Computed tomography perfusion as an early predictor of malignant cerebral infarction

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Complete List of Authors:	Rodríguez Vázquez, Alejandro; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Laredo, Carlos; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Magnetic Resonance Imaging Core Facility Reyes, Luis Alberto; Hospital Clínic de Barcelona, Neurosurgery Dolz, Guillem; Hospital Clinic de Barcelona, Radiology Doncel-Moriano, Antonio; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Llansó, Laura; Barcelona Clinic Hospital Neurology Department, Neurology Rudilosso, Salvatore; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Llull, Laura; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Renú, Arturo; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Amaro, Sergio; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Torné, Ramón; Hospital Clinic de Barcelona Instituto Clinic de Neurociencias Urra, X; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona Chamorro, Ángel; Barcelona Clinic Hospital Neurology Department, Comprehensive Stroke Center, Hospital Clínic of Barcelona
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Abstract:	Background Malignant middle cerebral artery infarction (MCI) needs rapid intervention. This study aimed to enhance the prediction of MCI using computed tomography perfusion (CTP) with varied quantitative benchmarks. Methods We retrospectively analyzed 253 patients from a single-center registry presenting with acute, severe, proximal large vessel occlusion studied with whole-brain CTP imaging at hospital arrival within the first 24 hours of symptoms-onset. MCI was defined by clinical and imaging criteria, including decreased level of consciousness, anisocoria, death due to

cerebral edema, or need for decompressive craniectomy, together with midline shift ≥6 mm, or infarction of more than 50% of the MCA territory. The predictive accuracy of baseline ASPECTS and CTP quantifications for MCI was assessed by receiver operating characteristic (ROC) area under the curve (AUC) while F-score was calculated as an indicator of precision and sensitivity.

Results

Sixty-three out of 253 patients (25%) fulfilled MCI criteria and had worse clinical and imaging results than the non-MCI group. The capacity to predict MCI was lower for baseline ASPECTS (AUC 0.83, F-score 0.52, Youden's index 6), than with perfusion-based measures: relative cerebral blood volume threshold <40% (AUC 0.87, F-score 0.71, Youden's index 34 ml) or relative cerebral blood flow threshold <35% (AUC 0.87, F-score 0.62, Youden's index 67 ml). CTP based on rCBV measurements identified twice as many MCI as baseline CT ASPECTS.

Discussion and conclusion

CTP-based quantifications may offer enhanced predictive capabilities for MCI compared to non-contrast baseline CT ASPECTS, potentially improving the monitoring of severe ischemic stroke patients at risk of life-threatening edema and its treatment.

CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ETHICAL APPROVAL

The local Clinical Research Ethics Committee from Hospital Clínic Barcelona approved the study protocol (registration number HCB/2020/0233) under the requirements of national legislation.

INFORMED CONSENT

Informed consent was not sought for this study due to its retrospective nature.

DISCLOSURES

This work has been accepted for presentation at the 10th European Stroke Organisation Conference (May 2024, Basel, Switzerland).

GUARANTOR

ARV, XU

CONTRIBUTORSHIP

- ARV, XU: study concept and design; major role in the acquisition of data; analysis and interpretation of data; drafting of the manuscript.
- CL: major role in the acquisition of data; analysis and interpretation of data.
- ADM, LR, LLla: major role in the acquisition of data.
- All authors interpreted the results, reviewed the manuscript and substantially contributed to the final manuscript.

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Computed tomography perfusion as an early predictor of malignant cerebral infarction

Alejandro Rodríguez-Vázquez, MD;[1,2] Carlos Laredo, PhD;[2] Luis Reyes, MD PhD;[3] Guillem Dolz, MD;[4] Antonio Doncel-Moriano, MD;[1] Laura Llansó, MD;[1] Salvatore Rudilosso, MD PhD;[1,2] Laura Llull, MD PhD;[1,2,5] Arturo Renú, MD PhD;[1,2] Sergio Amaro, MD PhD;[1,2,5] Ramón Torné, MD PhD;[2,3,5] Xabier Urra, MD, PhD;[1,2,5] Ángel Chamorro, MD PhD.[1,2,5]

1. Department of Neurology, Hospital Clínic de Barcelona, Barcelona, Spain
2. Fundació de Recerca Clínic Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Spain
3. Department of Neurosurgery, Hospital Clínic de Barcelona, Barcelona, Spain
4. Department of Radiology, Hospital Clínic de Barcelona, Barcelona, Spain.
5. Faculty of Medicine, University of Barcelona, Barcelona, Spain.

Corresponding author: Xabier Urra, 170 Villarroel, 08036 Barcelona, Spain; Fax: +34932275783;

Phone: +34932275414; E-mail: xurra@clinic.cat.

Keywords: computed tomography perfusion, malignant cerebral infarction, brain edema, acute stroke.

ABSTRACT

Background

Malignant middle cerebral artery infarction (MCI) needs rapid intervention. This study aimed to enhance the prediction of MCI using computed tomography perfusion (CTP) with varied quantitative benchmarks.

Methods

We retrospectively analyzed 253 patients from a single-center registry presenting with acute, severe, proximal large vessel occlusion studied with whole-brain CTP imaging at hospital arrival within the first 24 hours of symptoms-onset. MCI was defined by clinical and imaging criteria, including decreased level of consciousness, anisocoria, death due to cerebral edema, or need for decompressive craniectomy, together with midline shift ≥6 mm, or infarction of more than 50% of the MCA territory. The predictive accuracy of baseline ASPECTS and CTP quantifications for MCI was assessed by receiver operating characteristic (ROC) area under the curve (AUC) while F-score was calculated as an indicator of precision and sensitivity.

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INTRODUCTION

Ischemic stroke stands as the second leading cause of death worldwide and a significant contributor to disability.[1] Approximately 10% of ischemic strokes follow a 'malignant' course, primarily defined by extensive infarction within the middle cerebral artery (MCA) territory.[2] Such strokes rapidly progress to cerebral edema, leading to mass effects that may culminate in brain herniation and death.[3] Notably, younger patients lack cerebral atrophy, predisposing them to this severe outcome.[4]

Current medical interventions have yet to demonstrate efficacy in altering the natural progression of malignant infarctions.[5-9] To date, the only beneficial treatment is timely decompressive surgery, which has been shown to enhance survival, albeit often with residual moderate to severe disability.[10-14] Predictive models for malignant transformation traditionally rely on magnetic resonance imaging (MRI), which may not be universally available.[15] Computed tomography perfusion (CTP), while more accessible, has often been less precise than MRI for assessing ischemic damage.[16] Recent research, however, suggests that specific gray and white matter perfusion thresholds may enhance CTP's predictive accuracy.[17]

With new clinical trials expanding the use of mechanical thrombectomy in patients with low ASPECTS scores,[18-23] there is a growing need to identify individuals at high risk for malignant progression. This study evaluated the predictive value of acute CTP findings at hospital arrival for developing malignant cerebral infarction (MCI) in the following hours, compared with other potential clinical and radiological predictors of this severe complication.

METHODS

Patient selection

Data for this retrospective study were systematically extracted from our local stroke database, which prospectively compiles each patient's medical record. We assessed 804 patients considered for stroke reperfusion therapy from 2010 to 2017 and identified 253 patients at heightened risk for MCI, with the following inclusion criteria:

1- Proximal large vessel occlusion involving the carotid artery, M1 segment, or M2 segment (if the basal ganglia were affected) of the MCA.
2- Acute hemispheric syndrome with severe symptoms (National Institute of Health Stroke Scale (NIHSS) > 15 for dominant hemisphere or NIHSS > 13 for non-dominant hemisphere) within 24 hours post-admission.
3- Admission multimodal CT protocol, including non-contrast CT (NCCT), CT angiography (CTA), and CTP.
4- Follow-up neuroimaging (CT or MRI) conducted within 72 hours of admission.
5- Clinical evaluations conducted 24-72 hours post-admission and at a 3-month follow-up.

Demographic, clinical, and blood test variables were collected for each patient, along with the time from symptom onset to neuroimaging, occlusion site, type of revascularization treatment, and the degree of final recanalization. The clinical severity at admission and in the first 24 hours was addressed using the NIHSS, and the functional outcome at three months was addressed using the modified Rankin scale (mRS). As an observational cohort study, this work adheres to the STROBE guidelines.[24]

Study outcomes - Definition of MCI

The principal outcome, MCI, was defined through a combination of clinical and neuroimaging criteria:[2,4,25]

1- Clinical indicators of intracranial hypertension, such as a decreased level of consciousness (score ≥1 in the corresponding item on NIHSS), anisocoria, death due to cerebral edema, or need for decompressive craniectomy.
2- Neuroimaging evidence indicating significant cerebral edema, exemplified by a midline shift ≥6 mm or an infarct encompassing over half of the MCA territory.

A diagnosis of malignant stroke required the presence of at least one clinical and one neuroimaging criterion. An example of MCI is shown in **Figure 1**.

Neuroimaging analysis

The imaging protocol included a baseline multimodal whole-brain CT scan (total acquisition time, 83 seconds), which included NCCT (140 kV, 127 mAs, FOV = 225 mm, matrix = 512 × 512, section thickness = 5 mm); CTA (120 kV, 663 mAs, FOV = 261 mm, matrix = 512 × 512, section thickness = 0.6 mm); and CTP (80 kV[peak], 250 mAs, 1.5-second rotation, FOV = 18 mm, matrix = 512 × 512, and forty-nine 2-mm-thickness slices). Patients were scanned using a Somatom Definition Flash 128-section dual-source multidetector scanner (Siemens), with a 98-mm z-coverage and 26 time points acquired each 1.5 seconds and 4 last time points each 5 seconds (total acquisition time, 59 seconds). Fifty milliliters of nonionic iodinated contrast were administered intravenously at 5 mL/s using a power injector, followed by a saline flush of 20 mL at an injection rate of 2 mL/s.

The ASPECTS was assessed on the baseline NCCT. CTP maps were calculated by the commercial software MIStar (Apollo Medical Imaging Technology) using a model-free singular-value decomposition algorithm with a delay and dispersion correction. The software automatically performs motion correction and selects an arterial input function from an unaffected artery (usually the anterior cerebral artery) and a venous output function from a large draining vein (the sagittal sinus). The software generates cerebral blood flow (CBF), cerebral blood volume (CBV), mean transient time (MTT), and delay time (DT) maps. Of note, the delay-corrected deconvolution method produces delay time maps rather than the more extensively used time-to-maximum maps[26]. A threshold of 3 seconds on the delay time maps was used to define the hypoperfusion[27], and ischemic core was defined within the hypoperfused area with a series of relative CBF (rCBF) and CBV (rCBV) thresholds as a percentage of the mean perfusion values from the entire unaffected, contralateral hemisphere[16]. Estimates of the ischemic area were made using all rCBF and rCBV thresholds from 0 to 100%.

The follow-up imaging was performed on the same NCCT or on MRI (1.5T Magneton Aera unit, Siemens). Midline shift was measured as the perpendicular distance between the septum pellucidum and a line drawn between the anterior and posterior attachments of the falx to the inner table of the skull.

Two trained observers reviewed neuroimaging and clinical information for MCI evaluation, and a third acted as a referee in case of disagreement. A single observer assessed CTP calculations semiautomatically.

Statistical analysis

The statistical procedures were executed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY), and Python 3.8.5 with the Numpy, Pandas, Scikit-learn, Matplotlib, and Seaborn libraries.

Categorical variables were assessed using the Chi-square ($\chi 2$) test when appropriate, with Fisher's exact test as an alternative for small sample sizes. Continuous variables following a normal distribution were presented using means and standard deviations (SD), whereas those not normally distributed, along with ordinal variables, were described using medians and interquartile ranges (IQR). Group comparisons for means and medians were conducted via the Student's t-test, ANOVA, or Mann-Whitney U test, contingent upon the data's distribution. The relationship between perfusion patterns and clinical outcomes was evaluated using univariate logistic regression. The train test split function was employed for splitting datasets into training and test sets, ensuring a robust validation of the models' performance. To assess the predictive value, accuracy, and classification performance of various clinical and radiological variables for malignant stroke, we employed logistic regression models to evaluate individual predictors, including NIHSS, ASPECTS, and all perfusion parameters. Each variable's performance was quantified by calculating the Area Under the Receiver Operating Characteristic (AUC) curve, which reflects the model's ability to distinguish between malignant and non-malignant stroke cases with a higher AUC indicating better model performance. Accuracy was reported as the proportion of correct predictions over the total cases. Sensitivity, or the true positive rate, was prioritized to emphasize the correct identification of malignant stroke due to its clinical significance in prognosis and treatment planning. In addition, precision was calculated to assess the proportion of actual malignant stroke cases among those predicted as such, thereby reflecting the model's ability to produce a low rate of false positives. The F1-score, a harmonic mean of precision and sensitivity, was also determined to evaluate the model's balance between identifying true malignant cases (sensitivity) and avoiding false positive diagnoses (precision). These metrics provided a comprehensive view of the model's performance, especially considering the imbalanced nature of the dataset, where malignant strokes were less prevalent than non-malignant strokes. The election of optimal single cutoff values was based on Youden's J statistic, which maximizes the true positive rate (sensitivity) and minimizes the false positive rate. Significance was set at $P<0.05$ for all tests, and hypotheses were bilateral.

Data Availability:

Datasets produced and analysed during this study can be obtained from the corresponding author upon a reasonable request.

RESULTS

Out of 253 patients who satisfied the inclusion criteria (**Figure 2**), 63 individuals (25%) were classified as having MCI. The demographic and pre-stroke clinical characteristics—such as sex, age, and clinical history—were comparable between the MCI and non-MCI groups, as was the interval from symptom onset to initial imaging.

As shown in **Table 1**, patients with MCI exhibited a higher baseline glycemia, lower baseline ASPECTS scores, more carotid and tandem occlusions, and higher NIHSS scores at admission and after 24 hours. Reperfusion treatments, such as mechanical thrombectomy with or without intravenous alteplase, were more frequently administered in the non-MCI group, which also showed superior angiographic results. Hemorrhagic transformations occurred more often in the MCI group. At 3 months, the median mRS scores and mortality rates were higher in the MCI group.

Regarding the predictive capacity for MCI, baseline ASPECTS had a ROC AUC of 0.83 and F1-score of 0.52 for a cut-off lower than 6, which is also the limit traditionally used when considering treatment with mechanical thrombectomy. However, several CTP parameters outperformed it **(Figure 3)**.

Values based on cerebral blood volume performed best, with AUC of 0.87 and F1-scores of 0.71 for rCBV thresholds lower than 40%, with the best volume cut-off for CBV being 34 mL. Regarding cerebral blood flow, the most robust predictor was found to be a rCBF threshold of less than 35% for a 67 mL cut-off.

In our cohort of 253 patients, ASPECTS <6 identified 19 true positives for MCI compared to 38 matched by the 34 mL rCBV 40% threshold. False negatives were lower using CTP compared to ASPECTS (24 vs. 43), with a slight increase in false positives (20 vs. 12). A diagram of these statistical variables is shown in **Figure 4**. There were no significant differences between observers (Kappa coefficient for the definition of malignant infarction: 0.93, intraclass correlation coefficient for the quantitative assessment of midline shift: 0.99).

Given the asymmetry between the proportion of patients in each group (malignant and non-malignant) undergoing mechanical thrombectomy, a specific analysis was performed using ROC evaluating the ability of ASPECTS and the CTP rCBV 40% to differentiate between true and false positives according to the use of mechanical thrombectomy **(Figure 5)**. ASPECTS lost most of its predictive value in patients treated with thrombectomy (AUC of 0.82 in untreated patients, 0.52 in treated patients), while the decrease in predictive value was milder for rCBV 40% (AUC of 0.86 and 0.76 in untreated and treated patients, respectively).

DISCUSSION

In our cohort of patients with moderate to severe symptoms at first evaluation or during the first 24 hours after admission, CTP-based measurements outperformed those based only in NCCT ASPECTS for predicting malignant infarction. The pathogenesis of MCI is multifaceted. Severe presenting symptoms are well-recognized clinical harbingers of MCI.[2,4] While MRI is traditionally favored for its precision in quantifying infarct volume—especially volumes exceeding 145 mL on DWI—its predictive reliability hinges on the ADC thresholds applied.[15,27] MRI's sensitivity and specificity are heightened in evaluations conducted 24 hours post-symptom onset rather than in hyperacute assessments.[28] Although CT is less sensitive in the early phase, its greater accessibility and the augmentation of its predictive power through multimodal CT perfusion imaging are noteworthy.[29] Our investigation focused on multimodal CT scans executed upon admission, with a sub-6-hour window from symptom onset, aiming to swiftly pinpoint patients at elevated risk for MCI to expedite intervention. We purposely selected a cohort of patients at high risk of developing MCI, so the rate of malignant infarctions was 25%, higher than the 10% classically described in the general population.[2]

In patients with extensive symptoms, the optimal CTP thresholds for predicting malignant infarction were higher than the commonly used <30% threshold tied to DWI-MRI ischemic core definitions. Although DWI is traditionally used as the gold standard to define the extent of the ischemic lesion as an element related to the functional outcome,[30] the relevance of cerebral edema in the development of MCI—and potentially influencing these threshold discrepancies—cannot be understated.[32,33]

Compared to rCBF thresholds, rCBV showed slightly greater ability to predict MCI in our cohort. This may be because the volume drop is indicative of greater cerebral hypoperfusion, which could lead to greater development of cerebral edema and more ischemic tissue. Regardless of whether the measurement was based on in flow or volume, CTP-based models present greater sensitivity, precision, and accuracy than NCCT ASPECTS. Thus, considering the extreme clinical severity of MCI, it is especially important to use a tool that can identify the greatest number of patients at risk. In our cohort, CTP performed before any type of treatment identified twice as many patients who developed MCI compared to ASPECTS with half the number of false negatives and anincrease in false positives.

In routine clinical practice, the greater predictive capacity of models based on cerebral perfusion compared to NCCT ASPECTS could be useful for optimizing the management circuits of patients with acute ischemic strokes. For example, using the information provided by CTP to identify patients at high risk of MCI could serve to carry out more strict surveillance protocols or early control neuroimaging that would not be performed under normal conditions.

The strength of this work lies in its simple design that is applicable to routine clinical practice, based on a proven and widely accepted imaging methodology. In this way, it is an easy element to apply regardless of the available resources and the clinical severity of the patient.

On the other hand, the study's retrospective design, despite the prospective nature of data collection, may introduce limitations. The fact that it is a single-center study is also a limitation, although the accessibility of the technique favors potential reproducibility. Our data predate the routine consideration of mechanical thrombectomy for extensive strokes, potentially skewing outcomes for patients presenting with ASPECTS under 6 due to the infrequency of intervention at that time. Considering the use of the ASPECTS as a tool to choose patients eligible for treatment, this bias, might have overestimated the predictive capacity of the ASPECTS as patients with large infarcts and large vessel occlusions that do not recanalize are at higher risk of MCI. With the increasing inclination towards reperfusion therapies for extensive ischemic lesions, our findings could prove instrumental in identifying patients at increased risk for malignant cerebral edema if confirmed in patients with substantial infarct cores subjected to endovascular therapy.

CONCLUSIONS

CTP-based measurements showed heightened sensitivity and accuracy in predicting MCI compared to clinical criteria and NCCT ASPECTS. This approach could offer utility in identifying high-risk patients, potentially enabling more comprehensive monitoring and expediting the management of life-threatening complications in severe ischemic stroke patients. A prospective study with data from more than one center would be useful to confirm these findings.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

NCCT: non-contrast computed tomography

CTA: computed tomography angiography

CTP: computed tomography perfusion

rCBF: relative cerebral blood flow

rCBV: relative cerebral blood volume

MTT: mean transient time

DWI: diffusion-weighted imaging

ADC: apparent diffusion coefficient

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TABLES

Table 1. Clinical characteristics of the included patients according to the development of malignant MCA infarction

	Total n=253	Non-malignant n=190 (75%)	Malignant n=63 (25%)	P-value
Female, n (%)	129 (51)	98 (51)	32 (50)	0.74
Age (years), median (IQR)	75 (62-81)	75 (62-81)	75 (64-81)	0.91
Premorbid mRS, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.22
Hypertension, n (%)	165 (65)	122 (64)	43 (68)	0.55
Dyslipidemia, n (%)	114 (45)	84 (44)	30 (47)	0.63
Diabetes mellitus, n (%)	53 (21)	42 (22)	11 (17)	0.43
Smoker, n (%)	41 (16)	31 (16)	10 (15)	0.93
Ischemic cardiopathy, n (%)	44 (17)	31 (16)	13 (20)	0.43
Atrial fibrillation, n (%)	74 (29)	56 (29)	18 (28)	0.91
Previous stroke, n (%)	23 (9)	17 (8)	6 (9)	0.89
Occlusion site				<0.001
M1, n (%)	132 (52)	105 (55)	27 (42)	
M2, n (%)	53 (21)	52 (27)	1 (1)	
ICA, n (%)	30 (11)	14 (7)	16 (25)	
Tandem, n (%)	38 (15)	19 (10)	19 (30)	
ASPECTS, median (IQR)	9 (7-10)	9 (1-10)	7 (6-8)	0.001
NIHSS at admission, median (IQR)	17 (12-21)	16 (10-20)	19 (17-22)	0.001
NIHSS at 24 hours, median (IQR)	11 (5-11)	7 (3-15)	21 (18-25)	<0.001
Treatment				<0.001
None, n (%)	24 (9)	16 (8)	8 (12)	
rtPA, n (%)	52 (20)	29 (15)	23 (36)	
MT, n (%)	73 (28)	53 (27)	20 (31)	
MT+rtPA, n (%)	104 (41)	92 (48)	12 (19)	
TICI	N=176	N=145	N=31	0.001
0, n (%)	20 (11)	12 (8)	8 (25)	
1, n (%)	4 (2)	4 (2)	0 (0)	
2a, n (%)	19 (10)	13 (6)	6 (19)	
2b, n (%)	56 (31)	45 (23)	11 (35)	
2c-3, n (%)	77 (43)	71 (37)	6 (19)	
Time-to-CTP in hours, median (IQR)	2.98 (1.75-4.78)	2.94 (1.61-4.76)	3.18 (1.88-5.46)	0.40
Basal glycemia (mg/dL), mean (SD)	122 (106-144)	118 (101-142)	127 (114-148)	0.008
Systolic blood pressure (mmHg), median (IQR)	127 (114-148)	140 (130-156)	142 (125-165)	0.40
Hemorrhagic transformation				0.001
None, n (%)	170 (67)	135 (71)	35 (50)	

HI1, n (%)	14 (5)	10 (5)	4 (6)	
HI2, n (%)	19 (7)	15 (7)	4 (6)	
PH1, n (%)	17 (6)	13 (6)	4 (6)	
PH2, n (%)	11 (4)	2 (1)	9 (14)	
SAH, n (%)	20 (7)	14 (7)	6 (9)	
Symptomatic hemorrhagic transformation, n%	10 (3)	2 (1)	8 (4)	<0.001
TOAST				0.80
LAA, n (%)	41 (16)	28 (14)	13 (20)	
Cardioembolism, n (%)	125 (49)	97 (51)	28 (44)	
Undetermined, n (%)				
Other, n (%)	70 (27)	52 (27)	18 (28)	
	15 (5)	11 (5)	4 (6)	
mRS at 90 days, median (IQR)	3 (1-4)	2 (1-4)	6 (4-6)	<0.001

IQR: interquartile range; mRS: modified Rankin scale; M1: M1 segment of the middle cerebral artery; ICA: internal carotid artery; M2: M2 segment of the middle cerebral artery; ASPECTS: Alberta Stroke Programme Early CT Score; NIHSS: National Institute of Health Stroke Scale; rtPA: recombinant tissue plasminogen activator; MT: mechanical thrombectomy; TICI: thrombolysis in cerebral infarction scale; CTP: computed tomography perfusion; mg/dL: milligrams per deciliter; mmHg: millimeters of mercury; SD: standard deviation; HI: hemorrhagic infarction; PH: parenchymal hematoma; SAH: subarachnoidal hemorrhage; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA: large-artery atherosclerosis.

FIGURES

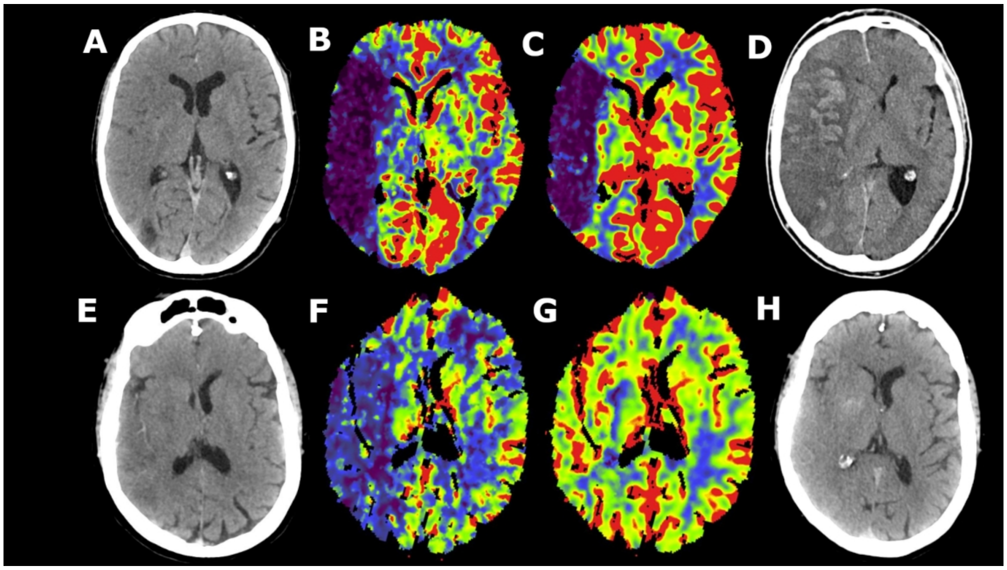
Figure 1. Non-contrast CT scan (A), rCBF (B), and rCBV (C) maps of a 63-year-old man with an acute stroke due to an occlusion of the M1 segment of the right middle cerebral artery. Complete recanalization was obtained with mechanical thrombectomy. CT performed 24 hours later (D) showed malignant cerebral edema with 12 mm midline shift. Non-contrast CT scan (E), rCBF (F), and rCBV (G) maps of a 60-year-old female with an acute stroke due to right MCA M1 occlusion and complete recanalization after mechanical thrombectomy. CT performed 24 hours later (H) showed mild edema without a midline shift. Note the difference in the perfusion maps, with a greater decrease in CBF and, especially, CBV in the first case, that developed malignant cerebral infarction.

Figure 2. Flow chart of the patients included in the study

Figure 3. Heatmap summarizing the predictive performance of ASPECTS and several perfusion-based metrics ordered by decreasing F1-scores. rCBF: relative cerebral blood flow; rCBV: relative cerebral blood volume.

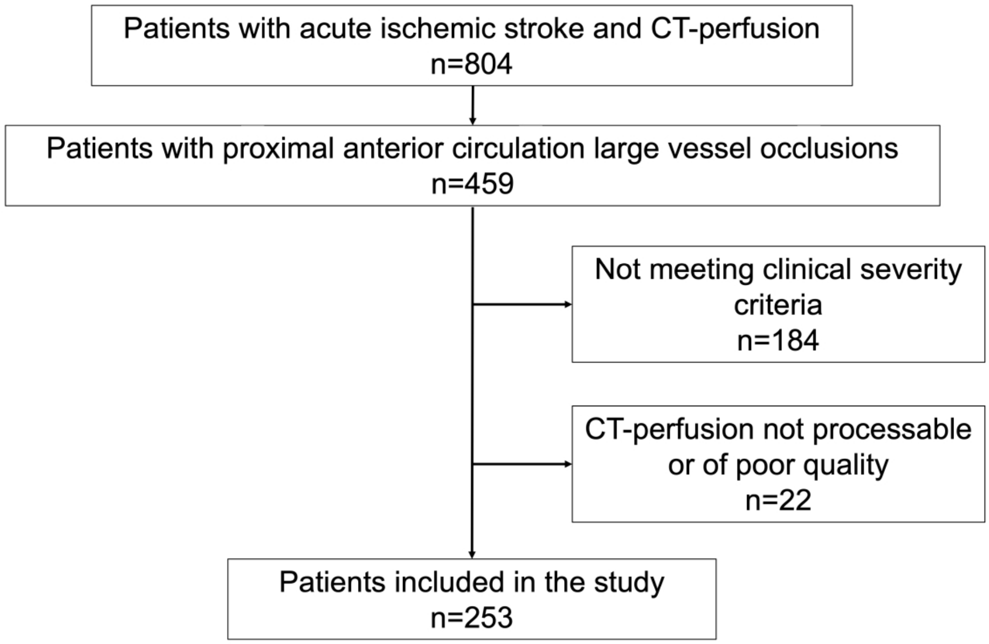
Figure 4. Diagram of the distribution of true positives, false negatives, false positives, and true negatives using ASPECTS cut-off values <6 and CTP rCBV 40% >34 mL. Considering the 25% prevalence of MCI in our study cohort, ASPECTS identified 8 true positives, with 17 false negatives and 5 false positives. The rCBF cut-off identified 16 true positives, with 9 false negatives and 8 false positives.

Figure 5. ROC curve of ASPECTS and CT-perfusion rCBV 40% in the whole cohort, patients who underwent mechanical thrombectomy and patients not treated with mechanical thrombectomy.



Non-contrast CT scan (A), rCBF (B), and rCBV (C) maps of a 63-year-old man with an acute stroke due to an occlusion of the M1 segment of the right middle cerebral artery. Complete recanalization was obtained with mechanical thrombectomy. CT performed 24 hours later (D) showed malignant cerebral edema with 12 mm midline shift. Non-contrast CT scan (E), rCBF (F), and rCBV (G) maps of a 60-year-old female with an acute stroke due to right MCA M1 occlusion and complete recanalization after mechanical thrombectomy. CT performed 24 hours later (H) showed mild edema without a midline shift. Note the difference in the perfusion maps, with a greater decrease in CBF and, especially, CBV in the first case, that developed malignant cerebral infarction.

413x232mm (118 x 118 DPI)



Flow chart of the patients included in the study

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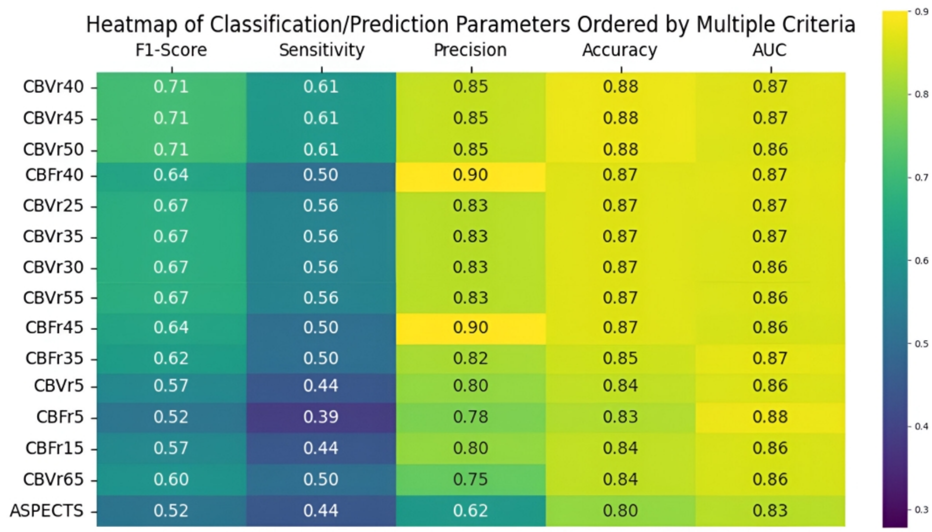


Heatmap summarizing the predictive performance of ASPECTS and several perfusion-based metrics ordered by decreasing F1-scores. rCBF: relative cerebral blood flow; rCBV: relative cerebral blood volume.

903x508mm (72 x 72 DPI)

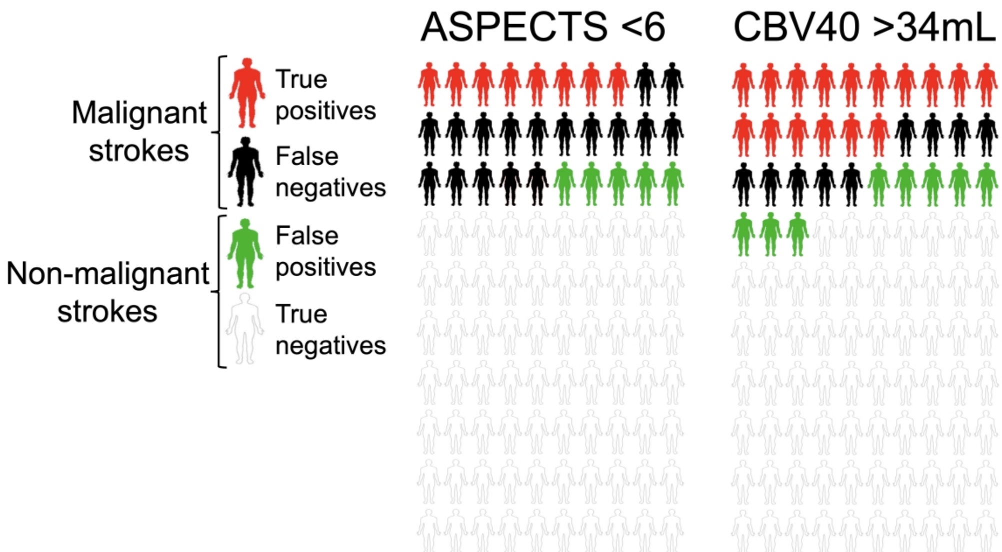
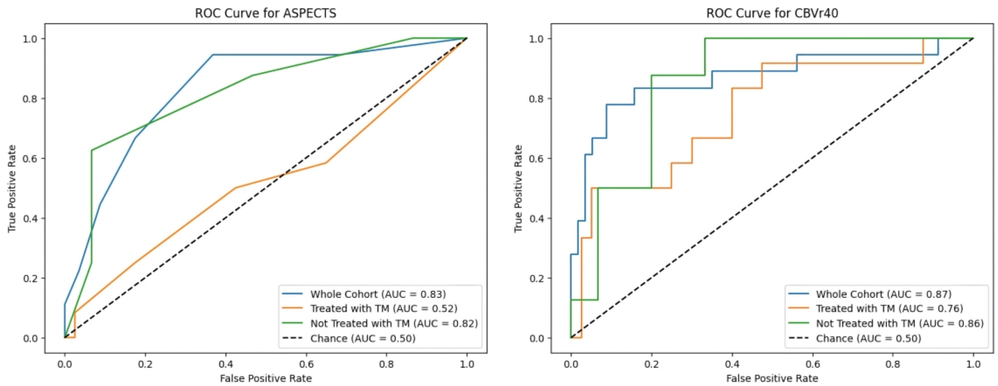


Diagram of the distribution of true positives, false negatives, false positives and true negatives using ASPECTS cut-off values <6 and CTP rCBV 40% >34 mL. Considering the 25% prevalence of MCI in our study cohort, ASPECTS identified 8 true positives, with 17 false negatives and 5 false positives. The rCBF cut-off identified 16 true positives, with 9 false negatives and 8 false positives.

721x399mm (144 x 144 DPI)



ROC curve of ASPECTS and CT-perfusion rCBV 40% in the whole cohort, patients who underwent mechanical thrombectomy and patients not treated with mechanical thrombectomy.

355x138mm (300 x 300 DPI)

Computed tomography perfusion as an early predictor of malignant cerebral infarction

Alejandro Rodríguez-Vázquez, MD;[1,2] Carlos Laredo, PhD;[2] Luis Reyes, MD PhD;[3] Guillem Dolz, MD;[4] Antonio Doncel-Moriano, MD;[1] Laura Llansó, MD;[1] Salvatore Rudilosso, MD PhD;[1,2] Laura Llull, MD PhD;[1,2,5] Arturo Renú, MD PhD;[1,2] Sergio Amaro, MD PhD;[1,2,5] Ramón Torné, MD PhD;[2,3,5] Xabier Urra, MD, PhD;[1,2,5] Ángel Chamorro, MD PhD.[1,2,5]

1. Department of Neurology, Hospital Clínic de Barcelona, Barcelona, Spain
2. Fundació de Recerca Clínic Barcelona - Institut d'Investigacions Biomèdiques ~~Agustí~~August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Spain
3. Department of Neurosurgery, Hospital Clínic de Barcelona, Barcelona, Spain
4. Department of Radiology, Hospital Clínic de Barcelona, Barcelona, Spain.
5. Faculty of Medicine, University of Barcelona, Barcelona, Spain.

Corresponding author: Xabier Urra, 170 Villarroel, 08036 Barcelona, Spain; Fax: +34932275783;

Phone: +34932275414; E-mail: xurra@clinic.cat.

Keywords: computed tomography perfusion, malignant cerebral infarction, brain edema, acute stroke.

ABSTRACT

Background

Malignant middle cerebral artery infarction (MCI) ~~necessitates~~needs rapid intervention. This study aimed to enhance the prediction of MCI using computed tomography perfusion (CTP) with varied quantitative benchmarks.

Methods

We retrospectively analyzed 253 patients from a single-center registry presenting with acute, severe, proximal large vessel occlusion studied with whole-brain CTP imaging at hospital arrival within the first 24 hours of symptoms-onset. MCI was defined by clinical and imaging criteria, including decreased level of consciousness, anisocoria, death due to cerebral edema, or need for decompressive craniectomy, together with midline shift ≥6 mm, or infarction of more than 50% of the MCA territory. The predictive accuracy of baseline ASPECTS and CTP quantifications for MCI was assessed by receiver operating characteristic (ROC) area under the curve (AUC) while F-score was calculated as an indicator of precision and sensitivity.

Results

Sixty-three out of 253 patients (25%) fulfilled MCI criteria and had worse clinical and imaging results than the non-MCI group. The capacity to predict MCI was lower for baseline ASPECTS (AUC 0.83, F-score 0.52, Youden's index 6), than with perfusion-based measures: relative cerebral blood volume threshold <40% (AUC 0.87, F-score 0.~~67~~71, Youden's index 34 ml) or relative cerebral blood flow threshold <35% (AUC 0.87, F-score 0.62, Youden's index 67 ml). CTP based on rCBV measurements identified twice as many MCI as baseline CT ASPECTS.

Discussion and conclusion

~~CTP-based quantifications provide better MCI prediction than non-contrast baseline CT ASPECTS~~ CTP-based quantifications may offer enhanced predictive capabilities for MCI compared to non-contrast baseline CT ASPECTS, potentially improving the monitoring of severe ischemic stroke patients at risk of life-threatening edema and its treatment.

INTRODUCTION

Ischemic stroke stands as the second leading cause of death worldwide and a significant contributor to disability.[1] Approximately 10% of ischemic strokes follow a 'malignant' course, primarily defined by extensive infarction within the middle cerebral artery (MCA) territory.[2] Such strokes rapidly progress to cerebral edema, leading to mass effects that may culminate in brain herniation and death.[3] Notably, younger patients lack cerebral atrophy, predisposing them to this severe outcome.[4]

Current medical interventions have yet to demonstrate efficacy in altering the natural progression of malignant infarctions.[5-9] To date, the only beneficial treatment is timely decompressive surgery, which has been shown to enhance survival, albeit often with residual moderate to severe disability.[10-14] Predictive models for malignant transformation traditionally rely on magnetic resonance imaging (MRI), which may not be universally available.[15] Computed tomography perfusion (CTP), while more accessible, has often been less precise than MRI for assessing ischemic damage.[16] Recent research, however, suggests that specific gray and white matter perfusion thresholds may enhance CTP's predictive accuracy.[17]

With new clinical trials expanding the use of mechanical thrombectomy in patients with low ASPECTS scores,[18-23] there is a growing need to identify individuals at high risk for malignant progression. This study evaluated the predictive value of acute CTP findings at hospital arrival for developing malignant cerebral infarction (MCI) in the following hours, compared with other potential clinical and radiological predictors of this severe complication.

METHODS

Patient selection

Data for this retrospective study were systematically extracted from our local stroke database, which prospectively compiles each patient's medical record. We assessed 804 patients considered for stroke reperfusion therapy from 2010 to 2017 and identified 253 patients at heightened risk for MCI, with the following inclusion criteria:

1- Proximal large vessel occlusion involving the carotid artery, M1 segment, or M2 segment (if the basal ganglia were affected) of the ~~middle cerebral artery~~MCA.
2- Acute hemispheric syndrome with severe symptoms (National Institute of Health Stroke Scale (NIHSS)~~NIHSS~~ > 15 for dominant hemisphere or NIHSS > 13 for non-dominant hemisphere) within 24 hours post-admission.
3- Admission multimodal CT protocol, including non-contrast CT (NCCT), CT angiography (CTA), and CTP.
4- Follow-up neuroimaging (CT or MRI) conducted within 72 hours of admission.
5- Clinical evaluations conducted 24-72 hours post-admission and at a 3-month follow-up.

Demographic, clinical, and blood test variables were collected for each patient, a~~s well as~~long with the time from symptom onset to neuroimaging, occlusion site, type of revascularization treatment, and the degree of final recanalization. The clinical severity at admission and in the first 24 hours was addressed using the NIHSS, and the functional outcome at three months was addressed using the modified Rankin scale (mRS). As an observational cohort study, this work adheres to the STROBE guidelines.[24]

Study outcomes - Definition of MCI

The principal outcome, MCI, was defined through a combination of clinical and neuroimaging criteria:[2,4,25]

1- Clinical indicators of intracranial hypertension, such as a decreased level of consciousness (score ≥1 in the corresponding item on NIHSS), anisocoria, death due to cerebral edema, or need for decompressive craniectomy.
2- Neuroimaging evidence indicating significant cerebral edema, exemplified by a midline shift ≥6 mm or an infarct encompassing over half of the MCA territory.

A diagnosis of malignant stroke required the presence of at least one clinical and one neuroimaging criterion. An example of MCI is shown in **Figure 1**.

Neuroimaging analysis

The imaging protocol included a baseline multimodal whole-brain CT scan (total acquisition time, 83 seconds), which included NCCT (140 kV, 127 mAs, FOV = 225 mm, matrix = 512 × 512, section thickness = 5 mm); CTA (120 kV, 663 mAs, FOV = 261 mm, matrix = 512 × 512, section thickness = 0.6 mm); and CTP (80 kV[peak], 250 mAs, 1.5-second rotation, FOV = 18 mm, matrix = 512 × 512, and forty-nine 2-mm-thickness slices). Patients were scanned using a Somatom Definition Flash 128-section dual-source multidetector scanner (Siemens), with a 98-mm z-coverage and 26 time points acquired each 1.5 seconds and 4 last time points each 5 seconds (total acquisition time, 59 seconds). Fifty milliliters of nonionic iodinated contrast were administered intravenously at 5 mL/s using a power injector, followed by a saline flush of 20 mL at an injection rate of 2 mL/s.

The ASPECTS was assessed on the baseline NCCT. CTP maps were calculated by the commercial software MIStar (Apollo Medical Imaging Technology) using a model-free singular-value decomposition algorithm with a delay and dispersion correction. The software automatically performs motion correction and selects an arterial input function from an unaffected artery (usually the anterior cerebral artery) and a venous output function from a large draining vein (the sagittal sinus). The software generates cerebral blood flow (CBF), cerebral blood volume (CBV), mean transient time (MTT), and delay time (DT) maps. Of note, the delay-corrected deconvolution method produces delay time maps rather than the more extensively used time-to-maximum maps[26]. A threshold of 3 seconds on the delay time maps was used to define the hypoperfusion[27], and ischemic core was defined within the hypoperfused area with a series of relative CBF (rCBF) and CBV (rCBV) thresholds as a percentage of the mean perfusion values from the entire unaffected, contralateral hemisphere[16]. Estimates of the ischemic area were made using all rCBF and rCBV thresholds from 0 to 100%.

The follow-up imaging was performed on the same NCCT or on MRI (1.5T Magneton Aera unit, Siemens). Midline shift was measured as the perpendicular distance between the septum pellucidum and a line drawn between the anterior and posterior attachments of the falx to the inner table of the skull.

~~Neuroimaging and clinical information for MCI evaluation were reviewed by 3 trained observers (ARV, LL and LR).~~Two trained observers reviewed neuroimaging and clinical information for MCI evaluation, and a third acted as a referee in case of disagreement. A single observer assessed CTP calculations semiautomatically.

Statistical analysis

The statistical procedures were executed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY), and Python 3.8.5 with the Numpy, Pandas, Scikit-learn, Matplotlib, and Seaborn libraries.

Categorical variables were assessed using the Chi-square (χ2) test when appropriate, with Fisher's exact test as an alternative for small sample sizes. Continuous variables following a normal distribution were presented using means and standard deviations (SD), whereas those not normally distributed, along with ordinal variables, were described using medians and interquartile ranges (IQR). Group comparisons for means and medians were conducted via the Student's t-test, ANOVA, or Mann-Whitney U test, contingent upon the data's distribution. The relationship between perfusion patterns and clinical outcomes was evaluated using univariate logistic regression. The train test split function was employed for splitting datasets into training and test sets, ensuring a robust validation of the models' performance. To assess the predictive value, accuracy, and classification performance of various clinical and radiological variables for malignant stroke, we employed logistic regression models to evaluate individual predictors, including NIHSS, ASPECTS, and all perfusion parameters. Each variable's performance was quantified by calculating the Area Under the Receiver Operating Characteristic (AUC) curve, which reflects the model's ability to distinguish between malignant and non-malignant stroke cases with a higher AUC indicating better model performance. Accuracy was reported as the proportion of correct predictions over the total cases. Sensitivity, or the true positive rate, was prioritized to emphasize the correct identification of malignant stroke due to its clinical significance in prognosis and treatment planning. In addition, precision was calculated to assess the proportion of actual malignant stroke cases among those predicted as such, thereby reflecting the model's ability to produce a low rate of false positives. The F1-score, a harmonic mean of precision and sensitivity, was also determined to evaluate the model's balance between identifying true malignant cases (sensitivity) and avoiding false positive diagnoses (precision). These metrics provided a comprehensive view of the model's performance, especially considering the imbalanced nature of the dataset, where malignant strokes were less prevalent than non-malignant strokes. The election of optimal single cutoff values was based on ~~the~~ Youden's J statistic, which maximizes the true positive rate (sensitivity) and minimizes the false positive rate. Significance was set at $P<0.05$ for all tests, and hypotheses were bilateral.

Data Availability:

Datasets produced and analysed during this study can be obtained from the corresponding author upon a reasonable request.

RESULTS

Out of 253 patients who satisfied the inclusion criteria (**Figure 2**), 63 individuals (25%) were classified as having MCI. The demographic and pre-stroke clinical characteristics—such as sex, age, and clinical history—were comparable between the MCI and non-MCI groups, as was the interval from symptom onset to initial imaging.

As shown in **Table 1**, patients with MCI exhibited a higher baseline glycemia, lower baseline ASPECTS scores, more carotid and tandem occlusions, and higher NIHSS scores at admission and after 24 hours. Reperfusion treatments, such as mechanical thrombectomy with or without intravenous alteplase, were more frequently administered in the non-MCI group, which also showed superior angiographic results. Hemorrhagic transformations occurred more often in the MCI group. At 3 months, the median mRS scores and mortality rates were higher in the MCI group.

Regarding the predictive capacity for MCI, baseline ASPECTS had a ROC AUC of 0.~~68~~83 and F1-score of 0.52 for a cut-off lower than 6, which is also the limit traditionally used when considering treatment with mechanical thrombectomy. However, several CTP parameters outperformed it

(Figure 3). Values based on cerebral blood volume performed best, with AUC of 0.887 and F1-scores of 0.71 for rCBV thresholds lower than 40%, with the best volume cut-off for CBV being 34 mL. Regarding cerebral blood flow, the most robust predictor was found to be a rCBF threshold of less than 35% for a 67 mL cut-off.

In our cohort of 253 patients, ASPECTS <6 identified 19 true positives for MCI compared to 38 matched by the 34 mL rCBV 40% threshold. False negatives were lower using CTP compared to ASPECTS (24 vs. 43), with a slight increase in false positives (20 vs. 12). A diagram of these statistical variables is shown in **Figure 4**. There were no significant differences between observers (Kappa coefficient for the definition of malignant infarction: 0.93, intraclass correlation coefficient for the quantitative assessment of midline shift: 0.99).

Given the asymmetry between the proportion of patients in each group (malignant and non-malignant) undergoing mechanical thrombectomy, a specific analysis was performed using ROC evaluating the ability of ASPECTS and the CTP rCBV 40% to differentiate between true and false positives according to the use of mechanical thrombectomy **(Figure 5)**. ASPECTS lost most of its predictive value in patients treated with thrombectomy (AUC of 0.82 in untreated patients, 0.52 in treated patients), while the decrease in predictive value was milder for rCBV 40% (AUC of 0.86 and 0.76 in untreated and treated patients, respectively).

DISCUSSION

In our cohort of patients with moderate to severe symptoms at first evaluation or during the first 24 hours after admission, CTP-based measurements outperformed those based only in NCCT ASPECTS for predicting malignant infarction. The pathogenesis of MCImalignant cerebral infarction is multifaceted. Severe presenting symptoms are well-recognized clinical harbingers of MCI.[2,4] While MRI is traditionally favored for its precision in quantifying infarct volume—especially volumes exceeding 145 mL on DWI—its predictive reliability hinges on the ADC thresholds applied.[15,27] MRI's sensitivity and specificity are heightened in evaluations conducted 24 hours post-symptom onset rather than in hyperacute assessments.[28] Although CT is less sensitive in the early phase, its greater accessibility and the augmentation of its predictive power through multimodal CT perfusion imaging are noteworthy.[29] Our investigation focused on multimodal CT scans executed upon admission, with a sub-6-hour window from symptom onset, aiming to swiftly pinpoint patients at elevated risk for MCI to expedite intervention. We purposely selected a cohort of patients at high risk of developing MCI, so the rate of malignant infarctions was 25%, higher than the 10% classically described in the general population.[2]

A key finding was that in patients with moderate to severe symptoms at first evaluation or during the first 24 hours after admissionIn patients with extensive symptoms, the optimal CTP thresholds for predicting malignant infarction were higher than the commonly used <30% threshold tied to DWI-MRI ischemic core definitions.3 Although DWI is traditionally used as the gold standard to define the extent of the ischemic lesion as an element related to the functional outcome,[30] the relevance of cerebral edema in the development of MCI—and potentially influencing these threshold discrepancies—cannot be understated.[32,33]

Compared to rCBF thresholds, rCBV showed slightly greater ability to predict MCI in our cohort. This may be because the volume drop is indicative of greater cerebral hypoperfusion, which could lead to greater development of cerebral edema and more ischemic tissue. Regardless of whether the measurement was based on in flow or volume, CTP-based models present greater sensitivity, precision, and accuracy than NCCT ASPECTS. Thus, considering the extreme clinical severity of MCI, it is especially important to use a tool that can identify the greatest number of patients at risk. In our cohort, CTP performed before any type of treatment identified twice as many patients who developed MCI compared to ASPECTS with half the number of false negatives and an ~~slight~~ increase in false positives.

In routine clinical practice, the greater predictive capacity of models based on cerebral perfusion compared to NCCT ASPECTS could be useful for optimizing the management circuits of patients with acute ischemic strokes. For example, using the information provided by CTP to identify patients at high risk of MCI could serve to carry out more strict surveillance protocols or early control neuroimaging that would not be performed under normal conditions.

The strength of this work lies in its simple design that is applicable to routine clinical practice, based on a proven and widely accepted imaging methodology. In this way, it is an easy element to apply regardless of the available resources and the clinical severity of the patient.

On the other hand, t~~T~~he study's retrospective design, despite the prospective nature of data collection, may introduce limitations. The fact that it is a single-center study is also a limitation, although the accessibility of the technique favors potential reproducibility. Our data predate the routine consideration of mechanical thrombectomy for extensive strokes, potentially skewing outcomes for patients presenting with ASPECTS under 6 due to the infrequency of intervention at that time. Considering the use of the ASPECTS as a tool to choose patients eligible for treatment, this bias, might have overestimated the predictive capacity of the ASPECTS as patients with large infarcts and large vessel occlusions that do not recanalize are at higher risk of MCI. With the increasing inclination towards reperfusion therapies for extensive ischemic lesions, our findings could prove instrumental in identifying patients at increased risk for malignant cerebral edema if confirmed in patients with substantial infarct cores subjected to endovascular therapy.

CONCLUSIONS

~~CTP-based measurements have greater sensitivity and accuracy in predicting MCI compared to clinical criteria and NCCT ASPECTS. This approach might be useful in identifying high-risk patients to apply more comprehensive monitoring and accelerate the management of life-threatening complications in patients with severe ischemic stroke.~~ CTP-based measurements showed heightened sensitivity and accuracy in predicting MCI compared to clinical criteria and NCCT ASPECTS. This approach could offer utility in identifying high-risk patients, potentially enabling more comprehensive monitoring and expediting the management of life-threatening complications in severe ischemic stroke patients. A prospective study with data from more than one center would be useful to confirm these findings.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

~~GM: gray matter~~

~~WM: white matter~~

NCCT: non-contrast computed tomography

CTA: computed tomography angiography

CTP: computed tomography perfusion

rCBF: relative cerebral blood flow

rCBV: relative cerebral blood volume

MTT: mean transient time

DWI: diffusion-weighted imaging

ADC: apparent diffusion coefficient

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TABLES

Table 1. Clinical characteristics of the included patients according to the development of malignant MCA infarction

	Total n=253	Non-malignant n=190 (75%)	Malignant n=63 (25%)	P-value
Female, n (%)	129 (51)	98 (51)	32 (50)	0.74
Age (years), median (IQR)	75 (62-81)	75 (62-81)	75 (64-81)	0.91
Premorbid mRS, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.22
Hypertension, n (%)	165 (65)	122 (64)	43 (68)	0.55
Dyslipidemia, n (%)	114 (45)	84 (44)	30 (47)	0.63
Diabetes mellitus, n (%)	53 (21)	42 (22)	11 (17)	0.43
Smoker, n (%)	41 (16)	31 (16)	10 (15)	0.93
Ischemic cardiopathy, n (%)	44 (17)	31 (16)	13 (20)	0.43
Atrial fibrillation, n (%)	74 (29)	56 (29)	18 (28)	0.91
Previous stroke, n (%)	23 (9)	17 (8)	6 (9)	0.89
Occlusion site				<0.001
M1, n (%)	132 (52)	105 (55)	27 (42)	
M2, n (%)	53 (21)	52 (27)	1 (1)	
ICA, n (%)	30 (11)	14 (7)	16 (25)	
Tandem, n (%)	38 (15)	19 (10)	19 (30)	
ASPECTS, median (IQR)	9 (7-10)	9 (1-10)	7 (6-8)	0.001
NIHSS at admission, median (IQR)	17 (12-21)	16 (10-20)	19 (17-22)	0.001
NIHSS at 24 hours, median (IQR)	11 (5-11)	7 (3-15)	21 (18-25)	<0.001
Treatment				<0.001
None, n (%)	24 (9)	16 (8)	8 (12)	
rtPA, n (%)	52 (20)	29 (15)	23 (36)	
MT, n (%)	73 (28)	53 (27)	20 (31)	
MT+rtPA, n (%)	104 (41)	92 (48)	12 (19)	
TICI	N=176	N=145	N=31	0.001
0, n (%)	20 (11)	12 (8)	8 (25)	
1, n (%)	4 (2)	4 (2)	0 (0)	
2a, n (%)	19 (10)	13 (6)	6 (19)	
2b, n (%)	56 (31)	45 (23)	11 (35)	
2c-3, n (%)	77 (43)	71 (37)	6 (19)	
Time-to-CTP in hours, median (IQR)	2.98 (1.75-4.78)	2.94 (1.61-4.76)	3.18 (1.88-5.46)	0.40
Basal glycemia (mg/dL), mean (SD)	122 (106-144)	118 (101-142)	127 (114-148)	0.008
Systolic blood pressure (mmHg), median (IQR)	127 (114-148)	140 (130-156)	142 (125-165)	0.40
Hemorrhagic transformation				0.001
None, n (%)	170 (67)	135 (71)	35 (50)	

HI1, n (%)	14 (5)	10 (5)	4 (6)	
HI2, n (%)	19 (7)	15 (7)	4 (6)	
PH1, n (%)	17 (6)	13 (6)	4 (6)	
PH2, n (%)	11 (4)	2 (1)	9 (14)	
SAH, n (%)	20 (7)	14 (7)	6 (9)	
Symptomatic hemorrhagic transformation, n%	10 (3)	2 (1)	8 (4)	<0.001
TOAST				0.80
LAA, n (%)	41 (16)	28 (14)	13 (20)	
Cardioembolism, n (%)	125 (49)	97 (51)	28 (44)	
Undetermined, n (%)				
Other, n (%)	70 (27)	52 (27)	18 (28)	
	15 (5)	11 (5)	4 (6)	
mRS at 90 days, median (IQR)	3 (1-4)	2 (1-4)	6 (4-6)	<0.001

IQR: interquartile range; mRS: modified Rankin scale; M1: M1 segment of the middle cerebral artery; ICA: internal carotid artery; M2: M2 segment of the middle cerebral artery; ASPECTS: Alberta Stroke Programme Early CT Score; NIHSS: National Institute of Health Stroke Scale; rtPA: recombinant tissue plasminogen activator; MT: mechanical thrombectomy; TICI: thrombolysis in cerebral infarction scale; CTP: computed tomography perfusion; mg/dL: milligrams per deciliter; mmHg: millimeters of mercury; SD: standard deviation; HI: hemorrhagic infarction; PH: parenchymal hematoma; SAH: subarachnoidal hemorrhage; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA: large-artery atherosclerosis.

FIGURES

Figure 1. Non-contrast CT scan (A), rCBF (B), and rCBV (C) maps of a 63-year-old man with an acute stroke due to an occlusion of the M1 segment of the right middle cerebral artery. Complete recanalization was obtained with mechanical thrombectomy. CT performed 24 hours later (D) showed malignant cerebral edema with 12 mm midline shift. Non-contrast CT scan (E), rCBF (F) ~~and rCBV (G) maps of a 60-~~, and rCBV (G) maps of a 60-year-old female with an acute stroke due to right MCA M1 occlusion and complete recanalization after mechanical thrombectomy. CT performed 24 hours later (H) showed mild edema without a midline shift. Note the difference in the perfusion maps, with a greater decrease in CBF and, especially, CBV in the first case, that developed malignant cerebral infarction.

Figure 2. Flow chart of the patients included in the study

Figure 3. Heatmap summarizing the predictive performance of ASPECTS and several perfusion-based metrics ordered by decreasing F1-scores. rCBF: relative cerebral blood flow; rCBV: relative cerebral blood volume.~~; GM: grey matter; WM: white matter.~~

Figure 4. Diagram of the distribution of true positives, false negatives, false positives, and true negatives using ASPECTS cut-off values <6 and CTP rCBV 40% >34 mL. Considering the 25% prevalence of MCI in our study cohort, ASPECTS identified 8 true positives, with 17 false negatives and 5 false positives. The rCBF cut-off identified 16 true positives, with 9 false negatives and 8 false positives.

Figure 5. ROC curve of ASPECTS and CT-perfusion rCBV 40% in the whole cohort, patients who underwent mechanical thrombectomy and patients not treated with mechanical thrombectomy.