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QUALITATIVE VERSUS AUTOMATIC EVALUATION OF CT PERFUSION PARAMETERS IN ACUTE POSTERIOR CIRCULATION ISCHEMIC STROKE

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ABSTRACT

AIM

To examine and compare the diagnostic performance in the detection of acute posterior circulation strokes between qualitative evaluation of software-generated colour maps and automatic assessment of CT perfusion (CTP) parameters by RAPID.

METHODS AND MATERIALS

Imaging data were retrospectively collected from a prospective database of consecutive patients undergone to multimodal CT scan dataset (GE “Lightspeed” a 64 slices) including CTP performed on admission (<24h after symptom onset) between January 2016 and December 2018. Follow-up imaging consisted in non-contrast CT (NCCT). If clinically indicated, MRI (Philips Intera 3.0 T or Philips Achieva Ingenia 1.5T) was performed either soon after the CTP at the admission or later as follow-up control including DWI and FLAIR sequences. The Posterior circulation - Acute Stroke Prognosis Early CT Score (pc-ASPECT score) was used for quantifying the extent of ischaemic areas on initial NCCT and color-coded maps generated by CTP4 software (cerebral blood flow, CBF; cerebral blood volume, CBV; mean transit time, MTT). Final pc-ASPECTS was calculated on follow-up NCCT and/or on MRI if performed. Afterwards, CTP data were also processed by RAPID software (iSchemia View) obtaining color-coded maps, including time-to maximum (Tmax), and automatic quantitative mismatch maps.

RESULTS

A total of 50 patients met the inclusion criteria. 6 out of the 50 patients did not show ischemic core at follow-up imaging neither alteration of at least two perfusion parameters in the same location and were grouped as negative controls. All patients underwent to follow-up NCCT and 28 of them also underwent DWI-MRI. Out of the 28 patients undergone MRI, 14 patients (50%) underwent DWI study within 8 hours after multimodal CT study at admission.

The sensitivity (SE) of qualitative evaluation of color-coded MTT-CTP4D map and color-coded Tmax-RAPID map resulted significantly higher than the other ones (MTT: 88.6%, $p<0.05$; Tmax: 90.9%, $p<0.05$) with comparable diagnostic accuracy (ACC) (88%> 84%, $p>0.05$). NCCT at baseline and CBF provided by RAPID quantitative perfusion mismatch maps had the lowest SE (29.6% and 6.8% $p<0.05$, respectively) and ACC (38% and 18% $p<0.05$, respectively).

CBF assessment provided by quantitative RAPID perfusion mismatch maps showed significant lowest SE (6.8%) in comparison to qualitative evaluations of both color-coded CBF-CTP4D and CBF-RAPID maps (81.8% and 61.4% respectively); no significant SE difference was found between qualitative evaluations of color-coded CBF-CTP4D and CBF-RAPID maps (81.8% > 61.4%, $p>0.05$).Qualitative evaluation of color-coded Tmax -RAPID maps showed significant higher SE and ACC than quantitative assessment of Tmax automatically provided by RAPID perfusion mismatch maps (90.9%>65.9% and 88%>70%, respectively).

No significant differences were found between the pc-ASPECT scores assessed on color-coded MTT and Tmax maps neither between the scores assessed on color-coded CBV-CTP4D and CBF-RAPID maps.

CONCLUSION

Independently to the software employed, qualitative analysis of color-coded maps resulted more sensitive in the detection of ischemic changes than automatic quantitative analysis. The most sensitive perfusion parameters were MTT and Tmax. RAPID software generated mismatch maps overlooked and underestimated the extent of the ischemic core in the major part of the patients as compared with the qualitative analysis. The limits of identification of the lesions by automatic quantitative mismatch maps mainly lied in the thalamus and brainstem. Visual assessment of CTP pc-ASPECTS on color-coded perfusion maps revealed equivalence of both mismatch models (MTT-CBV and Tmax-CBF) commonly applied in acute setting with implications for treatment decision-making.

1. INTRODUCTION

1.1 Acute ischemic stroke of posterior circulation

A posterior circulation (PC) stroke is classically defined by infarction occurring within the vascular territory supplied by the vertebrobasilar (VB) arterial system - the vertebral arteries in the neck, the intracranial vertebral, basilar, and posterior cerebral arteries, and their branches (Figure 1) [1,2]. Brain structures supplied by the VB arterial system are the brainstem, cerebellum, midbrain, thalamus, and areas of temporal and occipital cortex [2].

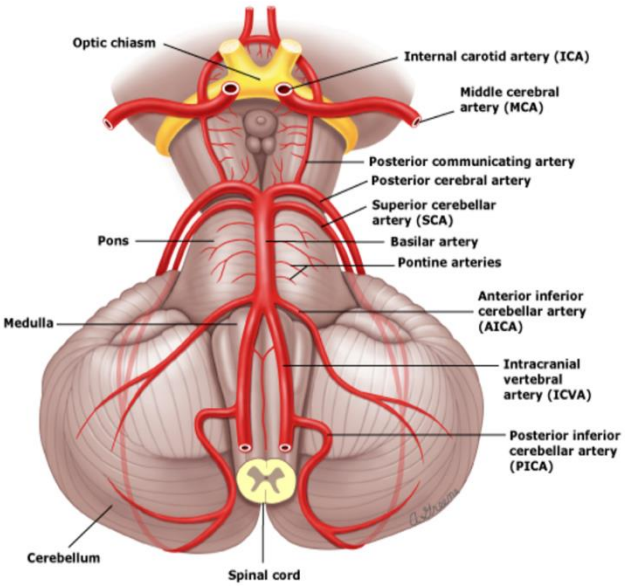

Figure 1

The posterior circulation is supplied by the vertebral arteries that combine to form the basilar artery which then divides into the posterior cerebral arteries. From these main vessels, many smaller vessels supply the posterior structures of the brain, including posterior inferior cerebellar artery, anterior inferior cerebellar artery, pontine branches superior cerebellar artery.

PC stroke accounts for 20-25% of ischemic strokes and is related to stenosis, in situ thrombosis, or embolic occlusion [2,3-7]. Ischemic stroke occurs when a region of cerebral blood flow (CBF) is suddenly limited. This may be due to vessel occlusion or by relatively low flow. The rate of neuronal death varies with blood flow, variability in individual anatomy and collateralization, and inherent

cerebral capacities (i.e., some cerebral regions are more resistant than others). CBF rates of less than 20 mL/100 g/min may produce infarction depending on these individual differences plus the duration of oligemia, with lower CBF rates (< 10 mL/100 g/min) requiring less time to produce irreversible injury. Rapid restoration of blood flow is the most effective means of preserving brain tissue [8].

The most common aetiologies of PC stroke are atherosclerosis, cardioembolism, and cervical artery dissections although other conditions (i.e., subclavian steal syndrome, giant cell arteritis, vertebrobasilar dolichoectasia, and Fabry disease) can be also involved [1].

Classical symptoms of PC stroke include vertigo, imbalance, unilateral or bilateral limb weakness, dysarthria, diplopia, headache, nausea, and vomiting. However, patients may also show signs and symptoms of multifocal PC strokes. Moreover, the PC is rich in potential collateral support and clinical manifestations of VB ischemia may be highly variable [1].Clinical findings include unilateral or bilateral limb weakness, gait ataxia, limb ataxia, dysarthria, and nystagmus. Infarcts involving the proximal PC territory usually cause dysphagia due to pharyngeal weakness, nausea, vomiting, and Horner's syndrome. Infarcts involving the middle territory are often associated with limb weakness, horizontal or vertical gaze palsy, and nuclear facial palsy. More distal territory infarctions are commonly associated with sensory loss, lethargy, and visual field defects. Patients typically have more than one finding and rarely have an isolated symptom or sign of PC ischemia. The severity of clinical presentation is related to the site of occlusion; the most devastating location is the midbasilar occlusion that induces a bilateral pontine ischemia [9].

Due to a wide range of clinical features, the diagnosis of PC stroke based on clinical symptoms remains challenging [4,5]. Indeed, clinical signs and symptoms of anterior and posterior ischemic stroke may overlap, causing a delay in making the correct diagnosis [3]. In the PC, relatively small infarcts can account for profound neurological disorders due to the compact arrangement of afferent and efferent fiber pathways as well as regions with survival functions and cranial nerve nuclei in the brainstem [3]. Delayed or incorrect diagnosis may have devastating consequences, including

potentially preventable death or severe disability, if acute treatment or secondary prevention is delayed [2,5].

Acute treatment options for PC stroke include intravenous recombinant tissue plasminogen activator, intra-arterial fibrinolysis, and endovascular thrombectomy [1]. The management of acute ischemic stroke is primarily governed by time from last known moment of good health and comorbidity. Within the therapeutic treatment window, stroke severity score based on the National Institutes of Health Stroke Scale (NIHSS) plays an important role. The NIHSS is the most used scoring system for quantification of neurologic deficits after acute stroke and it is an indispensable tool for the determination of acute stroke prognosis and decision making [10,11]. The time window for treatment for basilar occlusion may be longer than for other stroke types, and although treatment within 4.5 hours is desirable, it may be reasonable to consider treatment (intravenous or endovascular) up to 24 hours from onset [2].

1.2 Imaging in acute setting

Brain imaging plays a key-role in the evaluation of patients with suspected ischemic stroke allowing to reach a confident diagnosis of infratentorial infarction [5,12].

Brain computed tomography (CT) is typically performed as the initial imaging modality for patients presenting with acute stroke symptoms. Unfortunately, CT provides suboptimal visualization of the posterior fossa structures due to obscuration by artifacts produced by the bony structures of the cranial base and early ischemic changes may not be visible (Figure 2a) [1]. In contrast, magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is considered the diagnostic gold standard for the detection of ischemic lesions in the PC territories (Figure 2b) [4,5].

However, in many centres CT is more readily accessible in the acute phase and less time consuming than MRI and could be helpful if MRI is contraindicated or unavailable [1,4,5].

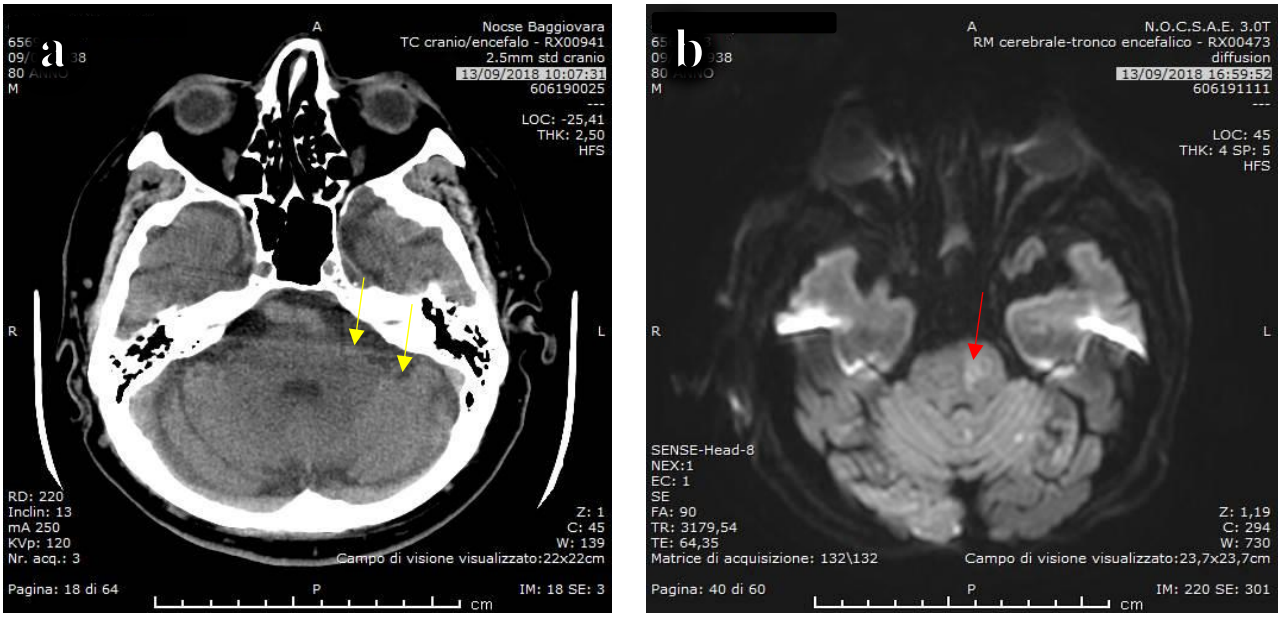

Figure 2

CT (a) and DWI-MRI (b) of a 80-year old male patient showing beam-hardening artefacts (yellow arrow) which hide an ischemic pontine lesion visible on DWI image (red arrow); DWI also reveals other smaller lesions in the left cerebellar hemisphere, vermis an right occipital cortex appearing hyperintense.

1.2.1 CT Perfusion

In patients with acute stroke undergoing emergency evaluation, dynamic CT perfusion (CTP) has been proposed as a particularly useful technique after unenhanced brain CT (which rules out intracranial haemorrhage) on account of its ease of use, reproducibility of quantitative measurements, ready availability, limited cost and tolerability [13-15]. CTP derives information on brain haemodynamic by analysing the first passage through the cerebral vessels of an intravenous contrast bolus. Because there is a direct linear relation between the concentration of contrast material and density, passage of contrast bolus results in an increase in density of the areas being examined that is proportional to the amount of contrast material present in the blood vessels. The blood-brain barrier prevents the contrast material from spreading into the interstitium, so that under normal conditions the increase in density is only transient, occurring during the first intravascular passage of the bolus.

CPT is based on the physical-mathematical “tracer kinetic model” , which assumes that the contrast bolus is instantaneous, is introduced into a single vessel, passes through a capillary network, remains totally intravascular and flows out through a single venous conduit [16].

CTP can be performed rapidly on any spiral CT scanner, and perfusion maps are readily generated by a workstation running dedicated software [15]. According to this, CTP has gained widespread application owing to its excellent accessibility, proved higher sensitivity than non-contrast CT (NCCT) alone and accuracy in detecting acute ischemic changes also in PC [3,5,12,17]. The PCT can generate prompt qualitative and quantitative parameters concerning cerebral perfusion; such parameters allow a delineation between normal tissue, ischaemic but not irreversibly injured tissue (“penumbra”) and the infarcted core [5,12]. A mismatch between the irreversibly damaged infarct core and the extent of hypoperfused tissue at risk for infarction is an attractive paradigm with which to select ischemic stroke patients for reperfusion therapies [18].

The physiological data derived from PCT is typically displayed in color-coded perfusion maps provided by dedicated software, including CBF, cerebral blood volume (CBV), mean transit time (MTT) and its derivatives, the time-to-peak (TTP) and time-to maximum (Tmax) (Figure 3) [12,19]. These are commonly derived from CTP source data by using deconvolution analysis [20]. CBV is measured in units of millilitres of blood per 100 g of brain and is defined as the volume of flowing blood for a given volume of brain. MTT is measured in seconds and defined as the average amount of time it takes blood to transit through the given volume of brain [20]. In the setting of acute infarction, areas of irreversibly infarcted tissue show matched areas of decreased CBF and CBV with increased MTT. This pattern suggests neuronal death with irreversible loss of function or core infarct. In several studies correlating CTP with DWI, severe decreases in CBV are particularly sensitive and specific for defining the extent of unsalvageable core [12,20,21]. While the infarcted core typically corresponds to a uniform decrease in CBF and CBV, the penumbra shows a reduction of the CBF value with a preserved or even increased CBV due to the vasodilation of the precapillary arteries and

venous obstruction [12,19]. Such areas can also be characterized by prolonged MTT extending beyond areas of core infarct and have been called CBV/MTT mismatch (Figure 3) [20].

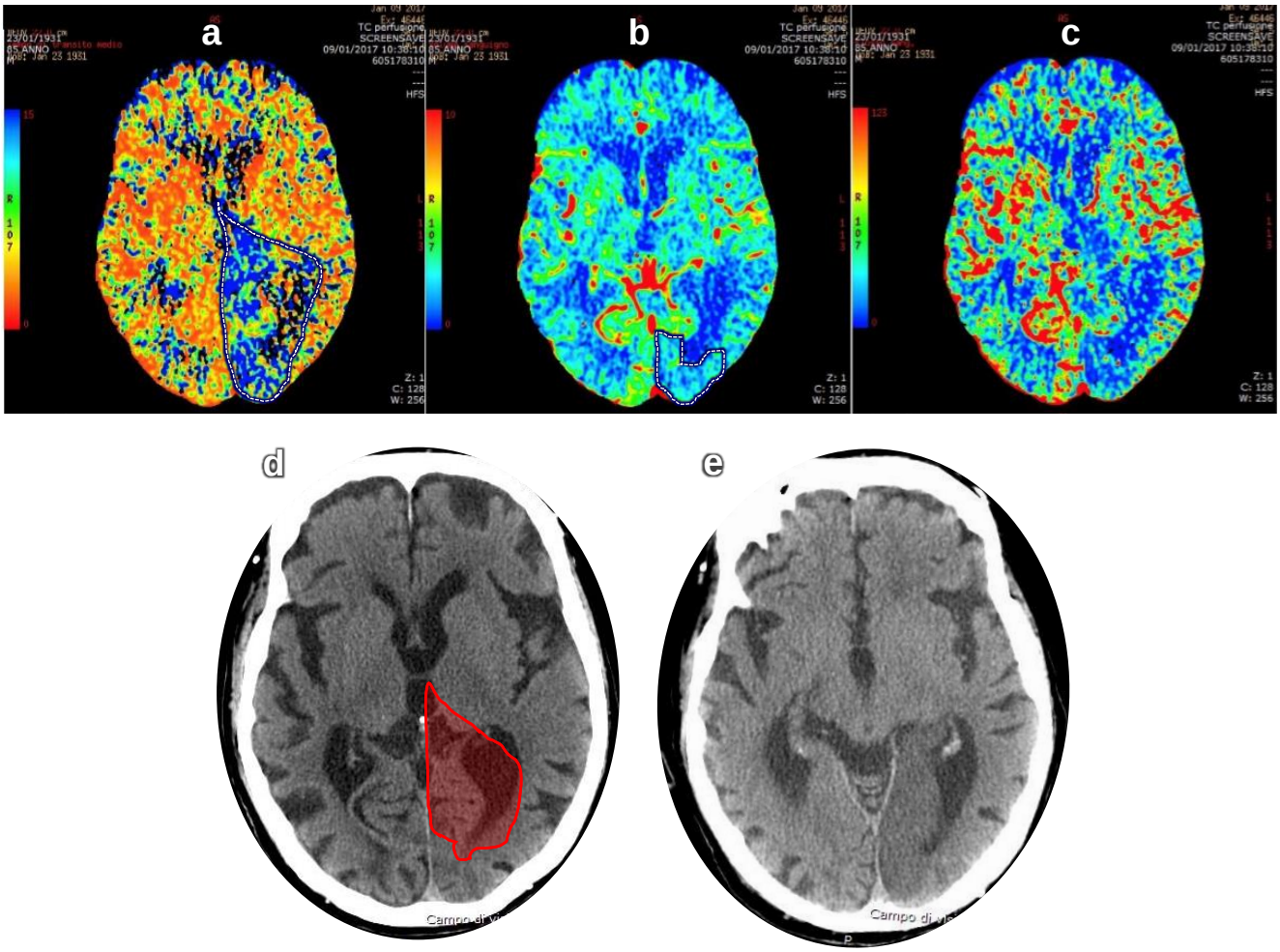

Figure 3

CTP a) MTT map, b) CBV map, c) CBF map; d) initial CT; e) follow-up CT; color-coded perfusion maps show an area of increased MTT (a - white dotted line) related to hypoperfusion associated to a smaller hypodense area on initial CT (d) characterized by reduction of CBV (b - white dotted line) representing ischemic core; the mismatch MTT-CBV indicates the presence of ischemic penumbra but follow-up CT reveals a more extensive hypodensity indicating that the tissue at risk (d – red coloured) have progressed to necrosis.

Recent evidence has emerged that relative cerebral blood flow (rCBF) performs better than other parameters, including CBV, in predicting the infarct core and that Tmax more accurately measures the penumbra in patients with acute ischemic stroke: CBF/Tmax mismatch [18,19,23].

Visual inspection of CTP color-coded maps can be an effective way of identifying areas of core infarct and penumbra and may be enough to guide decisions on intervention. Visual inspection has the advantage of speed and simplicity of use; however, this qualitative technique is dependent on user interpretation [20]. Furthermore, acute ischemic changes are often subtle and there is a great interobserver and intraobserver variability [5]. The strengths of perfusion imaging may be affected by variability in postprocessing, broad array of imaging and computational approaches, selection of parametric maps, expertise requisite and the generally qualitative nature of such approaches [23].

1.2.2 Alberta Stroke Program Early CT Score (ASPECTS)

The Alberta Stroke Program Early CT Score (ASPECTS) methodology - a semiquantitative method of visual assessment - has been recently applied to CTP parametric maps in an effort to impart standardization and mitigate subjective elements of perfusion analysis [23]. ASPECTS is a technique originally conceived for use in the setting of acute middle cerebral artery (MCA) stroke syndrome to grade the NCCT appearance of MCA territory regions on a 10-point grading system [20]. The score adapted to PC (pc-ASPECTS) allots 10 points for ischaemic changes assessed by visual inspection (Figure 4) [23,24]. Two points are subtracted in the cases of ischaemic change in any part of pons and midbrain, one point for either side of the cerebellum, one for either side of the thalamus and one for either side of the posterior cerebral artery supplied territory [4, 23-25]. A pc-ASPECTS of 10 indicates absence of ischaemic changes in the posterior circulation while a pc-ASPECTS of 0 indicates presence of ischaemic changes in all pc-ASPECTS [26]. While showing improvements compared with NCCT-ASPECTS in prior reports, the analysis remains fundamentally subjective and again lacks in its ability to subclassify tissues within ASPECTS regions [23].

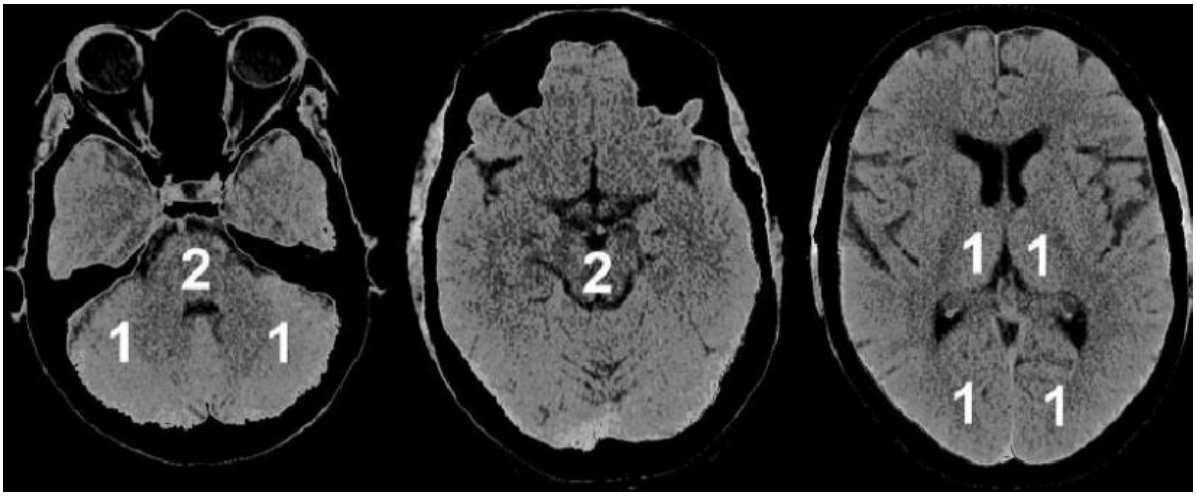

Figure 4

The posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS). From 10 points, 1 or 2 points each (as indicated) are subtracted for early ischemic changes (NCCT): left or right thalamus, cerebellum or posterior cerebral artery territory, respectively (1 point); any part of midbrain or pons (2 points). Pc-ASPECTS = 10 indicates a normal scan, pc-ASPECTS = 0 indicates early ischemic changes in all above territories.

1.2.3 Quantitative CTP

Beside qualitative evaluation it is also possible to calculate quantitative CTP parameters. These have been shown to be effective in demonstrating acute ischemia, distinguishing salvageable from unsalvageable tissue, and predicting therapeutic outcome, yet protocols and guidelines for quantitative thresholds vary [27-30].

Differences in CTP hardware and software can affect quantified metrics and clearly defined thresholds for guiding therapy have yet to be standardized [27-30]. Some studies suggest the use of CBF thresholds for defining areas of infarct, specifically CBF < 25 mL/100 g/min. In an analysis of 130 patients with acute stroke, Wintermark et al. suggested using absolute CBV< 2 mL/100 g to define core infarct, and relative MTT increase > 145% to define penumbra [19,28]. Prior studies have shown that ischemic core presents >70% reduction in CBF (rCBF<0.3) in comparison to the mean CBF of normally perfused brain parenchyma while a Tmax delay of >6 s is a good predictor of critically hypoperfused tissue that is destined to infarction in the absence of timely reperfusion

[18,23,31-36]. However, specific thresholds are also specific to the perfusion software platform being used and may not be automatically transferable to other vendors, scanners, and even software versions. Kudo et al. reported disparate results and variability in CTP imaging maps among competing software platforms even when using identical source data, presumably due to differences in tracer-delay sensitivity [37]. Thus, expert consensus has emphasized the need for standardization in the acquisition, processing, and analysis of perfusion imaging [23]. At this time, much work remains to standardize quantitative methods of CTP interpretation, which, in the future, may be addressed by a proposed consortium for acute stroke imaging [28].

In this context, the recently introduced use of a fast, vendor- and operator-independent computational tool using fully automated lesion segmentation and pixel-wise parametric thresholding for semi-quantitation (RApid processing of PerfusIon and Diffusion [RAPID]) seems to overcome the limitations of qualitative approaches to CTP imaging in acute stroke [23,38]. RAPID software (IschemaView, Menlo Park, CA) is an automated tool that analyses perfusion maps and demonstrates the ischemic core and penumbra within minutes (Figures 5,6) [40]. In addition to having the broadest Food and Drug Administration (FDA) clearance of any cerebrovascular imaging software, RAPID is the only platform that is clinically validated in more than 10 major trials — including use for patient selection in landmark stroke studies such as SWIFT PRIME, EXTEND IA, and most recently, EXTEND. The RAPID platform was also the exclusive imaging system used for patient selection for two landmark stroke trials published in The New England Journal of Medicine, DAWN and DEFUSE 3, that successfully treated patients up to twenty-four hours after onset.

This technological advance is reported to have the potential to improve the standardization and reproducibility of interpretation of advanced imaging [38].

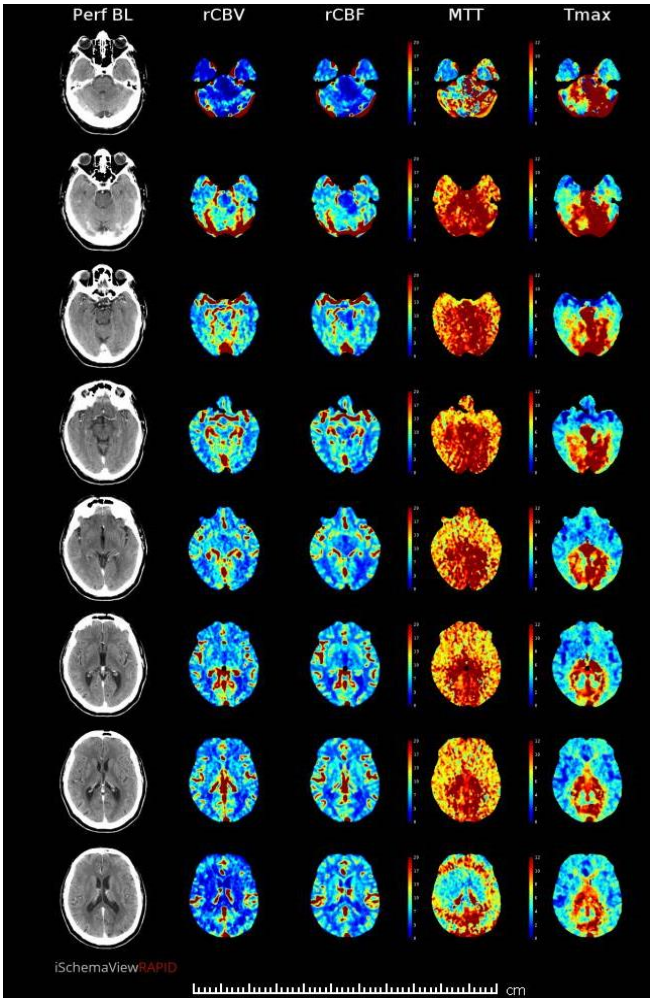

Figure 5

RAPID automatic color-coded perfusion maps (rCBV, rCBF, MTT, Tmax) operator-independently obtained in few minutes.

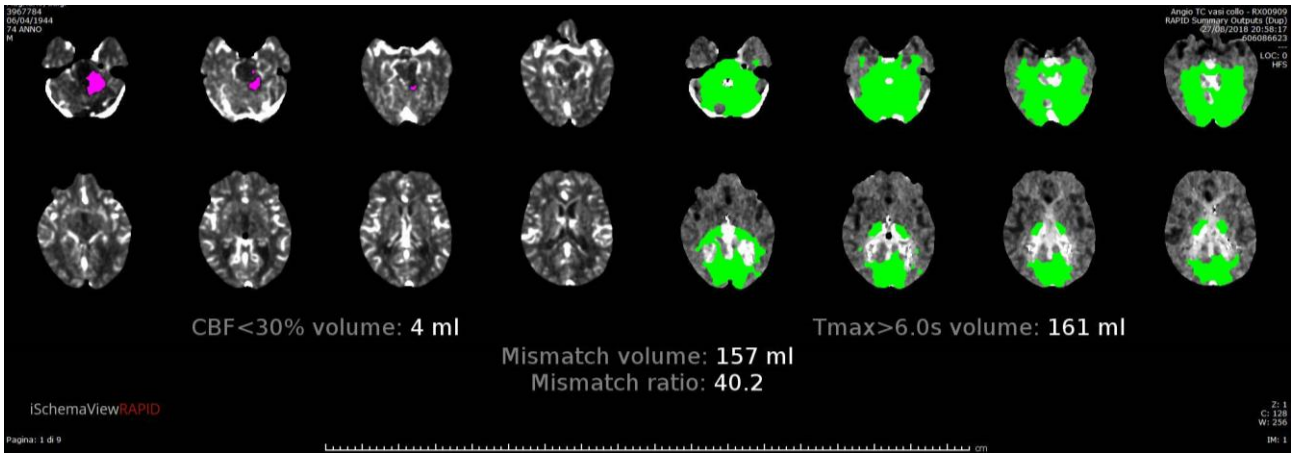

Figure 6

RAPID automatic quantitative mismatch map: the map shows in pink the ischemic core and in green the area of hypoperfusion; quantitative measures (reduced CBF, increased Tmax, mismatch volume and ratio) are also displayed.

1.3 Aim of the study

Whilst there has been extensive research concerning the diagnostic and prognostic value of CTP in the anterior circulation, the diagnostic value of CTP in the posterior circulation has been little investigated with few evidences of its reliability and accuracy; moreover, the diagnostic effects of RAPID introduction in the evaluation of infratentorial ischemic changes have not yet been clarified [3,4,26,41,42].

To the best of our knowledge, these are the first reported instances of PC stroke patient selection using RAPID from Italy. The aim of this study was to examine and compare the diagnostic performance [sensitivity (SE), specificity (SP), and accuracy (ACC)] in the detection of acute posterior circulation strokes between qualitative evaluation of software-generated colour maps (CBV, CBF, MTT and Tmax) and automatic assessment of CTP data by RAPID.

2. METHODS AND MATERIALS

2.1 Study population and patient selection

According to the approval of the institutional review board, imaging data were retrospectively collected from a prospective database of consecutive patients admitted to the stroke unit of our hospital between January 2016 and December 2018. Written informed consent was waived for this study. All patients were initially evaluated by vascular neurology in the emergency setting with initiation of an institutional stroke protocol facilitating expedited triage, imaging, interpretation and treatment when appropriate. Patients were enrolled regardless of therapy. The inclusion criteria for this study were (1) suspected acute posterior circulation ischemic stroke as defined in the Oxfordshire classification [43]; (2) multimodal CT scan dataset including NCCT, supra-aortic CT angiography (CTA) and CTP performed on admission; (3) CT performed <24h after symptom onset. Exclusion criteria were (1) nondiagnostic image quality, (2) evidence of another cause of neurological deficits (prior stroke with residual deficit, intracranial haemorrhage, tumour etc.), (3)incomplete coverage by the CTP slab of all posterior circulation ASPECTS (pc-ASPECTS) regions, and (4) missing follow-up CT or MRI.

Out of all patients who underwent multimodal CT due to suspected acute stroke, were selected control patients who fulfilled the same inclusion and exclusion criteria as our case cohort but did not show an acute posterior circulation ischemia on follow-up CT/MRI scan neither changes in at least two perfusion parameters in the same location.

2.2 Imaging protocol

Patients underwent an institutional stroke imaging protocol including NCCT, CTA and CTP at admission. CT protocol was conducted on a 40-mm, 64-detector row clinical system (Lightspeed VCT, GE Healthcare, Milwaukee, Wisconsin). NCCT helical scans were performed from the skull

base to the vertex (120 kV, 100-350 auto-mA, 5 mm section thickness). CTAs were conducted from the aortic arch to the top of frontal sinus (120 kV; 200-350 auto-mA; section thickness/interval 0.625/0.375 mm; scan start 6 s after bolus tracking at the level of the ascending aorta) after intravenous administration of 60-70 mL iodinated contrast medium injected at 4 mL/s and followed by 50 mL saline flush.

CTP scans (80 kV, 100 mA and 1 s rotation time) consisted of a continuous 50 s acquisition started 7 s after administration of 50 mL of iodinated contrast medium injected into an antecubital vein at 4 mL/s and followed by 50 mL saline flush; 776 images were reconstructed from each of the eight 5-mm-thick slice locations. CTP coverage was lowered to cover the cerebellum to the occipital lobes, including all three levels of the pc-ASPECTS.

Follow-up imaging consisted in NCCT. If clinically indicated, MRI was performed either soon after the CTP at the admission or later as follow-up control. MRI exams were achieved using two scanners (Philips Intera 3.0T and Philips Achieva Ingenia 1.5T, Philips Medical System, Best, The Nederlands) including DWI and fluid attenuated inversion recovery in the transverse plane.

2.2.1 CTP post-processing

Raw CTP data were initially processed by a commercially available delay-insensitive deconvolution software [CT Perfusion 4D (CTP4D), GE Healthcare, Waukesha, Milwaukee, Wisconsin]. For all patients were obtained CBF, CBV and MTT maps after positioning a region of interest manually in correspondence to a main arterial vessel and a vein.

Then raw CTP data was sent from scanner to a networked computer running fully automated RAPID software (iSchemaView, California) which generated CBF, CBV, MTT, Tmax maps and lesion segmentation and then sent processed images to institutional Picture and Achieving System (PACS). The software also generated a colour perfusion mismatch map for each patient based on the mismatch model Tmax – CBF, providing a comparison between brain regions with substantial

reductions in CBF (rCBF <30%) in pink and regions with significant hypoperfusion in green as reflected by delays in contrast arrival times (Tmax> 6.0 s). The difference between these volumes (mismatch volume) as well the ratio between these volumes (mismatch ratio) were automatically calculated.

2.3 NCCT and CTP images analysis

The neuroimaging data was independently reviewed by two experienced neuroradiologists blinded to patient clinical information using the institutional PACS by; any discrepancies were resolved through a consensus discussion in a separate session.

For NCCT, early ischaemic changes were assessed; an area was considered ischaemic if there was parenchymal hypoattenuation with or without cortical swelling of the brain [44,45]. Areas of cortical swelling without hypoattenuation were not considered ischaemic [45]. The pc-ASPECTS was used for quantifying the extent of ischaemic areas.

For CTP, a qualitative evaluation of perfusion deficit was initially performed on color-coded CBV, CBF and MTT maps generated by CTP4D software. Regions with colorimetric asymmetries on CTP maps in comparison with non-affected regions (i.e. contralateral side, different vascular territories) were rated as abnormal. A visible qualitative focally reduction in CBF or CBV, focally increase MTT on color-coded maps was rated as abnormal and evaluated with pc-ASPECTS. Territories not covered by the CTP were rated as normal (i.e. no subtraction of the pc-ASPECTS). When a perfusion deficit was suspected in the maps, it was compared with the NCCT scan in order to exclude false positive caused by beam hardenings artefacts, chronic infarct or overlapping with liquoral spaces [12].

In the same way, in a separate scoring session, color-coded CBF and Tmax maps automatically generated by RAPID software were then visually evaluated assessing pc-ASPECTS for each map. For each patient was also evaluated the quantitative colour perfusion mismatch map: brain

regions with reductions in CBF (<30%) appeared in pink suggesting ischaemic core while regions with significant increase of Tmax (> 6.0 s) indicating hypoperfusion appeared in green; the abnormal areas identified on perfusion mismatch maps were compared with perfusion changes location on color-coded maps to assess anatomic consistency in order to exclude artefacts.

PCT images showing no alterations in the same location in at least two perfusion parameter maps visually evaluated neither in automatic maps were considered negative [5].

2.3.1 Follow-up imaging evaluation

Standard follow-up imaging consisted in NCCT for all patient which was used to determine the presence of an infarct. Final pc-ASPECTS was calculated on follow-up NCCT and/or on MRI if performed.

Follow-up images were compared with PCT studies for anatomic correlation. The initial NCCT and PCT data was then compared with the follow-up NCCT data or MRI data if available, which was used as criterion standard to calculate sensitivity (SE), specificity (SP) and accuracy (ACC) of the abnormalities on NCCT scan and CTP maps for the detection of posterior circulation ischemic stroke.

2.4 Statistical analysis

Perfusion changes were considered true positives (TPs) for infarcted tissues if there was an anatomic correspondence to a new hypodense area on direct follow-up CT or an area of restricted diffusivity on MRI. A false positive (FP) was given to lesions in the case the perfusion change displayed no anatomic correspondence with the CT follow-up or DWI. A lesion was classified as false negative (FN) if a new onset hypodense lesion showed on direct follow-up CT or MRI that had not also been identified in NCCT and/or in the perfusion maps.

Main evaluations were:

– the correspondence between the infarcted area (core) assessed with qualitative evaluation of both color-coded CTP4D maps and color-coded RAPID maps and the ischemic lesion confirmed on direct follow-up CT or MRI;

– the correspondence among the perfusion changes identified with the qualitative analysis of color-coded CTP4D maps, color-coded RAPID maps and the lesions spotted in the RAPID software-generated colour perfusion mismatch map;

– the comparison of the respective ASPECTSs evaluated on NCCT, color-coded CTP4D maps and color-coded RAPID maps with the final ASPECTSs assessed on direct follow-up CT or MRI.

The statistical analysis was performed by Matlab statistical toolbox version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bit. SE, SP and diagnostic ACC for selected parameters were computed with correspondence confidence intervals at 95%. The multiple comparison Cochran's Q tests was used to compare differences of percentages among three or more dependent variables, under the consideration of the null hypothesis that there was no difference between the variables. A value of $p<0.05$ was considered statistically significant. When the Cochran's Q test was positive (p-value<0.05), then a minimum required difference for a significant difference between two proportions was calculated using the Minimum Required Differences method with Bonferroni p-value corrected for multiple comparisons according to Sheskin. The McNemar's exact test was used to test the difference between two paired proportions. Additional statistical tests were performed on stroke patient parameters using the Friedman's ANOVA test. Particularly, if Friedman's ANOVA test was positive (p-value<0.05) a Wilcoxon signed-rank post hoc test was performed to individualize significant differences between two diagnostic parameters.

Data are expressed as mean value ± standard deviation (SD) for continuous variables and as absolute number or percentage for categorical variables.

3. RESULTS

3.1 Study sample

A total of 50 patients met the inclusion criteria. 6 out of the 50 patients did not show ischemic core at follow-up imaging neither alteration of at least two perfusion parameters in the same location and were grouped as negative controls. All patients underwent to follow-up NCCT and 28 of them also underwent DWI-MRI. Mean time from multimodal CT study at admission to follow-up CT study and MRI were respectively 34.2 ± 72.6 hours and 76.6 ± 98.8 hours. Out of the 28 patients undergone MRI, 14 patients (50%) underwent DWI study within 8 hours after multimodal CT study at admission.

Table 1 provides an overview of demographic features of the study sample and displays the mean ASPECTS evaluated on NCCT at baseline, color-coded CTP4D maps, color-coded RAPID maps, follow-up NCCT and DWI-MRI.

Study sample

	Stroke patients		**Negative controls**	
	Nr./Percentage	**Mean ± SD**	**Nr./Percentage**	**Mean ± SD**
Nr. Patients	44	—	6	—
Age	—	71.09±15.64	—	69±9.52
Gender (Male)	(30/44) / 68.18%	—	(4/6) / 66.67%	—
		ASPECTS		ASPECTS
Baseline NCCT	—	9.48±1.12	—	10.0±0.0
MTT (CT Perfusion 4D)	—	6.80±2.84	—	9.17±0.90
CBV (CT Perfusion 4D)	—	8.16±2.40	—	10.0±0.0
CBF (CT Perfusion 4D)	—	7.52±2.61	—	10.0±0.0
Tmax (color-coded Rapid)	—	6.41±3.06	—	9.33±0.94
CBF (color-coded Rapid)	—	8.16±2.33	—	10.0±0.0
follow-up NCCT	—	6.98±2.51*(44 patients)*	—	10.0±0.0
Final ASPECTS	—	6.93±2.35*(44 patients)*	—	10.0±0.0
MR-DWI	—	7.04±2.14(*28 patients*)	—	—
Follow-up NCCT	—	6.93±2.69*(16 patients)*	—	10.0±0.0

Table 1. Demographic features and mean ASPECTSs evaluated on respective images of all 50 patients who fulfilled inclusion criteria.

3.2 Diagnostic performance

Table 2 displays SE, SP, ACC relative to baseline NCCT, visually evaluated color-coded MTT, CBV and CBF maps generated by CT Perfusion 4D software, visually evaluated color-coded Tmax and CBF maps generated by RAPID software, automatic quantitative Tmax and CBF parameters spotted in the RAPID software-generated colour perfusion mismatch map, using follow-up CT or MRI as criterion standard.

Diagnostic performance

Parameters	**Sensitivity (CI at 95%)**	**Specificity (CI at 95%)**	**Accuracy (CI at 95%)**
Baseline NCCT	29.6% (13/44) (16.8%-45.2%)	100% (6/6) (54.1%-100%)	38% (19/50) (25%-52.7%)
MTT *(CT Perfusion 4D)*	88.6% (39/44) (75.4%-96.2%)	50% (3/6) (11.8%-88.2%)	84% (42/50) (70.3%-92.8%)
CBV *(CT Perfusion 4D)*	63.6% (28/44) (47.8%-77.6%)	100% (6/6) (54.1%-100%)	68% (34/50) (53.2%-80.3%)
CBF *(CT Perfusion 4D)*	81.8% (36/44) (67.3%-91.8%)	100% (6/6) (54.1%-100%)	84% (42/50) (70.3%-92.8%)
Tmax[1] *(color-coded Rapid)*	90.9% (40/44) (78.3%-97.5%)	66.7% (4/6) (22.3%-95.7%)	88% (44/50) (75%-95.6%)
CBF[1] *(color-coded Rapid)*	61.4% (27/44) (45.5%-75.6%)	100% (6/6) (54.1%-100%)	66% (33/50) (51.1%-78.6%)
Tmax[2] *(quantitative Rapid)*	65.9% (29/44) (50.1%-79.5%)	100% (6/6) (54.1%-100%)	70% (35/50) (55.2%-81.9%)
CBF[2] *(quantitative Rapid)*	6.8% (3/44) (1.4%-18.7%)	100% (6/6) (54.1%-100%)	18% (9/50) (9.1%-31.5%)

Table 2. SE, SP, ACC relative to baseline NCCT, visually evaluated color-coded MTT, CBV and CBF maps generated by CT Perfusion 4D software, visually evaluated color-coded Tmax and CBF maps generated by RAPID software, automatic quantitative Tmax and CBF parameters spotted in the RAPID software-generated colour perfusion mismatch map, using follow-up CT or MRI as criterion standard.

SE, SP and diagnostic ACC of qualitative evaluation on baseline NCCT, color-coded CTP4D maps, color-coded Tmax and CBF RAPID maps (Tmax[1] and CBF[1]), and automatic quantitative Tmax and CBF RAPID software-generated perfusion mismatch map (Tmax[2] and CBF[2]), were compared. The SEs of qualitative evaluation of color-coded MTT-CTP4D map and color-coded Tmax[1]-RAPID map resulted significantly higher than the other ones (MTT: 88.6%, $p<0.05$; Tmax[1]: 90.9%, $p<0.05$),

while NCCT at baseline and CBF^2 provided by RAPID quantitative perfusion mismatch maps had the lowest ones (29.6% and 6.8% $p<0.05$, respectively). No significant difference was found between MTT-CTP4D map and $Tmax^1$-RAPID map SEs (88.6%<90.9%, $p>0.05$).

About SP there was a significant difference among parameters but by post hoc test no significant differences were found, considering all pairwise comparison. This result was probably due to small number of control group patients considered in this study.

About diagnostic ACC, between $Tmax^1$- RAPID map and MTT- CTP4D map there was no significant difference (88%> 84%, $p>0.05$), while CT at baseline and CBF^2 provided by RAPID quantitative perfusion mismatch maps had the lowest values in comparison to the others (38% and 18% $p<0.05$, respectively).

In addition, SE, SP and diagnostic ACC were compared among CBF, CBF^1 and CBF^2 parameters (respectively qualitatively evaluated on color-coded CTP4D, color-coded RAPID maps and automatically provided by RAPID quantitative perfusion mismatch maps), and between $Tmax^1$ and $Tmax^2$ parameters (respectively qualitatively evaluated on color-coded CTP4D and color-coded RAPID maps) (Table 3).

CBF^2 assessment provided by quantitative RAPID perfusion mismatch maps showed significant lowest SE (6.8%) in comparison to qualitative evaluations of both color-coded CBF-CTP4D and $CBF^{\mathbf{1}}$-RAPID maps (81.8% and 61.4% respectively); no significant SE difference was found between qualitative evaluations of color-coded CBF-CTP4D and CBF^1-RAPID maps (81.8% > 61.4%, $p>0.05$). Analogous results were observed for diagnostic ACC, while for SP there were no significant differences among CBF, CBF^1 and CBF^2 parameters (respectively qualitatively evaluated on color-coded CTP4D and RAPID maps and automatically provided by RAPID quantitative perfusion mismatch maps).

Qualitative evaluation of color-coded $Tmax^1$ -RAPID maps showed significant higher SE and ACC than quantitative assessment of $Tmax^2$ automatically provided by RAPID perfusion mismatch

maps (90.9%>65.9% and 88%>70%, respectively) while about SP there were no significant difference (69.7.9%<100%, p=0.5).

Comparison of qualitative and automatic quantitative perfusion parameter evaluations.

Parameters	**CBF (color-coded CT Perfusion 4D)**	**CBF[1] (color-coded Rapid)**	**CBF[2] (quantitative RAPID)**	**Statistical test**
Sensitivity	81.8% (36/44)	61.4% (27/44)	6.8% (3/44)	p<0.001 * (Q) CBF**, p<0.05 (Sh) CBF[1]**, p<0.05 (Sh) CBF[2] ***, p<0.05 (Sh)
Specificity	100% (6/6)	100% (6/6)	100% (6/6)	p>0.05 (Q)
Diagnostic Accuracy	84% (42/50)	66% (33/50)	18% (9/50)	p<0.001 * (Q) CBF**, p<0.05 (Sh) CBF[1]**, p<0.05 (Sh) CBF[2] ***, p<0.05 (Sh)
Parameters		**Tmax[1] (color-coded Rapid)**	**Tmax[2] (quantitative RAPID)**	**Statistical test**
Sensitivity		90.9% (40/44)	65.9% (29/44)	90.9%>65.9%, p=0.001 * (M)
Specificity		69.7% (4/6)	100% (6/6)	69.7.9%<100%, p=0.5 (M)
Diagnostic Accuracy		88% (44/50)	70% (35/50)	88%>70%, p=0.0225 * (M)

* = significant test, ** = most frequent, *** = less frequent; Q = Cochran's Q test, Sh = Sheskin's procedure; M = McNemar exact test.

Table 3. Comparison among CBF parameters and Tmax parameters evaluated in this study in terms of SE, SP and diagnostic ACC.

Furthermore, pc-ASPCETSs assessed for each qualitative imaging evaluation (NCCT at baseline, visually evaluated color-coded MTT, CBV and CBF maps generated by CTP4D software, visually evaluated color-coded $Tmax^1$ and CBF^1 maps generated by RAPID software and the reference standard imaging (follow-up NCCT or MRI) in stroke patients were analyzed by the Friedman's ANOVA test. If Friedman's ANOVA test resulted positive (p-value<0.05) a Wilcoxon signed-rank post hoc test was performed to individualize significant differences between two diagnostic parameters (Table 4). Friedman's ANOVA test demonstrated a significant difference between reference standard values and other parameters p<0.0001. Since the Friedman test was positive (p-value <0.05) a post hoc test was performed to individualize which parameters significantly differ from the reference standard; the results are illustrated in Table 4.

Post-hoc test

Variables	Mean rank	Significant differences (p<0.05)
(1) Reference standard imaging	2.82	(2) (4) (5) (7)
(2) NCCT at baseline	6.08	(1) (3) (4) (5) (6) (7)
(3) MTT (color-coded CT Perfusion 4D)	2.80	(2) (4) (5) (7)
(4) CBV (color-coded CT Perfusion 4D)	5.14	(1) (2) (3) (5) (6)
(5) CBF (color-coded CT Perfusion 4D)	3.80	(1) (2) (3) (4) (6) (7)
(6) Tmax[1] (color-coded Rapid)	2.48	(2) (4) (5) (7)
(7) CBF[1] (color-coded Rapid)	4.90	(1) (2) (3) (5) (6)

Table 4. Pairwise comparison with Wilcoxon test after positive Friedman's ANOVA test.

No significant differences were revealed among values corresponding to the reference standard (2.82), MTT (color-coded CTP4D, 2.80) and Tmax[1] (color-coded Rapid, 2.48) neither between MTT (color-coded CTP4D) and Tmax[1] (color-coded Rapid). No significant differences were even found between CBV (color-coded CTP4D, 5.14) and CBF[1] (color-coded Rapid, 4.90) values. NCCT at baseline, instead, significantly differed from all the other parameters.

3.3 PC- ASPECTSs

ASPECTSs assessed by qualitative evaluations were compared to the final score assigned by the reference standard imaging (control NCCT or MRI), distinguishing if the qualitative score was equal, higher and lower than the reference standard one. The comparison is resumed in Table 5.

Baseline NCCT showed significant most frequent higher values (84%, $p<0.05$) and less frequent equal values (16%, $p<0.05$). MTT (color-coded CT Perfusion 4D) and Tmax[1] (color-coded Rapid) were the parameters with significant less frequent higher values (24%, $p<0.05$; 22%, $p<0.05$, respectively) and more frequent lower values (32%, and 38% $p<0.05$, respectively) in comparison to the others; MTT (color-coded CTP4D) and Tmax[1] (color-coded Rapid) parameters resulted statistically equivalent to individualize perfusion changes.

Pc-ASPCETSs comparison with the final score evaluated on the reference standard imaging

Parameters	**% higher**	**% lower**	**% equal**
NCCTC at baseline	84% (42/50)	0.0% (0/50)	16% (8/50)
MTT (color-coded CT Perfusion 4D)	24% (12/50)	32% (16/50)	44% (22/50)
CBV (color-coded CT Perfusion 4D)	68% (34/50)	10% (5/50)	22% (11/50)
CBF (color-coded CT Perfusion 4D)	42% (21/50)	14% (7/50)	44% (22/50)
CBF[1](color-coded Rapid)	60% (30/50)	8% (4/50)	32% (16/50)
Tmax[1] (color-coded Rapid)	22% (11/50)	38% (19/50)	40% (20/50)
Statistical test	p<0.001 * (Q) NCCT **, p<0.05 (Sh) MTT ***, p<0.05 (Sh) Tmax[1]***, p<0.05 (Sh)	p<0.001 * (Q) MTT **, p<0.05 (Sh) Tmax[1] **, p<0.05 (Sh)	p<0.001 * (Q) NCCT***, p<0.05 (Sh)
* = significant test, ** = most frequent, *** = less frequent, Q = Cochran's Q test, Sh = Sheskin's procedure			

Table 5. Comparison among the ASPECTs assessed by qualitative evaluations with the final score assigned by the reference standard imaging.

4. DISCUSSION

4.1 Ischemic lesion detection

Improving the detection rate of posterior circulation strokes is important as every 5th ischemic stroke affects posterior circulation territories. In addition, clinical detection of posterior circulation strokes is challenging because clinical signs of anterior and posterior circulation stroke do not have any obvious distinction [41]. Concordant to other studies, our findings confirmed that CTP in posterior circulation allows to detect significantly more ischemic strokes than NCCT [4,5,41]. As NCCT presented low SE and ACC values, the addiction of CTP in the diagnostic work-up in our patients suspected of an ischemic posterior circulation stroke significantly increased diagnostic ACC.

4.2 MTT and Tmax

Perfusion disturbance in the posterior circulation have previously been reported to be most frequent on MTT and Tmax maps [4,5,26]. In agreement with other studies, MTT and Tmax visually assessed on color-coded maps (respectively generated by CTP4D and RAPID software) in our study were the most significant sensitive and accurate parameters in the detection of posterior circulation ischemic lesions [5]; furthermore, they showed no significant differences of SE (88.6%<90.9%, $p>0.05$) and ACC (88%> 84%, $p>0.05$) despite a superiority of Tmax as described in literature [32].

Automatic quantitative assessment of Tmax^2 (provided by RAPID perfusion mismatch maps) presented significant lower SE and ACC compared with qualitative visual evaluation of Tmax^1 maps; in particular, automatic Tmax^2 evaluation overlooked 11 ischemic lesions which mostly (8/11) were lacunar infarcts involving thalamus (4/8) or brainstem (4/8) while the remaining were larger lesions involving occipital lobe an cerebellum (3/11) (Figure 7). Visual qualitative evaluation of MTT overlooked ischemic changes in 5 patients located in pc-ASPECT pons-midbrain region in 5 cases

associated to thalamus involvement in 2 cases; visual qualitative evaluation of Tmax[1] overlooked ischemic changes in 4 patients located in pc-ASPECT pons-midbrain regions in 3 cases and thalamus in 1 case (Figure 8).

Despite potential shortcomings due to beam hardening artifacts, preceding studies investigating the SP of CTP in the detection on posterior circulation infarcts demonstrated SP values higher than 90% [5,17]. In our study, CTP parameters presented different SP values (ranging from 50% up to 100%) but post-hoc test revealed no significant differences of SP among all assessed CTP parameters considering all pairwise comparison and this result was probably due to small number of control patients considered in this study. As previously described in literature, we found that qualitatively evaluated MTT and Tmax[1] had low SP for perfusion deficits [12].

4.3 CBV and CBF

The detection of the ischemic core is most relevant for the prediction of the functional outcome of patients and core extent is described to be better delineated on CBF compared with CBV maps because CBV parameter may underestimate core extent [21,26].

In agreement with these evidences, in our study qualitative evaluation of CTP4D maps showed lower SE and ACC of CBV parameter compared with CBF ones although without significant difference (63.6 < 81.8%, $p>0.05$).

As expected CBF resulted more specific than MTT for stroke because MTT values can be prolonged in transitory ischemic attack as well as stroke [46]. CTP maps, especially CBF abnormalities, are described to significantly differ among commercial software even when using identical source data [37]; however, we found that visually evaluated CBF and CBF[1] maps - respectively generated both by CTP4D and RAPID software - presented no significant different SE (81.8% > 61.4%, $p>0.05$) and ACC (6.8% < 18%, $p>0.05$). Instead, the automatic quantitative assessment of CBF[2] (provided by RAPID perfusion mismatch maps) presented significant lower SE

and ACC as compared with qualitative visual evaluation of both CTP4D and RAPID color-coded CBF maps.

Despite previous reports using the mismatch concept have suggested that visual assessment is unreliable and that automatic processing of CTP can provide an objective mismatch classification improving standardization and reproducibility of interpretation, in our study RAPID perfusion mismatch maps failed to adequately reveal the ischemic core extent in the major part of the patients (41/44) as compared with the qualitative analysis [30].Out of 41 overlooked ischemic lesions, 20 were lacunar infarcts involving thalamus (15/20) and brainstem (5/20).

A relevant result of our study was that CBF^2 evaluation (rCBF automatically provided by RAPID quantitative perfusion mismatch map) was characterized by significant low SE and ACC value resulting less adequate even than NCCT for detecting ischemic lesions in posterior circulation regions. Indeed, automatic RAPID assessment did not identify ischemic lesions visually recognised on NCCT in 10 patients (thalamic lacunar infarct in 5 patients and small cerebellar infarct in 3 patients) (Figure 9). Only in 1 patient automatic RAPID mismatch map depicted an ischemic core (in the left cerebellar hemisphere) not identified on NCCT.

4.4 PC-ASPECTS

The determination of pc-ASPECTs on color-coded perfusion maps does not require any volumetric software and can be applied to NCCT as well to color-coded perfusion maps [25].

In our study, the pc-ASPECTs assessed by NCCT were mainly higher and significantly different from the corresponding final pc-ASPECTs evaluated on control CT/MRI scan and NCCT presented the lowest rate of scores equal to the final ones. These findings are clearly related to the low SE of NCCT which can depict only the ischemic core and not perfusion changes at risk of infarction.

We found no significant differences among the scores assessed on control CT/MRI scan, color-coded MTT and $Tmax^1$ maps resulting MTT and $Tmax^1$ the most efficient parameters to

evaluate the patients' status. This finding can be interpreted as the result of the progression of ischemic hypoperfusion to necrosis in most of our patients. Moreover, MTT and Tmax[1] maps led to assign lower ASPECTS significantly more (32%, $p<0.05$; 38%, $p<0.05$, respectively) and higher ASPECT significantly less (24%, $p<0.05$; 22%, $p<0.05$, respectively) frequently than the other parameters; a lower score than final one reflected the presence of hypoperfusion not progressed to necrosis while a higher score than final one can be interpreted as a worsening of ischemic damage and/or as an overlooked ischemic change. In 4 patients with midbrain infarct all perfusion color-coded maps were scored 10 and also the automatic quantitative assessment did not identify these lesions.

Interesting was that no significant differences were found between the scores assessed on color-coded MTT and Tmax[1] maps neither between the scores assessed on color-coded CBV and CBF[1] maps; according to this, in our study the mismatch models MTT-CBV and Tmax[1]-CBF could be considered comparable being not different the determination of hypoperfusion by MTT and Tmax[1] neither different the assessment of core extent by CBV and CBF[1].

4.5 Limits

A possible limitation of this study is the retrospective design. FP results ay have been caused by intravenous thrombolytic therapy and endovascular thrombectomy as tissue at risk may not have progressed to definite infarctions. Intravenous thrombolysis and thrombectomy may also have influenced SE an SP of perfusion maps because they can lead to temporarily reperfusion in the potentially salvageable penumbra. Furthermore, the use of 64-slice CT did not allow the study of the whole parenchyma and a careful positioning of the slab was necessary although resulting not always adequate. This could have influenced the SE of CTP maps.

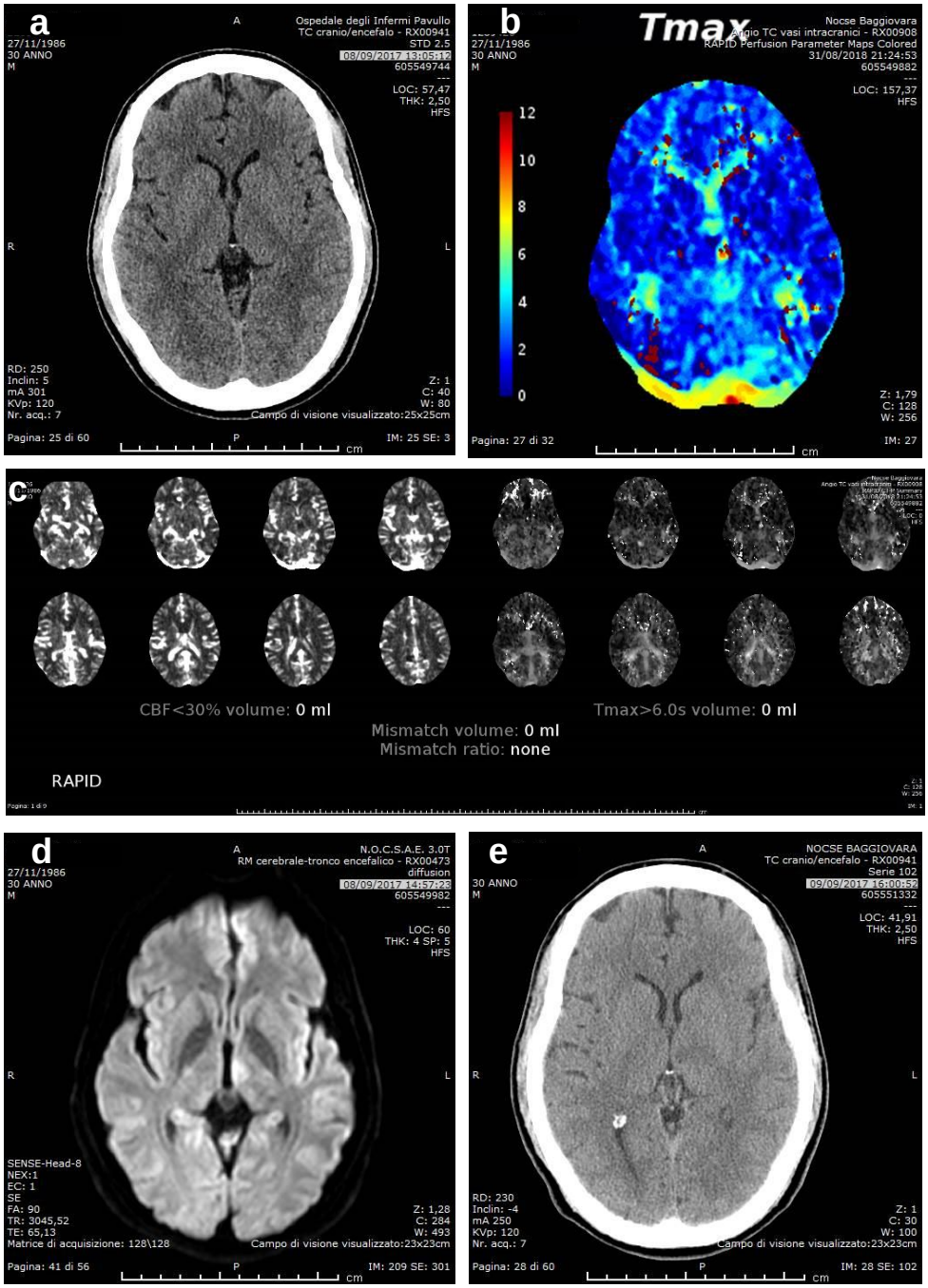

Figure 7

Left thalamic lacunar infarct: a) ASPECTS 10 on initial NCCT , b) RAPID color-coded Tmax map shows perfusion alteration at left thalamic level but not displayed on RAPID automatic mismatch map (c); the lesion is confirmed on DWI (d) and also visible on follow-up CT (e).

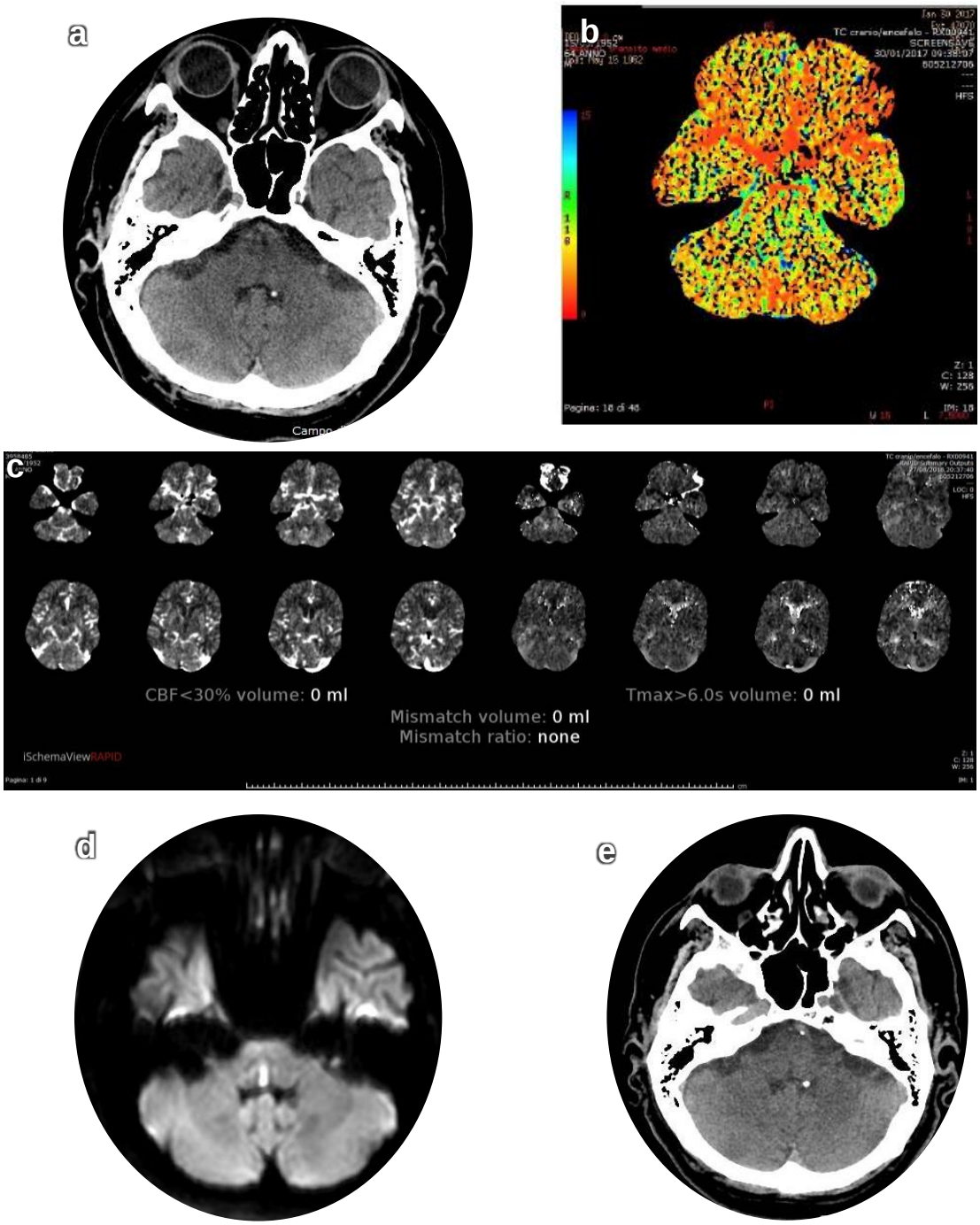

Figure 8

Mesencephalic lacunar infarct not clearly identified on initial NCCT (a), neither on color-coded MTT (b) map and RAPID automatic mismatch map (c) but detected by DWI (d) and confirmed on follow-up CT (e).

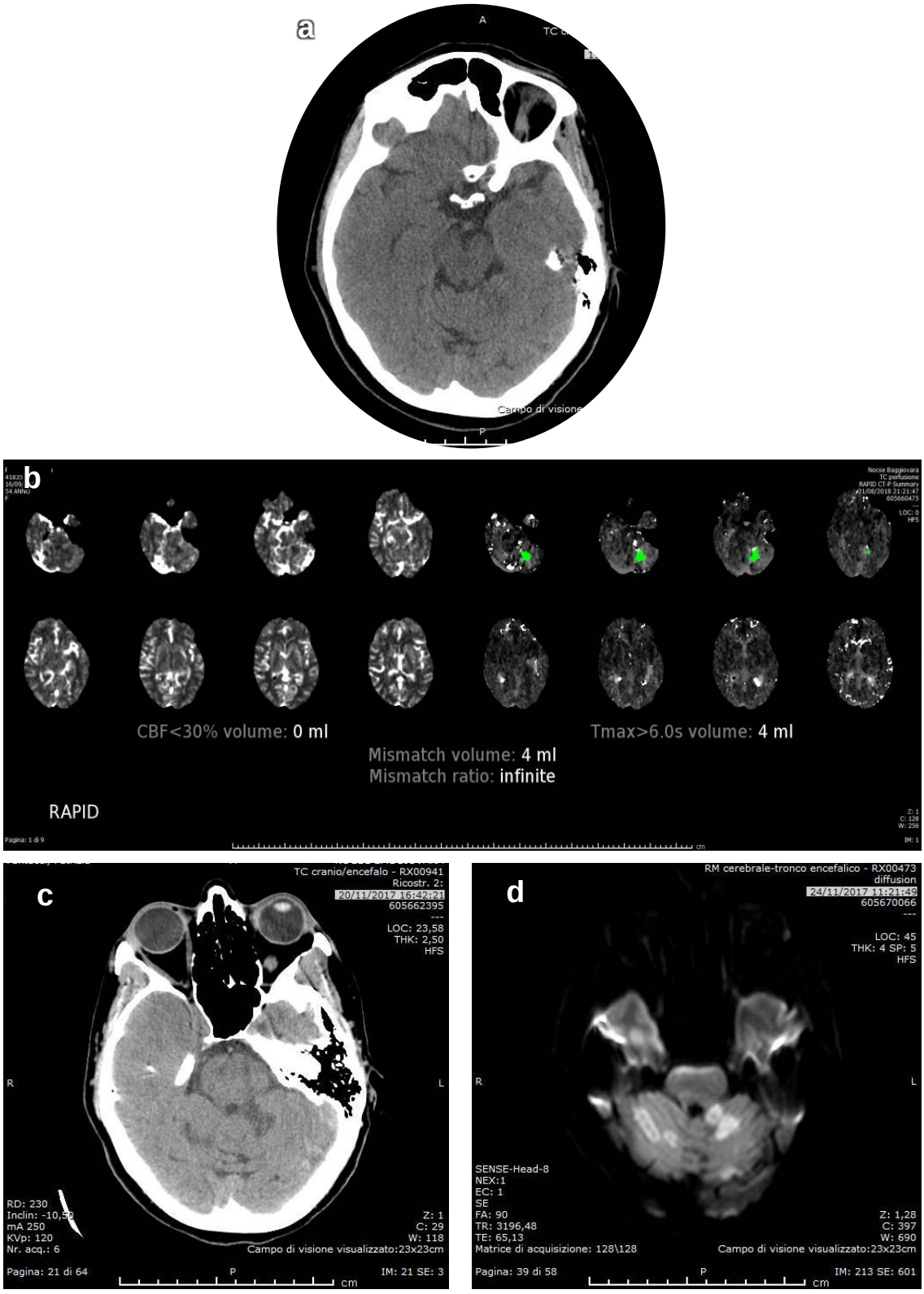

Figure 9

Left small cerebellar ischemic lesion visible on initial NCCT (a) as hypodensity, not recognised as ischemic core by the automatic RAPID mismatch map (b) but confirmed on follow-up CT (c) and DWI (d).

5. CONCLUSIONS

In this study, CTP showed good diagnostic ACC in the identification of acute vascular ischemic lesions of the posterior circulation and the infarct detection of CTP was significantly higher than NCCT [12,41]. The most sensitive perfusion parameters were MTT and Tmax. However, SE increases with infarct size being the draw-back of CTP in detection of small-volume infarctions [5]. Indeed, detection of ischemic lesion in the brainstem remains challenging due to beam hardening artifacts [5,25].

Independently to the software employed, qualitative analysis of color-coded maps resulted more sensitive in the detection of ischemic changes than automatic quantitative analysis. RAPID software generated mismatch maps overlooked and underestimated the extent of the ischemic core in the major part of the patients as compared with the qualitative analysis [12]. In our study, the limits of identification of the lesions by automatic quantitative mismatch maps mainly lied in the thalamus and brainstem. Visual assessment of CTP pc-ASPECTS on color-coded perfusion maps revealed comparable scores between MTT and $Tmax^1$ as well as between CBV and CBF^1 suggesting the equivalence of both mismatch models (MTT-CBV and Tmax-CBF) commonly applied in acute setting with implications for treatment decision-making.

Given the advantages of a more rapid and operator-independence elaboration of perfusion maps and their easier interpretation, this opens the potential for automatic software implementation and optimization of perfusion parameters' thresholds for the evaluation of posterior circulation ischemia [12,38].

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