

Role of Computed Tomography Perfusion in Early Evaluation of Acute Cerebral Ischemia

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ABSTRACT

Background: CT perfusion (CTP) is well-established equipment that is utilized for assessment of cerebral parenchyma viability, which had a crucial role in the evaluation and management of acute stroke. CTP allows for distinction between salvageable ischemic tissues of the brain, known as the “penumbra”, and irreversibly damaged infarcted brain tissue, referred to as the “infarct core”. **Methods:** This is a prospective study which was conducted on 36 patients with stroke symptom onset within 24 hours (Acute ischemic stroke; AIS). Patients were evaluated with non-enhanced CT to exclude hemorrhage; CTP was performed after exclusion of hemorrhage. Based on imaging, endovascular intervention was scheduled for patients with persistent dysfunction, large vessels occlusion and with salvageable brain tissue as detected by the DWI & perfusion CT scans. NIHSS, ASPECTS&mRS scores were used to assess stroke severity. **Results:**CTP had high sensitivity (88%) with 95% confidence interval (0.69-0.97) and high specificity (100%) with 95% confidence interval (0.71-0.1). CT perfusion infarct volume was associated with good functional outcomes in univariate analysis (OR, 0.93; 95% CI, 0.91-0.99; p=0.002) and remained a significant predictor in multivariable analysis after age, NIHSS, hypertension, diabetes mellitus had adjusted (OR: 0.93; 95% CI: 0.91-0.99; P= 0.03). **Conclusion:**It is suggested that the application of CTP as an adjunct test may provide some benefits in enhancing the certainty associated with the administration of stroke treatment. Furthermore, the recognized significance of employing imaging criteria in identification of individuals with AIS who get advantages from endovascular revascularization has been demonstrated.

Keywords:CTP, Ischemia, Acute, Cerebral.

INTRODUCTION

Ischemic stroke is an important contributor to worldwide morbidity and mortality, characterized by acute obstruction of cerebral blood flow resulting from arterial occlusion. The impairment of neuronal functioning occurs as a result of reduced perfusion, and if perfusion is not restored, irreversible damage to brain tissue occurs [1]. The primary objective of acute treatment is to restore blood flow in the obstructed

artery by employing intravenous thrombolytics and/or mechanical thrombectomy. Given the substantial expenses and potential adverse effects associated with both treatment choices, such as an elevated risk of bleeding, it becomes crucial to carefully identify and choose patients who are likely to derive benefits from both interventions [1]. Stroke syndromes exhibit considerable clinical and radiological diversity.

Nonetheless, arterial occlusion or infarction overwhelmingly represents a primary aetiology of stroke, constituting 80-85% of cases. This condition arises from compromised blood flow to the brain, resulting in eventual functional impairment. Approximately 24-46% of AIS are attributed to the occurrence of major vascular occlusion [2]. Computed tomography perfusion (CTP) serves as a valuable adjuvant to conventional non-contrast CT (NCCT) brain imaging and CT angiography (CTA) in the prompt evaluation and diagnosis of acute ischemic stroke (AIS). Cerebral perfusion imaging allows the distinction between salvageable ischemic brain tissue, known as the penumbra, and irreversibly damaged infarcted brain tissue, referred to as the infarct core [3]. CT Perfusion (CTP) involves the acquisition of a series of 3D computed tomographic scans following the intake of the contrast agent through intravenous injection. The resultant four-dimensional image demonstrates the movement of the contrast material within the brain tissues. Each spatial voxel contains a time-attenuation curve that depicts the changes in intensity caused by the presence of the contrast agent. Extensive research has been conducted to quantify these images, with a specific focus on estimating perfusion parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and T max [1].

The aim of the study was to assess the effectiveness of CT perfusion imaging in accurately detecting and quantifying cerebral blood flow abnormalities during acute phase of ischemic stroke, and to determine its potential for guiding early therapeutic interventions and predicting clinical outcomes.

METHODS

This prospective study involved 36 patients and was conducted at Zagazig University hospitals and International Medical Center.

Inclusion criteria: Patients presented with symptoms consistent with acute ischemic stroke within the initial 24-hour period, displaying a National Institutes of Health Stroke Scale (NIHSS) score of 2 points or higher. The National Institutes of Health Stroke Scale (NIHSS) served as the standardized assessment tool to quantify the extent of neurological deficits in stroke patients. The NIHSS assigns a score between 0 and 42, with higher scores indicating more severe neurological abnormalities.

Exclusion criteria: Patients exhibiting elevated arterial blood pressure exceeding 185/110 mmHg, individuals who had received intravenous (IV) thrombolytic therapy at a dose surpassing 0.9 mg per kg or 90 mg of alteplase, patients presenting coagulation abnormalities, such as platelet counts $< 40 \times 10^3/\text{dL}$, PTT (partial thromboplastin time) > 50 seconds, patients with an INR (international normalized ratio) > 3.0 , or those for whom contrast-enhanced CT was contraindicated due to renal impairment or iodine allergy.

Data Collection and Procedures:

All patients' demographic and clinical data were collected. Stroke onset was defined as the last time patient was seen well. The duration between the appearance of symptoms and the restoration of blood flow (reperfusion) was divided into two distinct intervals: the time from symptom onset to the initiation of imaging procedures, and the time from imaging to the actual reperfusion procedure.

Initially, non-contrast computed tomography (NCCT) analysis served the dual purpose of

ruling out intra-cranial hemorrhage and employing the Alberta Stroke Program Early CT Score (ASPECTS). ASPECTS, a quantitative topographic CT scan score designed for middle cerebral artery (MCA) stroke patients, employed a scoring system ranging from 0 to 10. In this study, a deduction of 1 point was applied for the presence of early ischemic changes in specific regions on the CT scan. When dealing with posterior cerebral artery (PCA) infarction, ASPECTS scoring was adapted for the posterior circulation (pc-ASPECTS). ASPECTS scoring aided in identifying the site of infarction and assisted in placing regions of interest (ROIs) in CT Perfusion (CTP) analysis. All patients underwent non-enhanced CT scans to ascertain the absence of intracranial hemorrhage. Following the exclusion of hemorrhage, CT perfusion (CTP) imaging was conducted. The CTP imaging procedure utilized an 80-detector 160-multichannel CT scanner (Aquilion model manufactured by Toshiba Medical Systems). For contrast enhancement, non-ionic contrast material; Iopromide, was administered.

The CT perfusion technique involved capturing images across four consecutive sections, each with an 8 mm thickness. Following the injection of 50 mL of contrast agent at a flow rate of 5 mL/s via an automatic injector, a time delay of 5 seconds was achieved. Subsequently, a cine series lasting 45 seconds was obtained, employing specific parameters: 120 kilovolts peak potential (kVp), 200 milliamperes (mA) of current, and a rotation time of 0.4 seconds. In case of an anterior circulation infarct suspicion, data acquisition was done at the basal ganglia level, while if a posterior circulation infarct was suspected, acquisition

was done at the level of mid-cerebellum. Post-processing of data was done using specialized software; Vitrea workstation (a commercially available software developed by Vital Images, Inc.). The software employs a closed-form deconvolution technique to generate maps measuring Mean Transit Time (MTT) and cerebral blood volume (CBV). It identifies arterial input within a specified Region of Interest (ROI) around the anterior cerebral artery.

Calculation of CBV considers the integral of time-enhancement curves while accounting for partial volume averaging, especially in the superior sagittal venous sinus. This adjustment ensures accuracy in assessing CBV. A simple formula using CBV and MTT values allows the software to determine cerebral blood flow (CBF). Additionally, Time to Peak (TTP) maps were also generated as part of the analysis. MTT is the time between the arterial inflow and the venous outflow. TTP refers to the time taken by the contrast to achieve maximum enhancement (HU value) in the selected region of interest (ROI) before its value starts decreasing. CBV is the volume of blood available per unit of brain tissue and is usually measured as milliliters per 100 gm of blood.

Data analysis was done qualitatively and quantitatively. Color-coded maps used for rapid assessment and provided a broad overview to detect large ischemic areas. Quantitative assessment involved placing multiple ROIs in suspected ischemic regions and their corresponding locations in the contralateral lobe.

In diagnosing acute ischemic stroke using perfusion CT, reduced Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV), alongside increased Mean Transit Time

(MTT) and Time to Peak (TTP), were identified. Areas with matched abnormalities in CBV and MTT maps were designated as "core infarct." Conversely, regions displaying prolonged MTT and decreased CBF while maintaining relatively preserved CBV indicated potentially salvageable tissue, known as the "ischemic penumbra."

After conducting Non-Contrast Computed Tomography (NCCT) and CT Perfusion (CTP), the emergency neurology team evaluates each patient's eligibility for revascularization procedures and determines the appropriate management strategy. For reference standards, MRI-DWI, follow-up MRI or CT, and CT angiography were employed. Upon patient discharge, the Modified Rankin Score (mRS) was used to assess outcomes. The mRS, a 7-point scale ranging from 0 (indicating the absence of symptoms) to 6 (representing death), indicated functional independence and a good outcome with a score of two or lower.

Ethical and administrative considerations: The study obtained approval from the institutional review board (IRB) under the designation (ZU-IRB#6799/8-3-2021), with all patients or their representatives granting informed consent. The research was conducted in adherence to the World Medical Association's Code of Ethics (Declaration of Helsinki) regarding human experimentation.

STATISTICAL ANALYSIS

The data entry, processing, and statistical analysis were performed using MedCalc version 20 (MedCalc, Ostend, Belgium). Various statistical tests were employed in this study, including the Mann-Whitney test, Chi-square testing, logistic univariate and multivariate regression analysis, and

ROC curve analysis. The data were presented and subjected to appropriate analysis based on the nature of the data (normally distributed or skewed) collected for each variable. Statistical significance was defined as p-values below the threshold of 0.05.

RESULTS

This study included 36 patients with early onset stroke symptoms within 24 hours; the mean age of all patients was 62.5 years \pm 6.85 SD. Regarding gender distribution of the patients, (75%) of the studied patients were males; while (25%) were females. The demographic data and comorbidities in all 36 patients who were included in the study are shown in (Table 1).

CTP was performed between 3 and 24 (median 8.5) hours after the symptoms onset. The most commonly affected artery among the studied patients was the MCA (52.8%), followed by the PCA in (22.2%) of patients, while the ACA was affected in only 4 patients (11.1%). Clinical data and CTP parameters among the studied patients were demonstrated in (Table 2).

Validity data of different CT perfusion parameters were mentioned in table (3), indicating infarct core volume AUC=0.778, penumbra volume AUC=0.736 and mismatch volume AUC=0.731.

With regard to the functional result observed in the patients under study table (4), it was found that 41.7% of the patients had a modified Rankin scale score of more than 2. A significant difference was observed between patients with favorable and unfavorable outcomes in relation to variables such as younger ages, lower frequencies of associated comorbidities as hypertension (HPN), diabetes, and history of atrial

fibrillation, as well as lower baseline NIHSS score were associated with good outcomes. When comparing the CT perfusion parameters between patients with favorable and unfavorable outcomes, a significant difference was observed in all parameters and functional outcomes. Higher CBF, CBV, and mismatch ratio, as well as lower MMT, mismatch ratio, penumbra volume, and infarct volume, were associated with good outcomes.

The volume of infarct core as measured by CT perfusion was found to be significantly associated with favorable functional outcomes in univariate analysis (odds ratio [OR] = 0.93, 95% confidence interval [CI] = 0.91-0.99, p = 0.002). This association remained statistically significant even after adjusting for age, NIHSS score, hypertension, and diabetes mellitus in multivariable analysis (adjusted OR = 0.93, 95% CI = 0.91-0.99, p = 0.03).

Nine patients (25%) underwent endovascular intervention, with time to intervention median 350 minutes (6.4 IQR). Significant statistical

differences were observed between patients who received endovascular therapy and those who did not, particularly in relation to NIHSS and time to imaging (p=0.009 and p=0.02, respectively). There were also significant differences between the two groups in mismatch volume (p=0.02), penumbra volume (p=0.02), and infarct core volume (p=0.03) (Table 5).

CTP had high sensitivity (88%) with 95% confidence interval (0.69-0.97) and high specificity (100%) with 95% confidence interval (0.71-1.00) as shown in (Table 6).

The current study revealed that the area under the curve (AUC) for predicting a positive outcome using CT perfusion to detect infarct core volume was 0.82. The best cutoff for predicting a favorable outcome was shown to be less than 14 mL, with a sensitivity of 0.87, a specificity of 0.71, a positive predictive value of 0.68, and a negative predictive value of 0.88.

Table (1): Demographic data & comorbidities among the studied participants.

Variable	All patients (n=36)
Age mean±SD	62.5±6.85
Sex n.%	
– Male	27 (75%)
– Female	9 (25%)
Comorbidities n.%	
– Hypertension	27 (75%)
– Diabetic	20 (55.6%)
– Cardiac	11 (30.6%)
– Obesity	22 (61.1%)

Table (2):Clinical data and CTP parameters among the studied participants.

Variable	All patients (n=36)
NIHSS at admission <i>median (range)</i>	7 (5-17)
Stroke onset time/h <i>median (range)</i>	7 (2.5-21)
Time from onset to imaging/h <i>median(range)</i>	8.5 (3-24)
ASPECTS <i>median(range)</i>	7 (5-9)
CBF <i>median (IQR)</i>	31 (14)
CBV <i>median (IQR)</i>	2 (0.9)
MTT <i>median (IQR)</i>	6.75 (3)
Mismatch volume <i>median (IQR)</i>	24 (43)
Mismatch ratio <i>median (IQR)</i>	2.1 (0.88)
Penumbra volume/mL <i>median (IQR)</i>	36 (93.5)
Infarct core volume/mL <i>median (IQR)</i>	12 (45.13)
Vessel occlusion <i>n. (%)</i>	
– MCA	19 (52.8%)
– PCA	8 (22.2%)
– Basilar artery	5 (13.9%)
– ACA	4 (11.1%)
Endovascular intervention <i>n.%</i>	9 (25%)
Time to intervention/h <i>median (IQR)</i>	3.5 (6.4)
Rankin score <i>median (IQR)</i>	2 (2)
Rankin score <i>n.%</i>	
– ≤ 2	21 (58.3%)
– > 2	15 (41.7%)
NIHSS at 7 days of admission <i>median (IQR)</i>	4 (1.25)
Final ischemic volume <i>median (IQR)</i>	12 (45.13)

Table (3): Validity data of different CT perfusion parameters.

	Cut-off	Sensitivity	Specificity	PPV	NPP	AUC
CBF	46	24 %	100%	100%	31.4%	0.398
CBV	1.5	15 %	96%	25%	68.57%	0.313

	Cut-off	Sensitivity	Specificity	PPV	NPP	AUC
MMT	5.5	88%	63.6%	84.6%	70%	0.782
Mismatch volume	56	52%	100%	100%	55.7%	0.731
Penumbra volume	116	48%	95.6%	97%	45.83%	0.736
Infarct volume	51	58%	100%	100%	62%	0.778

Table (4): Characteristics of patients in relation to functional outcome.

	Poor outcome mRS >2 (n=15)	Good outcome mRS ≤ 2 (n=21)	p-value
Age median (IQR)	62 (5.5)	53 (7)	0.03
Sex n.%			0.6
Female	3 (20%)	6 (28.6%)	
Male	12 (80%)	15 (71.4%)	
Comorbidities n.%			
Hypertension	14 (93.3%)	13 (61.9%)	0.04
Diabetic	13 (86.7%)	7 (33.3%)	0.001
Atrial fibrillation	8 (53.3%)	3 (14.3%)	0.01
Obesity	11 (73.3%)	11 (52.4%)	0.2
NIHSS median (IQR)	16 (3)	6 (1)	<0.001
ASPECTS median (IQR)	6 (1.5)	6 (1)	0.15
Time to imaging median (IQR)	17 (2)	15 (2)	0.4
CBF median (IQR)	28 (6)	40 (16)	0.03
CBV median (IQR)	1.7 (0.25)	2.5 (0.7)	0.002
MMT median (IQR)	8 (1.5)	5.5 (1.5)	<0.001
Mismatch volumemedian (IQR)	63 (23)	16 (13.5)	<0.001
Mismatch ratiomedian (IQR)	1.9 (0.4)	2.4 (0.8)	<0.001
Penumbra volumemedian (IQR)	136 (38.5)	28 (18)	<0.001
Infarct core volumemedian (IQR)	60 (34.5)	8.5 (6)	<0.001

Table 5: Characteristics of patients in relation to endovascular intervention.

	Endovascular intervention (n=9)	Non-intervention (n=27)	P-value*
Age median (IQR)	63 (5)	61 (7.5)	0.7
Sex n.%			
Female	3 (33.3%)	6 (22.2%)	
Male	6 (66.7%)	21 (77.8%)	0.5
NIHSS median (IQR)	7 (1)	9 (10)	0.009
ASPECTS median (IQR)	8 (1)	7 (2)	0.2
Large vessel occ.	5 (55.6%)	14 (51.9)	0.8
Time to imaging (hours)	8 (4)	10 (16)	0.02
Time to reperfusion (minutes)	350 (163)	-	-

*Mann-Whitney test, Chi square test.

Table 6: Diagnostic accuracy of CT perfusion in the detection of early ischemic stroke.

		Standard		Total
		Positive	Negative	
CTP	Positive	22 (TP)	0 (FP)	22
	Negative	3 (FN)	11 (TN)	14
	Total	25	11	36
<p>Sensitivity: 88%, 95% CI: (0.69 – 0.97) Specificity: 100%, 95% CI: (0.71 – 0.1) Accuracy: 91.67% CI (77.53 to 98.25)</p>				

* TP: True positive, TN: True negative, FP: False positive, FN: False negative, CI: Confidence Interval

* Standard: Available DWI MRI, post-intervention or follow up CT.

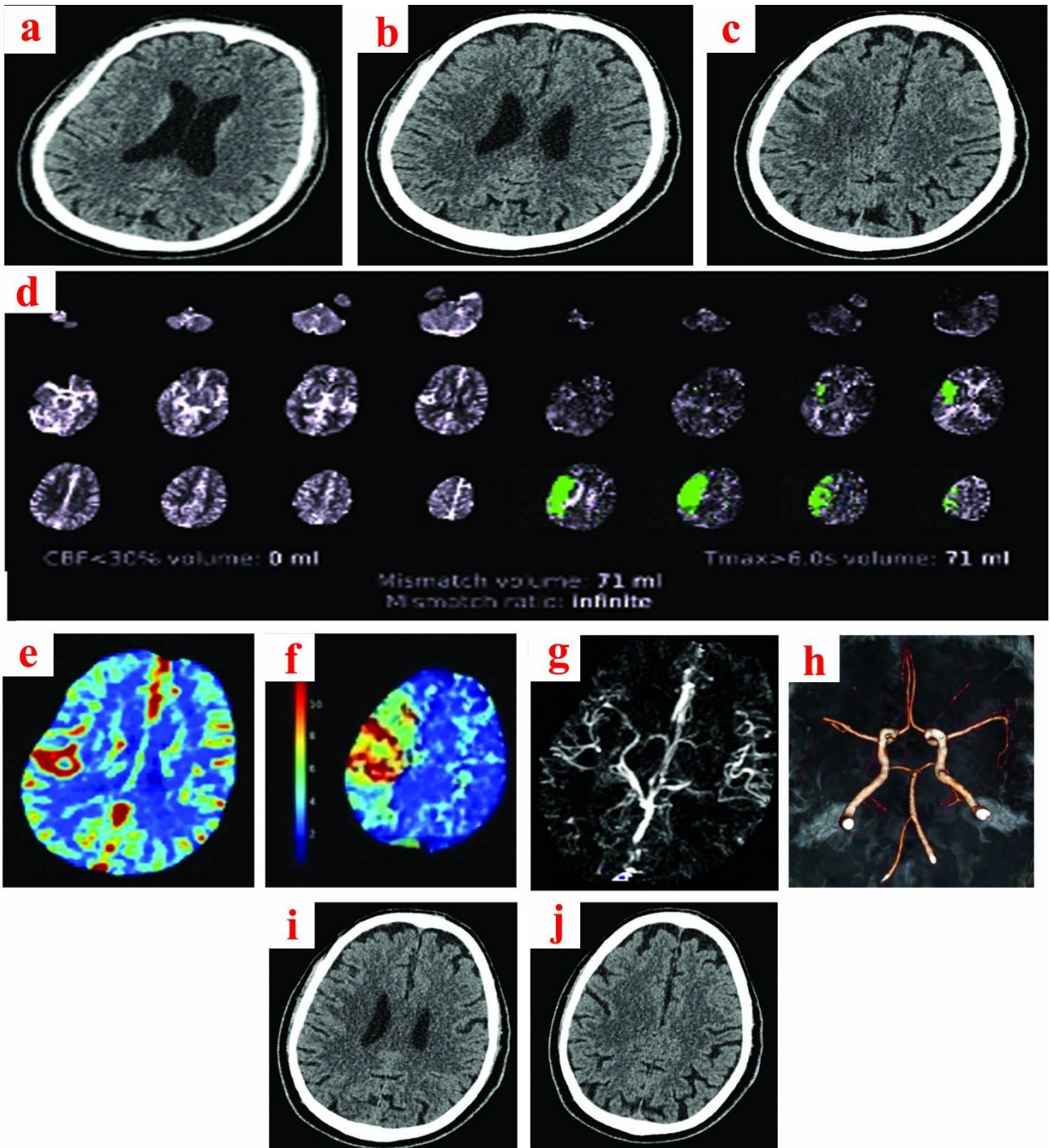


Figure (1).

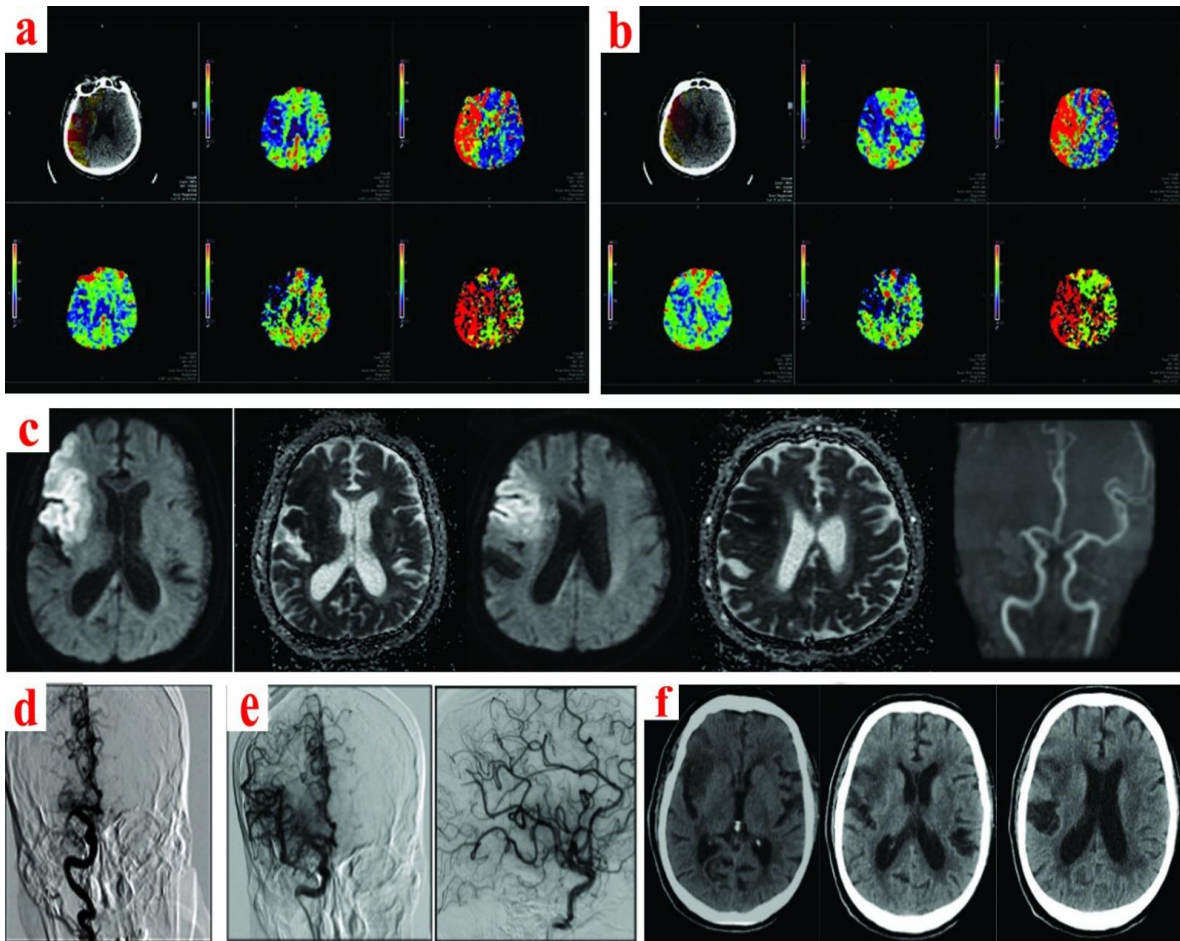


Figure (2).

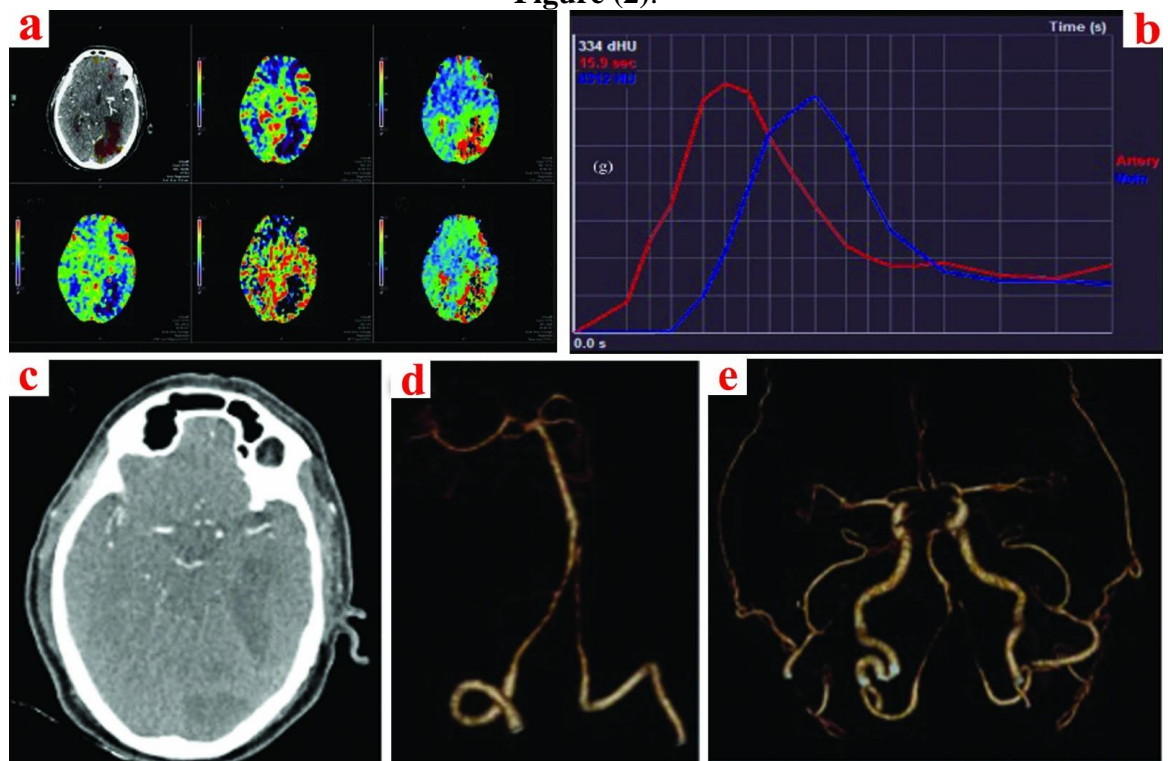


Figure (3).

DISCUSSION

The presence of early ischemic alterations observed on CT scans acquired within the initial hours following the onset of a stroke signifies the occurrence of early cytotoxic edema and the progression of irreversible damage. Despite the potential advantages of MRI with diffusion-weighted imaging (DWI) compared to CT, the majority of physicians involved in stroke treatment continue to rely on CT scanning due to its widespread availability and faster picture capture time. Nevertheless, the capacity of clinicians to accurately evaluate the first radiological indications of early stroke on CT scans is accompanied by uncertainties and disputes [4]. One of the primary benefits of CTP in the diagnosis of early onset stroke is its comprehensive coverage of the brain, which enables the identification of peripheral perfusion abnormalities. This observation suggests that the use of CTP can extend beyond being solely an assessment tool with limited scope, and instead presents it as a potentially effective diagnostic tool. As an integral component of the established acute stroke procedure, CTP possesses the theoretical capacity to enhance diagnostic accuracy in distinguishing small stroke cases from stroke imitators [5].

The findings obtained from our study indicated that CTP exhibited a moderate level of sensitivity (88%) with a 95% confidence interval ranging from 69% to 97%. Additionally, CTP demonstrated a high level of specificity (100%) with a 95% confidence interval ranging from 71% to 100%. The study demonstrates a high level of specificity, indicating that positive findings on CTP scans could serve as a valuable supplementary equipment for diagnosing stroke in patients

presenting with early neurological dysfunction symptoms. Nevertheless, the intermediate sensitivity suggests that negative CTP findings are not entirely conclusive in ruling out ischemic stroke. Consequently, it is not advisable to withhold prevention and reperfusion therapy from patients only based on negative CTP imaging, since it may not guarantee their safety and effectiveness.

A study by, Caposso *et al.*, [6]. found that sensitivity of CTP was 88.6% with 95% confidence interval (75.4%-96.2%) which was similar to our findings, but they reported a lower specificity 50% with 95% confidence interval (11.8%-88.2%). Their study had focussed on CTP parameters in acute posterior circulation ischemic stroke, which might explain the lower specificity obtained in their study. Another study carried by Frank *et al.*, [7] reported that CTP has a sensitivity of 57% (95% CI: 45%–69%) and a specificity of 82% (95% CI: 71%–90%). The positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 75%, 67%, 3.09, and 0.53, respectively. The discrepancy observed in our findings, especially their lower sensitivity findings, might be attributed to their focus on CTP parameters in cases with mild neurological symptoms.

The presence of variability in the thresholds of CTP parameters and the approaches used for image processing across various commercial software platforms leads to considerable variability in the computed volumes, resulting in poor repeatability. This emphasizes the necessity for uniformity among stroke centers [8]. There has been an increasing research focus on the study of CTP parameters that can predict the functional outcomes in individuals with AIS. At present,

there is a shortage of data about the predictive capability of CTP computed parameters in relation to acute cerebral stroke patients. One of the primary findings in the current study involves the identification of CTP parameters. These parameters, when combined with clinical data, have the ability to predict the neurological impairment results in acute cerebral stroke patients within a typical clinical setting. Based on imaging analysis, the implementation of endovascular intervention proved appropriate for patients who exhibited persistent symptoms, large-vessel occlusion, and revealed the presence of viable brain tissue as determined through the interpretation of MRI-DWI and CTP.

Patients with a larger volume of infarct core exhibited a correspondingly poorer prognosis in relation to the volume of infarct. Moreover, in the univariable analysis, no significant correlation was observed between a favorable outcome and conventional ASPECTS. However, a significant link was found between a favorable outcome and CTP core volume. Following the adjustment for clinical variables that are known to be linked with a positive outcome in univariable analysis, such as age, baseline NIHSS, hypertension, and diabetes mellitus, the correlation between a favorable outcome and CTP core volume persisted. These findings were nearly close to a study by Demeestere *et al.*, who also stated a close relation between the good outcome and lower median NISHH and younger age, while patients with poor outcomes developed more frequently ICH and had history of diabetes mellitus [9].

The calculated AUC for predicting a favourable outcome using core volume as a predictor was 0.85. The optimal cutoff value for predicting a favourable outcome was determined to be less than 14 ml, with a

sensitivity of 0.87, specificity of 0.71, positive predictive value of 0.68, and negative predictive value of 0.88. A study conducted by Chen *et al.*, stated that infarct core volume remained as an independent prognostic factor in the multivariable analysis. The multivariable model achieved an area under ROC (AUC) of 0.768 (95% CI, 0.666–0.870) [10]. Haranhalli N *et al.* also found CTP was associated with functional outcome after ischemic stroke, as measured by mRS score at discharge, and prognosis was poor in patients with large infarct core volume [11]. The concept of personalised medicine is steadily growing in various medical fields. However, it is crucial to further advance the creation of an individualized approach for managing patients with AIS. There is a requirement for a more precise evaluation of the prognostic significance of neuroimaging in order to address not only the determination of whether a patient possesses a viable penumbra, but also to delineate the extent of the penumbra region and establish a correlation between its location, neurological function, and subsequent prognostic and functional outcomes [11].

Limitations:

There are various limitations inherent in the current study. This study employed a single software design, hence neglecting to consider potential variations in CTP post-processing approaches among different centers. Currently, there are various commercially accessible software packages for processing raw CTP data. However, just one of these packages was utilized to measure the CTP-derived core. The standardization of perfusion imaging processing is still lacking, leading to significant variations across different software programs. Hence, it is important to conduct additional assessments using various software

applications.

Declaration of interest:

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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CONCLUSION

Based on our analysis, it is suggested that the utilization of computed tomography perfusion as a supplementary test may provide some benefits in enhancing the certainty associated with the administration of stroke treatment. Furthermore, the recognized significance of employing imaging criteria in the identification of individuals with AIS who get advantages from endovascular revascularization has been demonstrated. The current study demonstrates the significance of including CTP imaging criteria in the assessment of AIS for the purpose of determining prognosis. The findings of the current study indicate that there is a correlation between a larger infarct volume and a poorer functional result, as assessed by the mRS score.

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