior circulation acute stroke prognosis early computed tomography score
EVT = Endovascular thrombectomy
+ = Eligible for EVT
- = Ineligible for EVT

DISCUSSION

The concept of ASPECTS gives a topographic representation of the site and size or extent of ischemia in a uniform reproducible format. ASPECTS ≥ 7 within 4.5 hours of onset of symptoms qualifies for IVT and those who present after 4.5 - 6 hours with a minimum score of 6, qualify mainly for EVT when the occlusion involves the proximal segments of the middle cerebral artery and other large vessels**,** with a few also benefitting from IVT, especially in the distal smaller vessels (Van der Zijden *et al.,* 2019). However, ASPECTS or pc-ASPECTS does not differentiate between isolated brain swelling and hypoattenuation (they were awarded same score), and does not directly assess for infarct core and penumbra. Subsequently, X-ray attenuation (HU) ratio measurement was used as a more direct method of measuring the degree of ischemia hence, the differentiation between infarct core and penumbra.

In the index study, acute ischemic stroke was observed more in males than females (50.90% vs 49.10%). This is similar to the findings of 60.4% vs 39.65% and 53.5% vs 46.5% observed by Zhu *et al.* (2021) and Ogun *et al.* (2005) respectively. However, three other similar studies revealed a higher incidence among females: 52.9% vs 47.1%, 52.5% vs 47.5% and 58% vs 42% (Olamoyegun *et al.,* 2016; Reidler *et al.,* 2019; Arabambi *et al.,* 2021). The mean age of all the patients in this study was 58.80 years. The males had a higher average of 60.64 years, compared to 56.89 years for the females. The combined mean age in this study was lower than the 61.5 years observed by Alzahrani *et al.* (2023), 64.08 years by Olamoyegun *et al.* (2016) and 75.4 years by Mainali *et al.* (2014). Separately, the male and female mean ages were also lower than what was observed in a similar study: 76 years and 74 years respectively (Reidler *et al.,* 2019). Collectively, the 55 – 64 years age group were the most commonly (32.73%) affected with ischemic stroke in this study. This is contrary to the findings of Edzie *et al.* (2021) who observed that the commonest age group was ≥ 65 years, accounting for almost half (N=277, 46.09%) of the patients in their study, followed by those between 25 – 54 years (N=170, 28.29%).

The hemispheric involvement in ischemic stroke has been robustly researched. Most researchers favour the left over the right in frequency, even in relation to the common predisposing factors such as hypertension, diabetes, dyslipidaemia and cardiovascular diseases. In the anterior circulation, the left hemisphere was a common (53.2%) site of lodgement of blood clots, which were dislodged by atrial fibrillation, resulting in cardio-embolism; a major mechanism of large vessel or multiple foci ischemic stroke (Jaakkola *et al.,* 2019). In consonant with most of the previous assertion irrespective of the aetiology, our study revealed that the left hemispheres (cerebral or cerebellar) were more (N=29, 52.73%) involved in ischemic stroke. This agrees with Zhu *et al.* (2021), Wang *et al.* (2019) and Hedna *et al.* (2013). The anterior circulation was more commonly involved (67.27%) in ischemic stroke in the index study. A comparable trend with higher proportions of 75.08% and 70.0% demonstrated by Hedna *et al.* (2013) and Frid *et al.* (2020). Thus, anterior circulation ischemic stroke is said to have a better outcome compared to the posterior, when the patients arrives later than 4.5 hours and are treated with intravenous thrombolysis (Sener *et al*., 2008) characterised with single hypoattenuating lesion.

The ASPECTS scoring system depict the size of brain ischemia**.** Fifty-one (92.73%) patients in this study had a small size of brain tissue involved (ASPECTS ≥7) in the ischemic process and 49.09% of these were focal (ASPECTS = 9). With these high

ASPECTS scores alone, most, if not all the fifty-one patients would have had favourable outcomes, if they were treated with intravenous thrombolysis or endovascular thrombectomy within 4.5 hours from onset of symptoms (time window) in accordance with the current guideline at the study centre. However, they all presented late for the nonenhanced CT (NECT), between 4.5 to 24 hours and were not treated with intravenous thrombolysis and endovascular thrombectomy. In the present study, provided other items in the eligibility criteria were met**,** only one (1.82%) patient most definitely had a very high probability of favourable EVT or IVT treatment outcome, having scored 8 in the ASPECTS and a HUr of 0.95**,** as recommended by proponents of these quantitative diagnostic tools in their studies (0.93 – 0.96) (Mokin *et al.,* 2017; Alzahrani *et al*., 2023). However, since the optimal HUr differentiating penumbral from core lesions observed by Alzahrani *et al*. (2023) was 0.87, four (7.27%) patients had a high likelihood of having a positive treatment outcome. The calculated mean HUr of all the infarct core lesions was 0.79 in same study, suggesting that some hypoattenuations with HUr > 0.79 were penumbral. Therefore, the eight (14.55%) patients in our study whose lesion HU ratios were > 0.79 had the probability of favourable treatment outcomes, because they had corresponding high ASPECTS scores of ≥ 7**.** We observed that all the lesions in the posterior circulation had HUr less than 0.79, which suggest that they were infarct cores and were not eligible for EVT or IVT. This high rate of ineligibility for treatment in the posterior circulation was also supported by the higher rate of poor treatment outcomes compared to the anterior circulation among patients who present late after 4.5 hours from onset of symptoms in a related study (Sommer *et al*., 2018). One of the patients with multiple lesions who also had good HU ratios in a few of the hypoattenuations was ineligible for EVT or IVT because of the extensive nature of the ischemic process, having scored 3 in the ASPECTS. Hypoattenuation is not synonymous with irreversibly damaged brain tissue (infarct core).

CONCLUSION

Although, majority of the patients who presented late between 4.5 – 24 hours were late using the "tissue window", about eight patients (N=8, 14.55%) still had HU ratio suggestive of the possibility of a viable brain tissue (penumbra) that could have been successfully treated with either endovascular thrombectomy or intravenous thrombolysis. Estimating the size of ischemia with ASPECTS and pc-ASPECTS and assessing the viability of the hypodense ischemic brain tissue using X-ray attenuation ratio (HUr) are simple tools that can save lives in the absence of perfusion studies which are not readily available or none existent in some parts of sub-Saharan Africa. Thus, training in the practice of endovascular thrombectomy should be encouraged and made available in all stroke units. Also, recombinant tissue plasminogen activator (Alteplase) should be more readily accessible.

STUDY LIMITATIONS

The major limitations to the study are due to it being a single centre retrospective study and the small sample size. The access point for EVT was not evaluated to rule out possible difficulties and contra-indications including cervical vessel dissection, stenosis, vascular variant and abnormalities.

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Nil

CONFLICT OF INTEREST

There were no conflicts of interest declared

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