Computed tomography perfusion in detecting malignant middle cerebral artery infarct

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ABSTRACT

Background: Computed tomography perfusion (CTP) is an emerging modality which produces maps of time-to-peak (TTP), cerebral blood flow (CBF), and cerebral blood volume (CBV), with a computerized automated map of the infarct and penumbra. This modality provides a better evaluation of the extent of infarction, making it a potential method for assessing patients suffering from large middle cerebral artery (MCA) infarctions.

Methods: A prospective cohort study of all patients in Hospital Kuala Lumpur, Malaysia, who presented with the clinical diagnosis of a large MCA infarction within 48 h of onset were subjected to CT brain, and CTP scans on admission and were followed up to determine the development of malignant infarction requiring surgical decompression.

Results: CTP parameters were generally lower in patients with malignant brain infarct (MBI) group compared to the nonMBI group. The largest mean difference between the group was noted in the TTP values (P = 0.005). CTP parameters had a comparable positive predictive value (83%–90%) and high net present value (88–93). CBF with cutoff value of >32.85 of the hemisphere could accurately predict malignant infarctions in 81.4% of cases. The National Institutes of Health Stroke Scale score of more than 13.5 was also found to be able to accurately determine malignant infarct (97.6%). Functional outcome of patients based on Glasgow outcome scale was similar on discharge, however, showed improvement at 6 months during reviewed base on modified Rankin scale (P < 0.001).

Conclusion: CTP parameters should be included in the initial evaluation of patients to predict malignant brain infarction and facilitate surgical treatment of large MCA infarctions.

Keywords: Malignant brain infarction, Middle cerebral artery, Perfusion computed tomo

Key messages: CT perfusion parameters have an important role in predicting malignant brain infarction and should be included in the initial evaluation of patients to facilitate the early identification and surgical treatment of large middle cerebral artery infarctions, to improve patient's prognosis.

INTRODUCTION

Acute ischemic stroke is a leading cause of morbidity and long-term rehabilitation in adults. Acute ischemic stroke initiates a pathophysiological cascade that leads to the formation of brain edema. Malignant middle cerebral artery (MCA) infarction is a clinical entity affecting up to 10% of all patients diagnosed with ischemic stroke. It is defined as an infarction involving an
area encompassing at least two-thirds of that supplied by the MCA.\[10\] Cerebral edema that develops associated with infarcted brain tissue is responsible for the devastating effects of this condition. This edema results in mass effect, which causes displacement of brain tissue, and an increase in intracranial pressure (ICP). The initial presenting features include symptoms and signs of MCA occlusion such as hemiparesis, hemiplegia, gaze preferences, and altered consciousness.\[6,11\] These patients, however, deteriorate rapidly within the first 48 h heralding the presence of mass effect that can have potentially fatal consequences.\[12\] Intensive medical therapy with mechanical ventilation, osmotic diuretics, hypothermia, sedation, and hyperventilation has so far been ineffective, with reported mortality rates being as high as 80% despite optimum medical management.\[12,10,11,34\] Treatment for acute ischemic stroke includes recanalization with recombinant tissue plasminogen activator (rTPA), however, due to the strict eligibility criteria for treatment; only 10% or less of patients benefit from it. Endovascular intervention currently offers new hope for treatment in acute stroke patients. A recent publication of five trials has demonstrated its beneficial effects on recanalization and clinical outcome in patients. Compared to intravenous rTPA, endovascular treatment is not confined by strict criteria and is superior to surgical treatment in terms of salvaging ischemic penumbra in such patients. In cases of malignant MCA infarction; results from three European trials published in 2007; DECIMAL, HAMLET, and DESTINY trials have demonstrated significant benefits of surgical treatment with decompressive hemicraniectomy, with a significant reduction in mortality rate by 50%; and morbidity rate in younger patients; if done within 48 h of ictus.\[12,16,34\]

Decompressive hemicraniectomy, however, remains the mainstay of treatment in cases of space occupying edema with rapid clinical deterioration secondary to raise ICP.

Astrup et al. in 1981 first coined the term ischemic penumbra, defined as tissue within the threshold of functional impairment and morphological integrity which has the capacity to recover if blood flow is restored timely, surrounding the area of ischemic core which remains refractory to reperfusion. Identification and differentiation of these regions; core versus penumbra is critical in the evolution and treatment of patients with acute ischemic stroke.

The outcome in patients with stroke; in particularly, malignant MCA infarction is dependent on two principal factors; the severity of stroke on presentation and the speed of intervention. Thus, early and accurate diagnosis plays a crucial in determining outcome. Radiological investigation remains the primary diagnostic modality used in the triage of stroke patients on initial presentation; with computed tomography (CT) scan and magnetic resonance imaging (MRI) being the principle workhorses; but neither without its limitations. CT scan, although being fast in confirming diagnosis lacks sensitivity and the opposite applies to MRI. These limitations lead to a delay in accurate diagnosis and unfavorable outcome. To overcome this limitation, recent publications favours the use of CT Perfusion as an additional triage tool; bridging the gap between fast data acquisition of a CT scan and sensitivity of detection of MRI.

This study aims to explore the qualitative (and quantitative) benefits of CTP and potential predictive ability in diagnosing malignant MCA infarction.

**Background**

Outcome following treatment of strokes; particularly of malignant MCA infarction is dependent on various factors, including age of the patient; progression of symptoms, infarct volume, development of space occupying edema, presence of mass effect on CT scan, and interval between ictus and intervention. Central to the challenge of improving the outcome of malignant MCA infarction is an early and accurate diagnosis. Identifying patients at risk for developing space occupying edema are vital; particularly in the aspect of clinical decision making of treatment. The extent of ischemia cannot be assessed by neurological examination alone. Multiple trials, meta-analysis and opinions have been published describing early predictors of malignant MCA infarction. These include clinical, biochemical and radiological parameters, all aimed to improve the diagnostic accuracy of this life-threatening condition. Clinical parameters used are commonly the Glasgow coma scale (GCS) scoring system; and the National Institutes of Health Stroke Scale (NIHSS). Both these scoring scales have a strong correlation in predicting of outcome in patients with malignant MCA infarction. The GCS score is in most cases of triage, the primary tool of assessment in patients with neurological dysfunction. Weir et al noted that GCS score had a strong predictive value for early mortality and functional outcome in patients with malignant infarction.\[35\]

Wartenberg et al. have identified several predictors development of brain edema in MCA infarction; namely history of hypertension (HTN), history of congestive heart failure, elevated white cell count, involvement of MCA infarction territory >50%, and involvement of other vascular territories.\[10,17,26,34\]

Collateral circulation has been associated with recanalization, infarct volume, and clinical outcome in patients undergoing acute reperfusion therapies.

CT based evaluation of collaterals offers a promising alternative for assessing the ischemic injury. The pial collateral circulation limits the core infarct size by supporting penumbral tissue during acute ischemia. Multiple studies...
have evaluated collaterals using CT angiography and have demonstrated improved tissue and clinical outcomes in patients with more robust CTA collaterals. In patients with acute ischemic stroke of terminal ICA or proximal MCA occlusions, the degree of collateral circulation on admission CTA correlates with the admission diffusion-weighted imaging (DWI) lesion volume. However, due to their poor specificity, these grading systems are not particularly helpful for treatment decisions in individual patients.

A noncontrast CT scan has remained the mainstay in the evaluation of acute ischemic stroke chiefly as it is fast, cheap, effective and widespread availability, and good interobserver variability. Several pathognomonic signs have been identified as early markers of malignant MCA infarction: namely dense MCA sign, obscuration of the lentiform nucleus, effacement of sylvian cistern or insular ribbon sign, and effacement of sulci and gyri. Manno et al. showed that hyperdense MCA sign and >50% involvement of the MCA territory within 12 h were independent risk factors for neurologic deterioration. Von Kummer demonstrated that large (50%) or total hypodensity in the MCA territory predicted fatal outcome in 85% of cases with a high specificity (94%) but moderate sensitivity (61%). Midline shift more than 5 mm causes brain shift progressed faster and reached the maximum extent earlier in patients with a malignant course than in patients without (day 2–4 vs. day 3–7).

Although very sensitive in detecting hemorrhage in stroke, CT scan lacks the sensitivity in early detection of ischemic stroke; appearance and progression of infarct and edema are typically seen after an interval of 3–4 h postictus; resulting in a significant delay in treatment and increasing risk of morbidity and mortality.

MRI brain is superior in terms of early detection of malignant MCA infarction with cerebral edema and remains the gold standard in determining penumbra. Use of parametric MRI with DWI and perfusion-weighted imaging has defined the standards of diagnosing space occupying edema in malignant MCA infarction. In the study by Oppenheim et al. used DWIs performed within 14 h after stroke onset for a small series of patients, 10 patients with a malignant course and 18 patients with a nonmalignant course, a DWI lesion volume more than 145 ml was proposed as a predictor of a malignant hemispheric infarction with a 94% specificity, 100% sensitivity, and 91% positive predictive value (PPV). However, for the larger series of 61 patients in the present study, an infarct volume more than 145 ml only provided an 88% specificity and 86% sensitivity. Limitation to MRI as a gold standard of diagnostic modality is related to its logistical unavailability in medical facilities; slow acquisition time; requirement of trained personnel to operate the machine and interpret acquired data makes it less favorable as a primary imaging modality in such cases.

Evoking the concept of time is neurons, a heightened interest in identifying predictive markers of malignant infarction. Various clinical and biochemical markers have been proven to be sensitive markers, but they lack the required specificity. Radiological parameters remain the mainstay of diagnosis in the clinical setting of acute ischemic stroke. The ideal imaging modality in the triage of patients should be rapid; accurate and capable of identifying and differentiating areas of tissue infarction from areas of ischemic penumbra. Multi-parametric MRI remains the gold standard in identifying areas of infarct versus areas of risk, but limited due to technical and logistical acumen; while CT scan despite being rapid is inaccurate and incapable of detecting hyperacute stroke and areas of the penumbra.

Cerebral CTP measures the cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). CBF is a quantitative measurement of blood that perfuses 100 g of the brain in per unit of time (ml/100 g/min); CBV is the amount of blood in a given volume of brain (ml/100 ml); while MTT is the time taken for the blood to pass through the brain tissue. The total volume of flowing blood in a given brain volume is CBV, the total volume of blood passing through a given volume of brain per unit time is defined as CBF; and finally, the average time taken for blood passing through a given brain region is MTT. Intravenous contrast agent given during CT brain acquisition is monitored and analyzed by an imaging workstation to give the above values after the region of interest (ROI) is chosen. CTP helps in determining and differentiating extent of penumbra region from the infarcted brain region that would be otherwise indistinguishable in a plain CT brain. This is crucial for patient selection for thrombolytic therapy. CTP findings in the penumbra region will demonstrate reduced CBF with normal or elevated CBV due to cerebral autoregulation and increased MTT. This is a contrast to the infarcted brain region where the CBF and CBV are both reduced coupled with an increased MTT.

CTP fulfills the required model of imaging standard; in such that it offers rapid data acquisition and image analysis; and allows identification of penumbra region. The basic principle of CTP is tracing of a bolus of iodinated contrast material through the cerebral circulation through sequential spiral CT scanning in Cine Mode. This technique allows measurement of various parameters; namely CBF (normal 50 ml/100 g brain tissue/min); CBV (ml/100 g brain tissue) time to peak (TTP) (delay between intravenous administration and peak concentration at brain parenchyma); and MTT (mean time for blood to travel through brain parenchyma). These parameters reflect hemodynamic parameters with brain circulation and detect any difference or changes that occur.

In normal brain; all parameters are symmetrical; reflecting normal CBF and physiology. In acute infarction, areas of core infarction demonstrate a decrease in CBF and CBV,
with increase MTT and TPP. Areas of decrease CBV (<30%) accurately reflect areas of core infarct when compared to DWI MRI. In regions of ischemic penumbra, there is a decrease of CBF with preserved CBV, but increase MTT and TTP, reflecting collateral route circulation to supply ischemic regions. These findings reflect the normal pathophysiological changes that are mediated through cerebral autoregulation; impaired autoregulation within the region of core infarction results in a decrease of both CBF and CBV; while intact autoregulation at the margins of ischemic penumbra allows for recruitment and establishment of collateral circulation to preserve blood flow to critical areas.

Thus, CTP in a way is a form of physiologic imaging, reflecting active cerebrovascular physiology derived from multiple parameters; rather than a single parameter of hypodensity of signal intensity changes. Conventionally, CTP has been devised as a tool of qualitative assessment; done through simple visual study. The recent development of software has expanded its utility into quantitative measurement; and development of CTP threshold values depicting areas of infarct core and penumbra. These thresholds, however, remain to be validated.

In our center; CT scan remains the mainstay of triage in patients with ischemic stroke. All patients with suspected acute stroke undergo CT scan on admission; with the also measuring cerebral perfusion during the initial CT. Therefore, our study focused on CTP to identify the predictive factors of malignant brain edema in MCA infarction patients.

This study was done to determine the predictive value of CTP in cases of malignant MCA infarction. Using the permeability maps generated by CTP; we aim to identify imaging parameters most valuable in detecting tissue at risk and to identify the perfusion threshold for predicting the development of infarction.

Scientific rationale

Problem statement

Brain imaging with CTP has promising potential in providing valuable information regarding the importance of identifying malignant MCA infarct and current problems of its identification, which is vital to treatment decisions.

Importance and validity of research

The volume of patient admission due to acute stroke, especially MCA infarct has seen a steady increase over the years. To date, no quantitative studies have been performed to evaluate permeability maps by means of CTP and to establish its correlation with progression of clinical course. In Hospital Kuala Lumpur; all patients presenting with stroke undergo a CT scan as a primary diagnostic tool on admission, principally to identify the neurological pathology and differentiate between hemorrhagic and ischemic stroke. The CT scanner has the advantage of having equipped CTP machine. Thus performing CTP on these patients confers additional valuable information; with minimal time and cost. Therefore, I wish to evaluate the infarct permeability area on admission perfusion CT as a useful tool in predicting malignant MCA infarction and the need for hemicraniectomy.

Few procedural contraindications exist such as patients with metallic implants, poor renal function, or contrast allergy that is unable to undergo CTP. CTP remains a relatively new and unfamiliar technique to many radiographers. There has also been concern raised that adding CTP to the diagnostic workup may unnecessarily delay thrombolysis.

Potential benefits

Information obtained from this study will help improve decision-making process and improve outcomes in patients with acute ischemic stroke; as well as providing additional valuable information to the existing body of knowledge in this field.

Research objectives

General objectives

The purpose of this study is to investigate the role of CTP in detecting early malignant MCA infarct.

Specific objectives

The following objectives are as follows:
1. To measure CTP parameters (CBF, CBV, and MTT) in MCA infarct between malignant brain infarct (MBI) and nonMBI.
2. To identify predictive factors for the development of malignant MCA infarct based on clinical condition, CT scan, and CTP parameters.
3. To determine the relationship between CTP parameters (CBF, CBV, and MTT) with a mortality rate at 30 days, patient’s outcome based on Glasgow outcome scale (GOS) on discharge and modified Rankin scale (mRS) at 6 months.

SUBJECTS AND METHODS

Research methodology

Study design

This study is a prospective cohort study which was conducted over a period of 3 years from August 2015 to March 2018 in Hospital Kuala Lumpur. Approval to undertake the project
was obtained from the Medical Research Ethics Committee, Ministry of Health.

**Study sample**

A total of 95 patients with a clinical diagnosis of acute malignant MCA infarct, presenting with symptoms of hemiparesis, sensory or motor deficits, hemianopia, higher cerebral dysfunction dysphasia, aphasia, visuospatial loss at the Department of Neurology and Neurosurgery, Hospital Kuala Lumpur were included in this study. Patients were examined on admission, and a detailed clinical history along with vascular risk profile assessment, handedness, and neurological status including the NIHSS (refer Appendix A) was performed and documented. Routine blood investigations were taken which include full blood count, electrolytes, coagulation profile, and group cross and match in preparation for potential intervention as well as to ensure the renal profile is normal. In view of the CTP scanning that requires contrast administration, the renal profile needed to be normal and patients with history of allergy (except contrast allergy) were given intravenous hydrocortisone 100 mg or prednisolone 40 mg.

**Inclusion criteria**

The inclusion criteria in this study were patients of (1) age 18–90 years old (2) presentation of acute malignant MCA infarcts such as hemiparesis, sensory or motor deficits, hemianopia, higher cerebral dysfunction dysphasia, aphasia, and visuospatial loss which occur within 48 h of onset.

**Exclusion criteria**

The exclusion criteria were (1) concurrent hemorrhagic stroke, (2) concurrent other vascular territory infarction, (3) known allergy to iodinated contrast, and (4) renal dysfunction with estimated glomerular filtration rate (eGRF) <30 ml/min.

**Follow-up and outcome measurements**

Data collected include the patient’s demographic profile, NIHSS, time from onset of presentation, stroke etiology, and risk factors. CTP parameters (CBF, CBV, and MTT) were collected, and mean value was obtained. The presence of infarcted areas was based on the radiology report which is based on the CT brain done on the day of follow-up CT scan. Outcomes of the patients were assessed based on mortality rate at 30 days, GOS at discharge and mRS at 6 months follow-up. Good outcome was classified as GOS = 1–2 and poor outcome as GOS 3–5.

**Sampling size and method**

The sample size of this study was calculated based on the previous study by Dittrich, MD, Kloska et al. J Neurol (2008) 255:896–902) the expected sensitivity is 0.95 and expected specificity is 0.72 with an expected prevalence of 0.20. Calculation using sensitivity and specificity formula (Buderer, 1996), where α = 0.05, level of confidence is 95% and desire precision is 0.1. The calculated sample size using sensitivity and specificity formula is 98(both arms). Considering 20% drops from the study, the total required number of patient is 122.

**Statistical method**

The statistical software we employed was the IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. As most of the variables are numerical, their descriptive analyses are expressed as means and standard deviation.

Pearson’s Chi-square test and Fisher’s exact test were used to determine significant differences in outcome based on mortality rate at 30 days, GOS at discharge and mRS at 6 months between patients of two groups; MBI group and nonMBI group. The GOS was dichotomized as the good outcome (GOS 1–2) and poor outcome (GOS 3–5), and the mRS as the good functional outcome (mRS 0–4) and poor outcome (mRS 5–6).

\[ P < 0.05 \] is considered statistically significant.

**Data collection**

A specially-designed data collection form was used to gather information concerning the patient’s demography and the variables mentioned above (refer to Appendix B). The raw data were then translated into Microsoft Excel and then transferred to (SPSS) version 20.0.

**CTP scanning protocol and data processing**

All patients that were admitted to Hospital Kuala Lumpur with acute malignant MCA infarct symptoms such as hemiparesis, sensory or motor deficits, hemianopia, higher cerebral dysfunction dysphasia, aphasia, and visuospatial loss underwent noncontrast CT brain [Figure 1a]. Subsequently, those patients who fulfilled the selection (this includes exclusion criteria) criteria were subjected to CTP after obtaining consent [Figure 1b].

All examinations were performed on whole brain CTP using a 320-row CT system (Aquilion ONE, Toshiba Medical Systems). Contrast media were infused using the Infusor pump to inject 60 ml of nonionic contrast agent Omnipaque 350 which was infused at the rate of 5 ml/s through a branula of at least size 16G at the antecubital fossa followed by 40 ml of normal saline also at 5 ml/s once the patient is prepared. Power injector was set at a pressure of 300 psi.

The dynamic acquisition protocol, which used a gantry rotation speed of 1 rotation per 5 s acquisition delay allowed...
acquisition of a mask volume (80 kVp and 200 mAs) without contrast enhancement for subsequent subtraction of the other scans. All subsequent scans were acquired at 200 mAs with continuous scanning during the passage of the contrast medium through the brain. All subsequent scans were acquired at 200 mAs with continuous scanning during the passage of the contrast medium through the brain [refer Table 1].

Scan protocol

Scan protocol uses plain CT brain by selecting four-dimensional (4D) CT digital subtraction angiography acute stroke CBP. It used plain scan at 5 s postcontrast injection, followed by continuous arterial phase scans started at 7 s postcontrast injection until 22 s. Intermittent phase scans started at 27 s until 64 s with 6 s interval.

Postprocessing

Brain perfusion volume – Vitrea (4D-Vol DYNAMIC 4D CBP), brain perfusion volume to brain analysis CT (Head 0.5 HE) was loaded and 4D perfusion was selected.

The values were then calculated to obtain a mean value for each parameter. The values of interest were the MTT(s), TTP(s), regional CBV (ml/100 ml), and regional CBF (ml/100 g/min). Ischemic core was cytotoxic edema with irreversible ischemia of CBF <10 ml/100 g/min. Penumbra was reversible ischemia with CBF <10–18 ml/100 g/min and CBV that is reduced or normal. Areas that demonstrate matched defects in CBV and MTT represent salvageable infarct core, whereas areas which have prolonged MTT but preserved CBV are considered to be ischemic penumbra [Figure 1].

From the CTP data, normalized color-coded perfusion maps of CBF, CBV, and TTP were calculated using the commercially available software. All CTP investigations were reviewed and evaluated by two neuroradiologists with 10 years experience.

Patients recruited were grouped into two groups; malignant brain infarction who was indicated for operation and nonMBI which was treated nonsurgically.

Definition of MBI

The patients were divided into those who developed malignant brain infarction versus those who did not. MBI group patients were of: (1) acute, complete MCA infarction with early parenchymal hypodensity of at least 50% of the MCA territory and signs of local brain swelling such as sulcal effacement and compression of the lateral ventricle; (2) midline shift of >5 mm at the septum pellucidum or pineal gland with obliteration of the basal cisterns; and (3) neurological deterioration consisting of a NIHSS increase by >2 points and decrease in the level of consciousness to a score of ≥1 of the NIHSS.

**Figure 1a** : A noncontrasted computed tomography brain (a) were performed which showed no evidence of acute infarction.

**Figure 1b** : Computed tomography perfusion performed 6 hours after onset. Cerebral blood volume( CBV) map showed no abnormality. Cerebral blood flow (CBF) map showed a region of decreased perfusion at the posterior segment of left middle cerebral artery territory( white arrows). Mean transit time showed prolongation within the same region (white arrows).

| Table 1: CT perfusion scanning protocol. |
|-----------------------------------------|
| **Parameter**                           | **Perfusion CT** |
| Mode                                    | Dy-volume       |
| Gantry angle                            | 0°              |
| Slice thickness (mm)                    | 0.5 mm          |
| Kilovolt (kV)                           | 80              |
| Milliamperage (mA)                      | 200 mAs         |
| Rotation time (s)                       | 1               |
| Contrast material                       | Omnipaque 350   |
| Contrast volume (ml)                    | 60              |
| Injection rate (ml/s)                   | 5               |
| Saline flush (ml)                       | 40              |

CT: Computed tomography
Patients who develop MBI were compared to those without a malignant course. The mean sizes of the ischemic areas generated by the different perfusion maps (i.e., CBF, CBV, and TTP) were compared by means of the t-test between both patients groups for CBF; while CBV and TTP data were skewed, therefore median values were used with Z statistics, and Mann–Whitney U-test was used. To compare sensitivity and specificity, conventional binomial receiver operating characteristics (ROC) analysis was conducted. From the ROC curves, the sensitivity and specificity were calculated. In addition, the positive and negative predictive value for each perfusion map was determined.

RESULTS

Based on Table 2, a total of 95 patients who suffered a stroke in the territory of MCA between August 2015 and March 2018 were investigated with CT brain and CTP within a time window of <48 h from symptoms onset. Patients were grouped into two groups based on MBI and nonMBI. Patients in nonMBI had younger age group; mean (standard deviation [SD]) of 56 years (12.22%) compared to the MBI group; 63 years (11.73%).

About three-quarter of the study population was male (72.9%) and from Malay ethnicity (72.7%) in nonMBI group compared to (27.1%) male and (27.3%) Malay in MBI group.

Comorbidities such as obesity, diabetes mellitus (DM), hypercholesterolemia (CHO), smoking, and HTN were documented. Among them, there were lesser patients who had HTN in nonMBI group accounting for 29 patients (61.7%) while higher in MBI group accounting for 18 patients (38.3%) [Figure 2].

On admission, stroke severity as measured by NIHSS was found to be higher in the group with MBI; 19 (1.8%).

Majority of the patients were right-handedness in both malignant (30.5%) and nonMBI groups (68.5%). Time of presentation was longer in the MBI group with a mean (SD) of 19 h and 13.5 h in nonMBI group.

Twenty-eight (66.7%) patients developed MBI, which requires decompressive surgery while 14 (33.3%) patients from nonMBI eventually turned malignant requiring decompressive surgery; as evidence by serial imaging and clinical deterioration.

Overall, mean CTP maps were generally larger in patients with nonMBI compared to the MBI. For nonMBI group of patients, results showed CBV with a mean (SD) of 34.2 (5.00) and TTP of 39.0 (4.00) and CBF of 38.3 (5.76), TTP has the highest mean value compared to CBV and CBF. As for MBI group of patients, mean CBV was 25.8 (30.74), TTP of 29.1 (12.78), and CBF of 31.3 (5.29). CBF has the highest mean

| Table 2: Demographic characteristics and clinical results of study participants (MBI). |
|----------------------------------|------------------|------------------|------------------|
| NonMBI  | MBI    | P-value |
|----------------------------------|------------------|------------------|------------------|
| Age, mean (SD)                   | 56 (–12.22)      | 62.9 (–11.73)    | 0.027<sup>a</sup> |
| Race                                           |                  |                  |
| Malay                                  | 39 (–72.7)       | 16 (–27.3)       | 0.957<sup>b</sup> |
| Chinese                                | 13 (–72.2)       | 5 (–27.8)        |                  |
| Indian                                 | 15 (–68.2)       | 7 (–31.8)        |                  |
| Sex                                      |                  |                  |
| Male                                    | 43 (–72.9)       | 16 (–27.1)       | 0.519<sup>b</sup> |
| Female                                  | 24 (–66.7)       | 12 (–33.3)       |                  |
| Obesity                                 |                  |                  |
| Yes                                      | 10 (–71.4)       | 4 (–28.6)        | 0.936<sup>b</sup> |
| No                                       | 57 (–70.4)       | 24 (–29.6)       |                  |
| HTN                                       |                  |                  |
| Yes                                      | 29 (–61.7)       | 18 (–38.3)       | 0.071<sup>b</sup> |
| No                                       | 37 (–78.7)       | 10 (–21.3)       |                  |
| DM                                         |                  |                  |
| Yes                                      | 34 (–70.8)       | 14 (–29.2)       | 0.947<sup>b</sup> |
| No                                       | 33 (–70.2)       | 14 (–29.8)       |                  |
| CHO                                        |                  |                  |
| Yes                                      | 41 (–70.7)       | 17 (–29.3)       | 0.965<sup>b</sup> |
| No                                       | 26 (–70.3)       | 11 (–29.7)       |                  |
| Smoking                                    |                  |                  |
| Yes                                      | 43 (–68.3)       | 20 (–31.7)       | 0.495<sup>b</sup> |
| No                                       | 24 (–75)         | 8 (–25)          |                  |
| NIHSS, median (IQR)                    | 13 (–1)          | 19 (–1.8)        | <0.001<sup>d</sup> |
| Handedness                               |                  |                  |
| Right                                    | 41 (–68.5)       | 18 (–30.5)       | 0.777<sup>b</sup> |
| Left                                      | 26 (–72.2)       | 10 (–27.8)       |                  |
| Time of presentation, mean (SD) (h)     | 13.5 (–3.94)     | 19 (–0.98)       | <0.001<sup>*</sup> |
| Treatment                                |                  |                  |
| Decompressive craniectomy              | 14 (–33.3)       | 28 (–66.7)       | <0.001<sup>b</sup> |
| Medical treatment                        | 53 (–100)        | 0 (0)            |                  |

SD: Standard deviation, HTN: Hypertension, NIHSS: National Institutes of Health Stroke Scale, DM: Diabetes mellitus, MBI: Malignant brain infarct, IQR: Interquartile range, <sup>a</sup>Independent t-test, <sup>b</sup>Chi-square test, <sup>d</sup>Mann- Whitney U test
between the parameters of CTP. This showed that all three parameters of CTP were statistically significant ($P < 0.001$, 0.005).

Thirty-four patients showed hypodensity on CT scan, and 11 patients showed a hyperdense MCA sign on the native scan. In the ROC curve analysis for native CT scan, hypodense signs have 50.0 sensitivity and 100.0 specificity while hyperdense MCA sign has a sensitivity of 16.2 and 100.0 specificity.

The most accurate values were obtained for CBF in a mean ROI of >32.85 of the whole hemisphere with a sensitivity of 82.4, a specificity of 77.8, a PPV of 90.3, and a net present value (NPV) of 63.6. The TTP with a cutoff value of >30.68 led to high sensitivity of 97.1 while having low specificity of 59.3, a low PPV of 85.7 and higher NPV of 88.9. For CBV reduction in a mean ROI of >24.83 ROC curve calculations led to a higher sensitivity of 98.5, a lower specificity of 51.9, a similar PPV of 83.8, and a comparable high NPV of 93.3 in predicting a MBI.

The analysis of optimal cutoff NIHSS value which was a stroke severity of NIHSS more than 13.5 on admission showed the highest sensitivity of 98.5 and highest specificity of 96.3 and highest NPV of 98.5 compared to all CTP parameters.

Comparison of the area under ROC curves between different CTP maps and native CT scan revealed a better prediction of a malignant course. In comparison with CTP maps, NIHSS was almost as accurate to determine malignant brain swelling. There was a clear trend toward better prediction for mean CBF and it has reached the level of significance. Prediction of MBI using all CTP maps was superior to hyperdense MCA sign and hypodensity on native cranial CT scan (mean CBF: $P < 0.001$, mean CBV: $P < 0.001$, and mean TTP: $P = 0.005$).

CTP analysis for outcome based on 30-day mortality showed no significant difference in a mean difference of the CTP parameters and mean TTP was higher in both groups of alive group 38.2 (7.00) and death group 38.8 (8.97) [Table 3a].

Functional outcomes on discharge were measured based on GOS where good (GOS 1–2) and poor (GOS 3–5) functional outcome were measured for different CTP parameters; CBF was 37.3 (6.08), CBV was 34.2 (5.03), and TTP was 38.5 (5.25) for good outcome and for poor outcome CBF was 33.5 (6.80), CBV was 29.3 (30.62), and TTP was 38.2 (12.56). CBF and CBV were statistically significant ($P = 0.011$) and ($P = 0.012$) [Table 3b].

Clinical condition of patients were also accessed at 6 months on reviewed in neurosurgery clinic using mRS [Appendix C] where good outcome (mRS <4) was seen in all parameters of CTP with mean value ranging from 34.2 to 38.5 for good

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**Table 3**: Comparison of functional outcome of the patients with malignant MCA infarct based on 30-day mortality, (a) GOS on discharge (b) and mRS on 6 months (c) assessment.

|                        | Alive | Death | Mean diff (95% CI) | $t$ (df) | $P$-value |
|------------------------|-------|-------|--------------------|----------|-----------|
| **a**: Functional outcome of patients with malignant MCA infarct based on 30-day mortality |       |       |                    |          |           |
| Mean                   | SD    | Mean  | SD                 |          |           |
| CBF                    | 36.2  | 6.46  | 36.8               | -6.71    | -0.58 (-4.56, 3.40) | -0.29 (93) | 0.773* |
| CBV                    | 34.2  | 5.89  | 29.8               | -24.66   | -1.752    | -0.101    | 0.919* |
| TTP                    | 38.2  | -7    | 38.8               | -8.97    |           |           |         |

|                        | Good  | Poor  | Mean diff (95% CI) | $t$ (df) | $P$-value |
|------------------------|-------|-------|--------------------|----------|-----------|
| Mean                   | SD    | Mean  | SD                 |          |           |
| CBF                    | 37.3  | 6.08  | 33.5               | -6.8     | 3.8 (0.88, 6.68) | 2.59 (93) | 0.011* |
| CBV                    | 34.2  | 5.03  | 29.3               | -30.62   | -2.525    | -1.264    | 0.206* |
| TTP                    | 38.5  | 5.25  | 38.2               | -12.56   |           |           |         |

|                        | Good  | Poor  | Mean diff (95% CI) | $t$ (df) | $P$-value |
|------------------------|-------|-------|--------------------|----------|-----------|
| Mean                   | SD    | Mean  | SD                 |          |           |
| CBF                    | 36.9  | 6.22  | 28.3               | -3.37    | 8.6 (5.43, 11.86) | 6.02 (9.7) | <0.001* |
| CBV                    | 34.2  | 5.78  | 3.7                | -25.91   | -3.095    | -3.168    | 0.002* |
| TTP                    | 38.5  | 5.42  | 27.1               | -4.89    |           |           |         |

*The data skewed and present median (IQR), *Z statistics, *independent t-test, *Mann–Whitney U-test. IQR: Interquartile range, GOS: Glasgow outcome scale, CI: Confidence interval, SD: Standard deviation, mRS: Modified Rankin scale, MCA: Middle cerebral artery, CBF: Cerebral blood flow, CBV: Cerebral blood volume, TTP: Time-to-peak
outcome and mean value for poor outcome ranging from 3.7 to 28.3 with significant results ($P = 0.002$ and $P < 0.001$) [Table 3c].

**DISCUSSION**

Acute stroke remains the leading cause of morbidity and mortality worldwide and accounts for up to 20%–30% of emergency admissions. Among the groups of patients who develop acute stroke, a small subset of 10% of patients, unfortunately, progress to develop malignant MCA infarction, with a reported mortality rate of 80% if left untreated. Decompressive craniectomy is an effective treatment option in reducing morbidity and mortality, as proven by several trials worldwide. Since the publication of the landmark European trials on the effectiveness of decompressive craniectomy in improving the overall outcome of this subset of patients, subsequent trials have raised new questions and fueled debates particularly on the topic of ideal candidates and timing of surgery. Performing early decompressive craniectomy before the onset of neurological deterioration still remains debatable and not commonly performed due to the uncertainty of edema progression and surgical related complications. Current trends in the research on stroke management emphasizes on the development of predictive tools or models in predicting progression of MBI for clinical decision-making. Previous studies have identified various predictive factors such as NIHSS score, Alberta Stroke Program Early CT score, and diffusion and perfusion MRI imaging to predict the development of malignant brain infarction. In the assessment of acute stroke syndrome, neuroimaging plays a critical role in confirming the diagnosis and determining patient care and outcome. Noncontrast CT scan remains the primary diagnostic modality; being readily available in most if not all centers, fast imaging time and relatively cheaper in cost to acquire and maintain. It, however, lacks the ability to provide crucial information vital to the planning of management in patients with acute stroke, in particular, predicting potential deterioration from space occupying cerebral edema in patients with MCA territory stroke. MRI DWI remains the gold standard in measuring edema volume and predicting high-risk patients; but its limitation in terms of logistics availability, longer acquisition time, requirement of specialized personnel in data interpretation, and higher cost-benefit ratio makes it less than ideal as a principal diagnostic tool of choice in light of urgent decision-making situations.

The role of CTP is rapidly developing and evolving into a diagnostic modality of choice in the management of acute stroke. It has a distinct advantage of relative cost-effectiveness, availability, rapid information acquisition time, and ease of interpretation. CTP allows for accurate identification and differentiation of areas of ischemic penumbra tissue from infarcted tissue; with an additional ability of quantifying CBF. We investigate whether CTP could help in predicting the subsequent development of malignant MCA infarction.

The mean age of patients in this cohort is 56 (SD = 12.22) years old in nonMBI group and 63 (SD = 11.73) in MBI group; the majority of the patients were aged between 30 and 80 years old. Age generally remains a predictor of outcome, in that older patients are protected from the deleterious effects of space occupying edema due to cerebral atrophy resulting in a less malignant course of progression and they deteriorate over a longer time interval. Conversely, younger patients who have not suffered the effects of cerebral atrophy may deteriorate faster, and present with a lower preoperative GCS score. In this study, we did not find an association between age and MBI, possibly due to an increased number of older patients in our study population (54% older than 68 years old). According to Gulensoy et al., as age advances, the result becomes less successful and the mortality increases. This is because elderly patients usually have more medical risk factors, which may increase the risk of poor outcomes and mortality and majority of them are in their late 60’s. This is consistent with the patient in this population of patients. It is also suggested that perhaps younger patients with age <50 years have a better functional outcome. Until recently, the efficacy of decompressive hemicraniectomy in patients 60 years of age or older has been uncertain. A recent randomized clinical trial showed that malignant MCA infarction in patients aged >60 years who were treated with early (<48 h postictus) hemicraniectomy had a higher survival rate and the better functional outcome more than patients who were managed conservatively. Thus, old age per se should not be regarded an exclusion criteria for hemicraniectomy after malignant MCA infarct. There is still ongoing debate with regard to the exact age limit that influences the outcome in patients. Patient’s health status, functional and cognitive status, daily living index, comorbidities, neurological condition on presentation and extent of infarction, social and employment situation, as well as patient’s and family expectations should be taken into account in treatment decisions.

Male patients (27.1%) were more frequently affected compared to females (33.3%); in contrast to trends reported in literature. In Malaysia, there is no available data for acute MCA stroke, patients of Malay ethnicity (27.3%) were more frequently affected, reflecting the racial distribution in Malaysia.

Patients were stratified based on risk factors for which they play an important role in acute treatment decisions as well as influencing both short-term and long-term outcome in patients. Comorbidities associated with an increased incidence of primary and recurrent strokes such as obesity, DM, smoking, hypercholesterolemia, and HTN were taken...
into account. Majority of the study population with MBI were hypertensive; 61.7% as compared to 23.2% in the MBI group. The variation of blood pressure and HTN is known risk factors for malignant MCA infarct.\textsuperscript{[13]}

Clinical parameters remain of upmost importance as the first-line assessment in predicting the development of malignant infarction in patients. Conscious level on admission as well as progressive deterioration of conscious level remains an ominous sign in patients with stroke. The early studies and publication commonly used the GCS scoring system in stroke patients for the purpose of clinical triage and monitoring, primarily due to its reliable interpretation among clinicians. The NIHSS is a reliable, although more detailed score that provides a quantitative measure of stroke-related deficits and is valid in predicting lesion size and measure of stroke severity and important predictor of outcome in stroke patients. In this study, the median NIHSS score among patients with MBI on admission was 19 as compared to 13 in the nonMBI group ($P < 0.001$). This is similar with previously published papers, elucidating the useful role of NIHSS is in predicting development or progression to MBI in conjunction with other predictors to determine the risk of MBI. An NIHSS >18 was strongly associated with MBI and a NIHSS score at 7 days after admission, of at least 6 accurately forecasts a poor long-term outcome after stroke.\textsuperscript{[11]}

This is an essential clinical tool for rapid bedside decision-making and treatment strategies as well as in predicting the long-term prognosis in patients. Although clinical symptoms are very sensitive to cerebral ischemia, they are nonspecific. Early ischemic signs on plain CT scans reflect intracellular edema and are specific but not sensitive for stroke at an early stage. They show existing irreversible infarction within 2 h of ischemic stroke but do not show tissue at risk.

When compared to clinical parameters, CT findings are less sensitive than the NIHSS in determining early predictors of malignant MCA infarct as clinical presentation of patients still remains the most important indicator compare to radiological results. NIHSS has a sensitivity of 98.5% and specificity of 96.3% in determining predictors of malignant MCA infarct. Presence of good collateral circulation sustains brain viability to arterial occlusion while poor leptomeningeal collaterals can be ominous of continued tissue damage in the presence of an ischemic insult. Leptomeningeal collateral circulation is critical in maintaining blood flow to the ischemic regions to reduce ischemic injury. Collateral scoring is a useful tool for assessing leptomeningeal collateral circulation on CTA. Assessment of perfusion by collateral flow and ischemic area volume is important; however, it does not show the perfusion state and ischemic core size. Despite its importance, it has been difficult to simply and quantitatively measure the degree of collateral flow. We chose not to include this parameter in our study because this requires CT angiography for collateral scoring.\textsuperscript{[14]}

This study is aimed at identifying the usefulness of CTP parameters in predicting development or progression of malignant edema in MCA territory infarction. We aimed to identify the scanning parameters best suited to indicate tissue at risk and to measure a perfusion limit to predict infarction and correlating CTP findings with the patient’s outcome based on mRS. CTP based mapping of CBF, CBV, and TTP allowed for the discrimination between patients without a relevant risk and those with considerable risk of developing life-threatening brain swelling and a malignant course of the infarct.

Our results show a significant difference between perfusion parameters [Table 4] between MBI and nonMBI patients. A significant difference was noted in the mean CBF and CBV values in MBI group; 25.8 and 31.3, respectively, as compared to the nonMBI group; 38.3 and 34.2, respectively. Similar differences were also seen in TTP values between these two groups; 29.1 in MBI and 39.1 in nonMBI group. These values when considered singularly or collectively both indicate significant changes and differences in cerebral physiology in cases of ischemic infarction; with a decrease of CBF <30% of normal indicating areas of infarction in MBI patients, and corresponding TTP values indicating recruitment of collateral circulation in an attempt to salvage regions of ischemic penumbra. Comparative values of these parameters between the two cohorts points to the potential predictive

| Table 4: Comparison of mean parameters of CT perfusion (CBF, CBV, and TTP) between nonMBI and MBI for patients with malignant MCA infarct. |
| --- |
| **NonMBI** | **Mean** | **SD** | **MBI** | **Mean** | **SD** | **Mean diff (95% CI)** | **t (df)** | **P-value** |
| CBF | 38.3 | (–5.76) | 31.3 | (–5.29) | 7.0 (4.50, 9.53) | 5.54 (93) | <0.001* |
| CBV* | 34.2 | (–) | 25.8 | (–30.74) | 7.0 (4.50, 9.53) | 5.54 (93) | <0.001b |
| TTP* | 39 | (–4) | 29.1 | (–12.78) | 9.0 (4.50, 9.53) | 7.73 (93) | <0.001b |

*The data skewed and present median (IQR), *Z statistics, *independent t-test, *Mann–Whitney U-test. CT: Computed tomography, MBI: Malignant brain infarct, SD: Standard deviation, CBF: Cerebral blood flow, CBV: Cerebral blood volume, TTP: Time-to-peak, MCA: Middle cerebral artery, CI: Confidence interval, IQR: Interquartile range
value of CTP identifying patients at risk of development or progression to MBI infarction. This translates into ease and rapidity of clinical triage and decision-making for patients with suspected malignant infarction. CT brain imaging using perfusion CT allows improved prediction in the very early stage of disease whether or not malignant MCA infarction will occur. This is of promising potential clinical use in that CTP scanning can be performed rapidly during standard cranial CT and allows for early bedside decision-making as compared to MRI diffusion/perfusion scans, which is time consuming and requires specialized personnel for technical and interpretation purposes.

The CBF and TTP maps describe the extent of the hypoperfusion lesion, whereas the most profoundly affected regions can be shown as a decrease in CBV. Cerebral autoregulation can be diagnosed when there is an increase in CBF and TTP but no difference in CBV. Increased TTP coupled with increased CBF but no increase in CBV is an indication of cerebral autoregulation. The increased TTP in the ischemic state indicates that there are changes in the cerebral perfusion. The prolonged TTP shows that our brain is trying to maximize its oxygen retrieval by prolonging the time of blood flow passing through that particular area of brain tissue. When cerebral perfusion pressure is low, cerebral autoregulation will cause precapillary resistance vessel to dilate to increase the CBV. This will then maintain cerebral perfusion pressure. Unfortunately, prolonged TTP is also associated with high mortality, especially when cerebral autoregulation fails. This is usually accompanied by increased CBF and decreased CBV. In addition, according to Tateyama et al., MTT can predict patient outcome, most likely due to the reasons discussed earlier.

CTP is able to assess the microcirculation and distal cerebral vessels; it is not operator dependent and reproducible in addition to providing details of the CBF, CBV, and TTP that may be used to determine the areas of MCA infarct. CTP is an easy, readily available and has a fast acquisition time, especially for critically ill patients with reproducible results. It was possible to differentiate between infarcted tissue (infarcted core) with viable tissue (penumbra) using CT parameters by absolute CBF and CBV values and in larger series of 130 patients, by relative TTP delay and absolute reduction of CBV.[27] CTP can detect early changes in brain perfusion that will eventually affect the patients’ prognosis and predict their outcome.

Before the use CTP as a potential tool for predicting malignant brain edema, several signs were indicative as early markers of malignant MCA infarction on plain CT brain, being the primary diagnostic modality in all cases of acute stroke. Among the signs of identification for malignant MCA infarct, the most ominous are hyperdense MCA sign, signifying large MCA trunk occlusion and are found to be related to a fatal outcome. Therefore, close observation of the clinical condition of patients and measures must be taken to prevent worsening of neurology.

In this series, when comparing sensitivity and specificity of imaging parameters between plain CT and CTP parameters in a cohort of patients with MCA territory infarction [Table 5] findings of hypodensity on CT scan and hyperdense MCA signs have a sensitivity of 49.3% and 83.6% respectively as compared to CTP parameters. If early parenchymal hypodensity covered more than 50% of the MCA territory, mortality was as high as 85% due to the progressive development of edema and outcome was poor in survivors, which is highly specific for poor and fatal clinical outcome regardless of therapeutic measures. Moreover, the lack of large or total hypodensity in early CT does not exclude the possibility of fatal outcome in patients with MCA trunk occlusions. Because local brain swelling was associated with more extended infarctions, the high specificity and predictive value of this finding for the fatal outcome is not unexpected. In von Kummer series, MCA territory hypodensity more than 50% (sensitivity of 61%, specificity of 98%, and PPV of 85%) and local brain swelling (sensitivity of 78%, specificity of 83%, and PPV of 70%) were found to be good predictors of mortality.[15]

Between CTP parameters, reduction in CBF values had high sensitivity and specificity rate for the development of MBI; 82.4% and 77.8%, respectively. CBV was highly

| Table 5: ROC curve analysis for CT brain findings, CT perfusion parameters, and clinical findings for sensitivity, specificity, PPV, and NPV in predicting malignant MCA infarct (all values in %). |
|---|---|---|---|---|---|
| Hypodensity | Sensitivity % | 50.0 (37.6–62.4) | Specificity % | 100.0 (87.2–100) | PPV | 100.0 | NPV | 44.3 | Accuracy | 64.2 |
| Hyperdense MCA | 16.2 (8.4–27.1) | 100.0 (87.2–100) | 100.0 | 32.1 | 40.0 |
| NIHSS (13.5) | 98.5 (92.1–99.9) | 96.3 (81.0–99.9) | 98.5 | 96.3 | 97.6 |
| CBF (>32.85) | 82.4 (71.2–90.5) | 77.8 (57.7–91.4) | 90.3 | 63.6 | 81.4 |
| CBV (>24.83) | 98.5 (92.1–99.9) | 51.9 (32.0–71.3) | 83.8 | 93.3 | 74.0 |
| TTP (>30.68) | 97.1 (89.8–99.6) | 59.3 (38.8–77.6) | 85.7 | 88.9 | 68.5 |

ROC: Receiver operating characteristics, CT: Computed tomography, PPV: Positive predictive value, NPV: Net present value, MCA: Middle cerebral artery, NIHSS: National Institutes of Health Stroke Scale, CBF: Cerebral blood flow, CBV: Cerebral blood volume, TTP: Time-to-peak
In this study, it was shown as time of ictus to 
table
In terms of functional outcome, there was 
Timing of surgery plays an 
in our group. 
Te mortality was considerably higher than that of 15% 
25% in the MBI group while 6% in nonMBI in our study. 
The percentage of a good outcome at 6 months in this 
series is lower than the reported figures in three randomized 
trials, DESTINY, HAMLET, and DECIMAL trials.12,16,32,34 
A possible explanation for this is the inclusion of patients 
beyond the age of 60 years in this study population, compared 
to the randomized trials, where the patient age limit was set 
at 60 years. The significant functional recovery is related 
to the phases of neurological recovery that can be broadly 
divided into two stages; first being the resolution of initial 
damage which may take up to 6 months to occur, followed 
by improvement in functional and cognitive disability. 
This result shows that within the group of MBI, early and 
aggressive treatment with decompressive craniectomy 
significantly reduces mortality and results in reasonable 
functional recovery among patients. Many patients survive 
with moderate-to-severe disability and controversy exists as 
to whether this should be considered a good outcome. In our 
study, we have insufficient data to assess the quality of life 
of patients which are essential in estimating the therapeutic 
effect. The role of developing and objective model for early 
identification of the potential group of patients which may 
deteriorate and subjecting them to aggressive monitoring 
and treatment measures cannot be overemphasized. Caution 
remains however on the boundaries of what constitutes 
therapeutic intervention against prophylactic interventions; 
as these results clearly state that patients who did not develop 
or progress to MBI fared better than the group which 
was subjected to surgical decompression. The argument 
against prophylaxis treatment is still partially debatable, 
primarily due to the paucity of the available rapid predictive 
tool of triage. Surgery is not without complications, and 
previous publications have noted poor outcomes secondary 
to the surgical complication of infection, hemorrhagic 
transformation, sunken flap syndrome and wound infections, 
particular among the older patient population.35 
The question of hemispheric dominance and outcome in 
stroke remains under constant debate. Key to the argument 
stems from the measures of outcome used, common in all 
cases is the Rankins’ score system. The Rankins’ score system 
has been criticized as primarily focusing predominantly on 
motor function outcome, and in such case, cognitive function 
assessment is not given the required weightage in the overall 
sensitive (98.5) in detecting potential progression or 
development of MBI but lack specificity (51.9); with higher 
negative predictive value at 93.3%. TTP values exhibited 
a similar rate of high sensitivity and low specificity (97.1% 
and 59.3%, respectively) with comparable PPV and NPV. 
(85.7% and 88.9%) The values of CBV and TTP relates to 
pathophysiological changes that occur secondary to defective 
cerebral autoregulation. A reduction in CBV values indicate 
areas of core infarction, contributing to its sensitivity, 
while areas of peripheral ischemia or penumbra results in 
unchanged values of CBV with a reduction of CBF, possibly 
resulting in the lack of specificity. 

Similar accounts can be attributed to a high sensitivity 
value of TTP, which relates to penumbra region reperfusion 
in cases of ischemia-infarction. Thus, when interpreting 
values of CTP parameters, a reduction of CBV is a sensitive 
indicator of the progression of malignant brain infarction, 
while a global reduction of CBF is both sensitive and specific 
to the development of malignant brain infarction. CTP ability 
to depicts the extent of ischemia tissue indirectly helps to 
predict the patients’ clinical outcome. The highest sensitivity 
in depicting ischemic tissue was achieved by mapping the 
CBV (98.5%) and TTP (97.1%) while CBF were found to be 
of moderate specificity (77.8%) with moderate sensitivity 
(82.4%).

MBI portends poor outcome and high mortality rate as 
are seen in numerous prior publications. Decompressive 
cranietomy performed within 24–48; and in a few small 
studies, up to 96 h significantly reduce mortality in patients 
severe ischemic brain edema.37 Timing of surgery plays an 
important role in the final outcome following malignant 
MCA infarct. Randomized studies showed better results 
when decompression was performed within 48 h after 
the symptoms emerge and suggest early surgery when 
indicated.43 There are little data regarding the efficacy of 
surgery outside 48 h, but it was shown that patients operated 
outside 48 h also fared well although the number of patients 
with good recovery was not as good as operated within 
48 h. However, Foerch et al. reported that neither mortality 
rate nor functional outcome was associated with the timing 
of surgery.7 In this study, it was shown as time of ictus 
presentation for the malignant group was 19 whereas in 
nonmalignant group was 14, and it is statistically significant 
(P < 0.001). Decompression should, therefore, be performed 
as soon as possible in cases not responding to medical 
treatment if it is to be used.

The 30-day mortality of malignant MCA infarct is up to 
25% in the MBI group while 6% in nonMBI in our study. 
The mortality was considerably higher than that of 15% 
reported by Ng and Mimmannitiya possibly due to a high 
incidence of malignant MCA infarct affecting older patients 
in our group.24 In terms of functional outcome, there was 
a clear statistical significance between the MBI and nonMBI 
group based on the mRS score at 6 months. All patients 
within the nonMBI group made good progress in terms of 
the functional outcome as compared to the MBI group. 
Within the MBI group, there was a clear trend of significant 
functional recovery and outcome in the interval between 
discharge and 6 months. This is probably a reflection of 
the natural healing process by neuromodulation over time. 
Additional contributing factors include aggressive 
rehabilitation measures, physiotherapy, management of 
secondary complications, and control of underlying risk 
factors. The percentage of a good outcome at 6 months in this 
series is lower than the reported figures in three randomized 
trials, DESTINY, HAMLET, and DECIMAL trials.12,16,32,34 

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outcome and functional recovery. Despite the ongoing debate and variation in published outcomes among patients with dominant or nondominant malignant MCA infarction, it is generally agreed that the results are better when surgery is performed on the nondominant hemisphere in most series. Patients with an infarct in the dominant hemisphere may have a lower quality of life than patients with an infarct in the nondominant hemisphere because they have more severe language impairment. However, a meta-analysis found no difference in functional outcome between right and left hemispheric infarcts. In our study, we obtained results of 68.5% in MBI and 30.5% in nonMBI of the right hemisphere; nondominant.

CONCLUSION

In summary, objective and comprehensive predictive models require both clinical and radiological parameters to assist in rapid and safe clinical decision making in acute stroke patients. This study shows that among the various published predictive markers, CT perfusion parameters of TTP & CBF values; in combination with severity of clinical presentation using the NIHSS score system is sensitive and specific in predicting development of malignant brain infarction in patients presenting with acute stroke. This may potentially be used as a relevant and effective bedside assessment tool for rapid and safe decision making process.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIXES

Appendix A

| Category                                      | Score/Description                  | Date/Time Initials | Date/Time Initials | Date/Time Initials | Date/Time Initials | Date/Time Initials |
|----------------------------------------------|------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| 1a. Level of Consciousness                   | 0 = Alert                          |                    |                    |                    |                    |                    |
| (Alert, drowsy, etc.)                        | 1 = Drowsy                          |                    |                    |                    |                    |                    |
|                                              | 2 = Stuporous                       |                    |                    |                    |                    |                    |
|                                              | 3 = Coma                            |                    |                    |                    |                    |                    |
| 1b. LOC Questions                            | 0 = Answers both correctly         |                    |                    |                    |                    |                    |
| (Month, age)                                 | 1 = Answers one correctly           |                    |                    |                    |                    |                    |
|                                              | 2 = Incorrect                      |                    |                    |                    |                    |                    |
| 1c. LOC Commands                             | 0 = Obeys both correctly            |                    |                    |                    |                    |                    |
| (Open/close eyes, make fistlet go)           | 1 = Obeys one correctly             |                    |                    |                    |                    |                    |
|                                              | 2 = Incorrect                      |                    |                    |                    |                    |                    |
| 2. Best Gaze                                 | 0 = Normal                         |                    |                    |                    |                    |                    |
| (Eyes open - patient follows examiner’s finger or face) | 1 = Partial gaze palsy             |                    |                    |                    |                    |                    |
|                                              | 2 = Forced deviation                |                    |                    |                    |                    |                    |
| 3. Visual Fields                             | 0 = No visual loss                  |                    |                    |                    |                    |                    |
| (Introduce visual stimuli/threat to pt or visual field quadrants) | 1 = Partial Hemianopia              |                    |                    |                    |                    |                    |
|                                              | 2 = Complete Hemianopia            |                    |                    |                    |                    |                    |
|                                              | 3 = Bilateral Hemianopia (Blind)    |                    |                    |                    |                    |                    |
| 4. Facial Paresia                            | 0 = Normal                         |                    |                    |                    |                    |                    |
| (Show teeth, raise eyebrows and squeeze eyes shut) | 1 = Minor                          |                    |                    |                    |                    |                    |
|                                              | 2 = Partial                        |                    |                    |                    |                    |                    |
|                                              | 3 = Complete                       |                    |                    |                    |                    |                    |
| 3a. Motor Arm - Left                         | 0 = No drift                       |                    |                    |                    |                    |                    |
|                                              | 1 = Drift                          |                    |                    |                    |                    |                    |
|                                              | 2 = Can’t resist gravity            |                    |                    |                    |                    |                    |
|                                              | 3 = No effort against gravity      |                    |                    |                    |                    |                    |
|                                              | 4 = No movement                    |                    |                    |                    |                    |                    |
|                                              | X = Unstable                       |                    |                    |                    |                    |                    |
|                                              | (Joint fusion or limb amputee)     |                    |                    |                    |                    |                    |
| 5b. Motor Arm - Right                        | 0 = No drift                       |                    |                    |                    |                    |                    |
| (Elevate arm to 90° if patient is sitting, 45° if supine) | 1 = Drift                          |                    |                    |                    |                    |                    |
|                                              | 2 = Can’t resist gravity            |                    |                    |                    |                    |                    |
|                                              | 3 = No effort against gravity      |                    |                    |                    |                    |                    |
|                                              | 4 = No movement                    |                    |                    |                    |                    |                    |
|                                              | X = Unstable                       |                    |                    |                    |                    |                    |
|                                              | (Joint fusion or limb amputee)     |                    |                    |                    |                    |                    |
| 6a. Motor Leg - Left                         | 0 = No drift                       |                    |                    |                    |                    |                    |
|                                              | 1 = Drift                          |                    |                    |                    |                    |                    |
|                                              | 2 = Can’t resist gravity            |                    |                    |                    |                    |                    |
|                                              | 3 = No effort against gravity      |                    |                    |                    |                    |                    |
|                                              | 4 = No movement                    |                    |                    |                    |                    |                    |
|                                              | X = Unstable                       |                    |                    |                    |                    |                    |
|                                              | (Joint fusion or limb amputee)     |                    |                    |                    |                    |                    |
| 7. Limb Ataxia                               | 0 = No ataxia                      |                    |                    |                    |                    |                    |
| (Finger-nose, heel down shin)                | 1 = Present in one limb            |                    |                    |                    |                    |                    |
|                                              | 2 = Present in two limbs           |                    |                    |                    |                    |                    |
| 8. Sensory                                   | 0 = Normal                         |                    |                    |                    |                    |                    |
| (Pin pick to face, arm, trunk, and leg - compare side to side) | 1 = Partial loss                   |                    |                    |                    |                    |                    |
|                                              | 2 = Severe loss                    |                    |                    |                    |                    |                    |
| 9. Best Language                             | 0 = No aphasia                     |                    |                    |                    |                    |                    |
| (Name item, describe a picture and read sentences) | 1 = Mid to moderate aphasia        |                    |                    |                    |                    |                    |
|                                              | 2 = Severe aphasia                 |                    |                    |                    |                    |                    |
|                                              | 3 = Mute                           |                    |                    |                    |                    |                    |
| 10. Dysarthria                               | 0 = Normal articulation            |                    |                    |                    |                    |                    |
| (Evaluate speech clarity by patient repeating words) | 1 = Mild to moderate slurring of words |                    |                    |                    |                    |                    |
|                                              | 2 = Near to unintelligible or worse |                    |                    |                    |                    |                    |
|                                              | X = Intubated or other physical barrier |                    |                    |                    |                    |                    |
| 11. Extinction and Inattention               | 0 = No neglect                     |                    |                    |                    |                    |                    |
| (Use information from prior testing to identify neglect or double simultaneous stimuli testing) | 1 = Partial neglect                |                    |                    |                    |                    |                    |
|                                              | 2 = Complete neglect               |                    |                    |                    |                    |                    |

**TOTAL SCORE**
Collection Data Form
CT perfusion in detecting malignant brain infarct

Demographic Data
1. Serial ID: __________________________
2. Age: __________________________ 3. Gender: __________________________
3. Race:
   1. Malay
   2. Chinese
   3. Indian
   4. Others (specify:)
4. Comorbid:
   1. Hypertension
   2. Diabetes Mellitus
   3. Ischemic heart disease
   4. Old CVA
   5. Dyslipidemia
   6. Bronchial Asthma
   7. Renal Failure
   8. Others

On treatment? Yes [ ] No [ ] Non-compliant [ ]
5. Dominance – Left MCA infarct: Yes / No
6. Presentation:
   Date/ Time of onset: _______________
   DOA: _______________
   DOD: _______________
   Duration of stay: ___________ days
   NIHSS on admission: _______________
   BP on arrival: _______________
7. Symptoms:
   1. Hemiplegia (R) (L)
   2. Facial asymmetry
   3. Slurring of speech
   4. Blurring of vision
   5. Headache, nausea, vomiting
   6. Others
8. CT brain findings: __________________________
9. CT perfusion findings: __________________________
   CBV: ______  CBF: _______ TTP: ______
10. Progress in ward:
    GCS: __________________________
    Repeat CT brain: __________________________
11. Follow up:
    On discharge: GCS: __________________________
    Ryle tube feeding: Y [ ] N [ ]
    At 6 months: GCS: __________________________
    Ryle tube feeding: Y [ ] N [ ]
12. Any adverse effect from contrast study?
   i) Allergic reaction (Yes / No)
      If yes, type of allergic reaction: __________________________
   ii) Contrast induce nephropathy (Yes / No)
      - Creatinine (pre contrast)
      - Creatinine (after 72 hours)
      If yes, subsequent management: __________________________
### Appendix C: mRS (Bonita R, 1988).

| Score | Description |
|-------|-------------|
| 0     | Patient is asymptomatic |
| 1     | Patient has no significant disability despite symptoms; able to carry out all usual activities |
| 2     | Slight disability unable to perform all previous activities but is able to look after own affairs without assistance |
| 3     | Moderate disability requiring help with activities but able to walk without assistance |
| 4     | Moderately severe disability unable to walk without assistance and unable to carry out own body needs without assistance |
| 5     | Severe disability; bedridden, incontinence and requiring constant nursing care |
| 6     | Dead |

mRS: Modified Rankin scale