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Hemorrhagic transformation of ischemic stroke – prediction and evaluation with different computed tomography modalities

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Abstract

Background: Hemorrhagic transformation (HT) of ischemic stroke is a complex and heterogeneous phenomenon, which involves numerous parameters whose knowledge remains partial. Large HT is often associated with poorer outcome and higher mortality, especially parenchymal hematoma type 2, that's why the search of strong HT predictors is very important and can improve management of ischemic stroke patients. Our aim was to review the literature regarding computed tomography (CT) imaging predictors of HT and possible input of different computed tomography modalities in diagnosis and evaluation of HT following acute ischemic stroke. The contribution of non-contrast computed tomography, computed tomography angiography (CTA) and dynamic Perfusion CT (PCT) investigation in the prediction of the hemorrhagic transformation risk were studied. Multiple multicentre studies revealed useful information on different CT patterns predictors of symptomatic intracerebral hemorrhage after stroke, which is the most important type of hemorrhagic transformation from a clinician's point of view.

Conclusions: Data from the multiple studies and trials revealed that different CT modalities show high potency in HT prediction and evaluation. Non-contrast CT standard investigation showed high accuracy in HT prediction by assessment of early ischemic signs, quantification of the Alberta Stroke Program Early CT Score (ASPECTS), grading of leukoaraiosis severity. CTA is useful in HT prediction by the assessment of collateral vessels; intra-arterial occlusion and ASPECTS score calculated from the CTA source images. PCT showed the best predictive values by the measurement of blood-brain barrier permeability.

Key words: acute ischemic stroke, hemorrhagic transformation, non-contrast computed tomography, computed tomography angiography, perfusion computed tomography.

Introduction

Stroke is the third leading cause of death in industrialized countries and the most frequent cause of permanent disability in adults worldwide [1, 2]. One of the most undesirable complications of ischemic stroke is hemorrhagic transformation (HT), which may further complicate already devastating clinical condition. HT after acute ischemic stroke is known to associate with poor outcome and delays the initiation of proper anticoagulation treatment for stroke with cardioembolism [3]. Historically, hemorrhagic transformation, initially designated as "red softening," has long been recognized by neuropathologists to occur as a natural consequence of ischemic brain injury. To search for new treatments as well as intervention measures for HT, it is important to understand its underlying mechanism and identify its predictors [4].

Epidemiology. The true incidence of hemorrhagic transformation remains uncertain, and reported frequencies vary depending on the methodology used and the underlying pathogenesis of the ischemic insult [5]. Autopsy series have reported secondary bleeding from 51% to 71% of recent embolic infarctions as compared to a 2% to 21% incidence in non-embolic strokes [6, 7]. Computed tomography (CT) studies have reported hemorrhagic infarction from 26% to 43% of non-anticoagulated patients with predominantly embolic infarcts [8, 9]. With the recent large use of new different treatment modalities of acute ischemic stroke (AIS), HT rates were in detail evaluated in multiple clinical trials of therapeutic (intravenous and intra-arterial fibrinolysis) and surgical (mechanical thrombectomy and arterial stenting) AIS interventions.

Basic rates reported in those trials for asymptomatic hemorrhagic transformation (AHT) and symptomatic hemorrhagic transformation (SHT) constitute: National Institute of Neurological Disorders and Stroke (NINDS) – 4.5% (14 patients/ from 312 cohort size) AHT and 6.4% (20/312) SHT [10]; European Co-operative Acute Stroke Study-II (ECASS-II) – 39.6% (161/407) AHT and 8.8% (36/407) SHT [11]; European Co-operative Acute Stroke Study-III (ECASS-III) – 27% (113/418) AHT and 2.4% (10/418) SHT [12]; Alteplase thrombolysis for acute noninterventional therapy in ischemic stroke (ATLANTIS) – 11.4% (31/272) AHT and 7.0% (19/272) SHT [13]; Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) – 9.6% (617/6438) AHT and 7.3% (468/6483) SHT [14]; Prolyse in Acute Cerebral Thromboembolism II (PROACT-II) – 68% (73/108) AHT and 10% (11/108) SHT [15]; the Interventional Management of Stroke I (IMS I) – 43% (34/80) AHT and 6.3% (5/80) SHT [16]; the Interventional Management of Stroke III (IMS III) – 27.4% (119/434) AHT and 6.2% (27/434) SHT [17]; Safety and efficacy of mechanical embolectomy in acute ischemic stroke (MERCI Trial) – 27.7% (39/141) AHT and 7.8% (11/141) SHT [18]; The Penumbra Pivotal Stroke Trial (Penumbra System for Clot Removal in Intracranial Large Vessel Occlusive Disease)-16.8% (21/125) AHT and 11.2% (14/125) SHT [19]; Solitaire flow restoration device versus the Merci Retriever in patients with acute ischemic stroke (SWIFT Trial) -15.5% (9/58) AHT and 2.0% (1/58) SHT [20]; Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO-2) – 40.9% (36/88) AHT and 4.5% (4/88) SHT [21].

CT classification. There is a broad spectrum of severity of hemorrhagic transformation, ranging from subtle petechial hemorrhage within infarcted tissue to large-volume hematoma extending beyond the borders of the infarction [22]. All types of HT are classified regarding their Computed Tomography (CT) patterns in 2 large groups: hemorrhagic infarction (HI) and parenchymal hematoma (PH) and include two subtypes of HI (HI1 and HI2) and two subtypes of PH (PH1 and PH2) (Table 1) [23]. The term *hemorrhagic infarction* describes heterogeneous hyperdensity occupying a portion of an ischemic infarct zone on CT-imaging, whereas *parenchymatous hematoma* refers to a more homogeneous, dense hematoma with mass effect [24].

Table 1

Radiographic classification of the spectrum of hemorrhagic transformation, based on criteria proposed by Fiorelli et al. (1999)[23]

Hemorrhage classification	Radiographic appearance
Hemorrhage infarction type 1 (HI1)	Small hyperdense petechiae
Hemorrhage infarction type 2 (HI2)	More confluent hyperdensity throughout the infarct zone; without mass effect
Parenchymal hematoma type 1 (PH1)	Homogeneous hyperdensity occupying <30% of the infarct zone; some mass effect
Parenchymal hematoma type 2 (PH2)	Homogeneous hyperdensity occupying >30% of the infarct zone; significant mass effect. Or, any homogenous hyperdensity located beyond the borders of the infarct zone

Figure 1 represents examples of four patients hospitalized at the Institute of Neurology and Neurosurgery (Chisinau, Moldova), between 01.2015-03.2015, diagnosed with acute ischemic stroke in the right middle cerebral artery vascular territory. During hospital treatment was registered hemorrhagic transformation, proved by the presence of characteristic Computed Tomography pattern – hyperdense inclusions of different size and intensity, supporting various types of HT from HI1 to the extensive PH2.

Risk factors and predictors of HT. Several factors are associated with or predict HT. Although the usefulness of some of these markers in clinical practice might be limited, the development of imaging techniques and the identification of predictive biomarkers might help in the selection of patients at increased risk of HT [25]. Reliable clinical and radiologic predictors are needed to identify patients at highest risk for hemorrhagic transformation in order to guide the safe use of anticoagulants or thrombolytic therapy [26]. Initial stroke

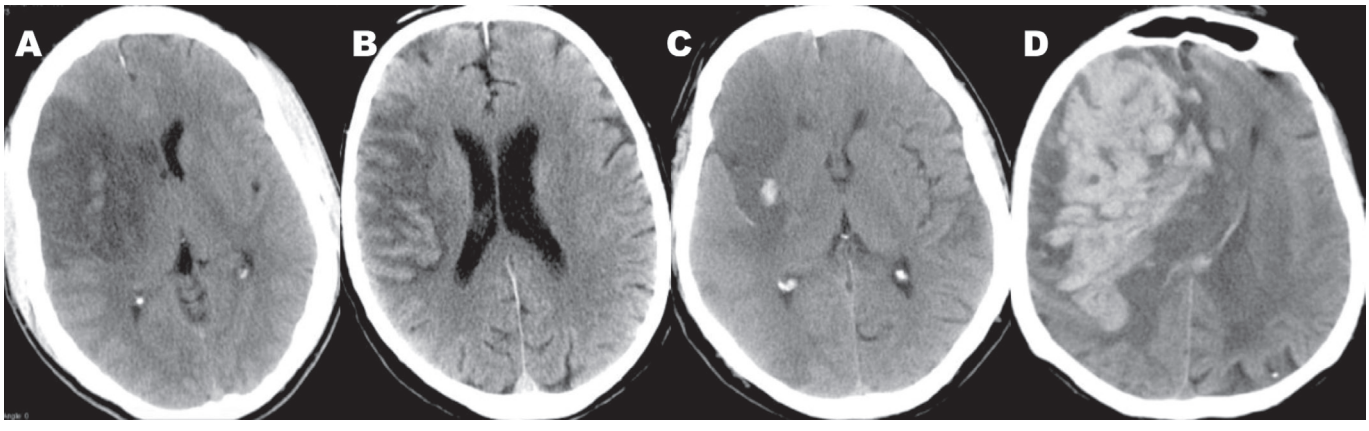

Fig. 1. Non-contrast Multislice Computed Tomography.

A – Male 51 years, 3 days after symptoms (acute left hemiplegia) onset, HI type 1 transformation (small hyperdense petechiae in the center of large right parietal hypodensity with edema and contralateral shift of median brain structures). B – Male 71 years, 10 days after symptoms onset, HI type 2 (confluent hyperdensities throughout the ischemic right parietal zone, without mass effect). C – Male 60 years, 24 hours of onset (acute deep left hemiplegia, sopor), PH type 1 transformation (homogeneous hyperdensity 5 mm in diameter in the projection of the external capsule on the medial contour of large right hemispheric infarction). D – Woman 85 years, 2 hours after symptoms onset (The Glasgow Coma Scale 3), Right hemorrhagic transformation – hemispheric parenchymal hematoma type 2, death in a few hours of onset.

severity, older age, heart disease, high blood pressure, male gender, obesity, baseline hyperglycemia or history of diabetes, uncontrolled hypertension at presentation, antiplatelet therapy prior to hospitalization were reported to have sensitivity in HT prediction [27-31]. But the strongest predictors are characteristic imaging patterns, which are useful in diagnosis, evaluation and prognosis assessment in all cases of ischemic stroke and especially in such complication as HT. Computed tomography (CT) is recommended by the American Heart Association as the initial modality of choice for stroke investigation.

CT imaging in HT diagnosis and prediction. It is usually assumed that CT is the gold standard for the detection of ICH. The diagnostic performance of CT stroke protocols is improved with modification of window and level settings [32] interpretation of CT angiographic source images, and CT perfusion. Imaging of ischemic stroke and its hemorrhagic transformation has 4 main priorities: 1) Imaging the Cerebral Parenchyma (mostly is provided by non-contrast CT (NCCT), but additional information is supplied by Angiography CT source images (CTA-SI) and Perfusion CT (PCT) maps), 2) Intracranial Vascular Evaluation (CTA), 3) Assessment of cerebral perfusion parameters (basic PCT maps), 4) Blood-Brain Barrier Permeability evaluation (permeability surface (PS) PCT product).

Non-contrast CT (NCCT). Non-enhanced, or non-contrast, CT represents the first step of all more complicated CT modalities (angiography and neuroperfusion), or can be used alone as an urgent tool in stroke management protocol. NCCT is the preferred modality because of its accessibility, speed, and patient's tolerance, thereby permitting the rapid triage of patients suspected of having experienced a stroke [33]. Imaging the Cerebral Parenchyma by NCCT combines three basic roles in assessing the status of brain tissue in the acute stroke patient: the exclusion of hemorrhagic stroke, the detection of the ischemic tissue, and the exclusion of conditions that mimic acute cerebral ischemia. The perfection of multidetector technology has enabled a CT scan of the head to be obtained with submillimeter slice thickness in a few seconds and with superior tissue differentiation (contrast resolution). Besides pure exclusion of brain hemorrhage, however, early data about site and severity of brain ischemia and their respective pathogenesis are clinically requested.

Early computed tomographic (CT) signs of cerebral infarction seen within 6 hours after onset of symptoms of stroke may be predictive of poor functional outcome and clinically significant hemorrhagic transformation of the infarct [34, 35, 36]. Early CT signs include: dense MCA, loss

Table 2

Definition of Early CT Signs of Ischemic Stroke [37]

CT Sign	Definition	Type of Measure
Hypoattenuation in thirds of middle cerebral artery territory	Decreased attenuation of less or more than one-third of the presumed middle cerebral artery territory	Semiquantitative
Obscuration of lentiform nucleus	Decreased attenuation involving the lentiform nucleus and inducing the loss of the precise delineation of this area	Qualitative
Cortical sulcal effacement	Decreased contrast, loss of precise delineation of the gray-white interface in the margins of the cortical sulci, corresponding to localized mass effect	Qualitative
Focal hypoattenuation	Increased radiolucency of brain structures relative to other parts of the same structure or to contralateral counterparts	Qualitative
Loss of insular ribbon, obscuration of sylvian fissure	Decreased precision in delineation of gray-white interface at lateral margin of the insula	Qualitative
ASPECTS value*	One point is subtracted for each area of hypoattenuation in a defined region (normal = 10).	Semiquantitative
Hyperattenuation of vessel	Attenuation higher than that in any other visualized artery or vein	Qualitative
Loss of gray and white matter differentiation in the basal ganglia	Decreased contrast, loss of precise delineation of the gray-white interface of the basal ganglia	Qualitative
Hypoattenuation of basal ganglia	Decreased attenuation (measured in Hounsfield units) in basal ganglia	Quantitative

* ASPECTS = Alberta Stroke Programme Early CT Score

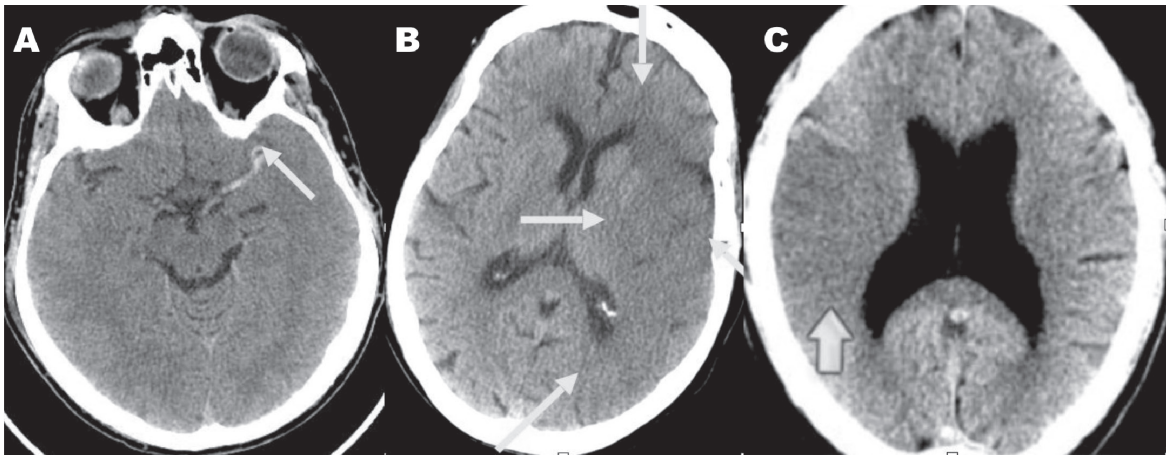

Fig. 2. Non-contrast Computed Tomography. Early CT signs of acute ischemic stroke.
A – dense middle cerebral artery sign (arrow). B – early ischemic signs in left hemisphere, slice on the level of basal ganglia: loss of gray and white matter differentiation, large hypodensity, effacement of sulci, loss of lentiform nucleus outline (arrows). C – early ischemic signs in right hemisphere, slice on the level of the body of the lateral ventricles: loss of gray and white matter differentiation, hypodensity, effacement of sulci (arrow).

of basal ganglia outline, loss of insular ribbon, hypodensity, effacement of sulci or ventricles, dense cortical sulci, loss of gray and white matter differentiation [38, 39, 40] (definition of early CT signs is shown in tab. 2).

One of the most important early CT sign is the increased density within the occluded vessel, which represents the thrombus. When this is the MCA, it is called the hyperdense MCA sign [42, 43], and it is seen in one third to one half of all cases of angiographically proven thrombosis (Fig. 2 A). Hence, it is an appropriate indicator of thrombus when present, but its absence does not exclude thrombus.

Another significant early CT sign of cerebral ischemia within the first few hours after symptom onset is loss of gray-white differentiation (fig. 2 B, C), because there is an increase in the relative water concentration within the ischemic tissues. This sign includes loss of distinction among the nuclei of the basal ganglia and a blending of the densities of the cortex and underlying white matter in the insula and over the convexities. The subsequent swelling of the gyri produces sulcal effacement, which may lead to ventricular compression. The sooner these signs become evident, the more profound is the degree of ischemia. However, the ability of observers to detect these signs on NCCT is quite variable, depending on the size of the infarct, the time between symptom onset and imaging, and the methodology of the trial itself; the detection rate appears to be 67% in cases imaged within 3 hours. The rate of detection increases to 82% at 6 hours [41]. To offer the reliability and utility in assessing early ischemic changes on NCCT examination was developed special score system – The Alberta Stroke Program Early CT Score (ASPECTS) with a reproducible grading system of acute ischemic stroke in the middle cerebral artery (MCA) circulation territory.

The Alberta Stroke Program Early CT Score (ASPECTS). The ASPECTS is a 10-point quantitative topographic CT scan score used in patients with MCA stroke. Segmental assessment of MCA territory is made and 1 point is removed from the initial score of 10 if there is evidence of infarction in that region [44, 45]. A normal CT scan receives ASPECTS of 10 points. A score of 0 indicates diffuse involvement throughout the MCA territory. An ASPECTS score less than or equal to 7 predicts worse functional outcome in 3 months as well as symptomatic hemorrhagic transformation.

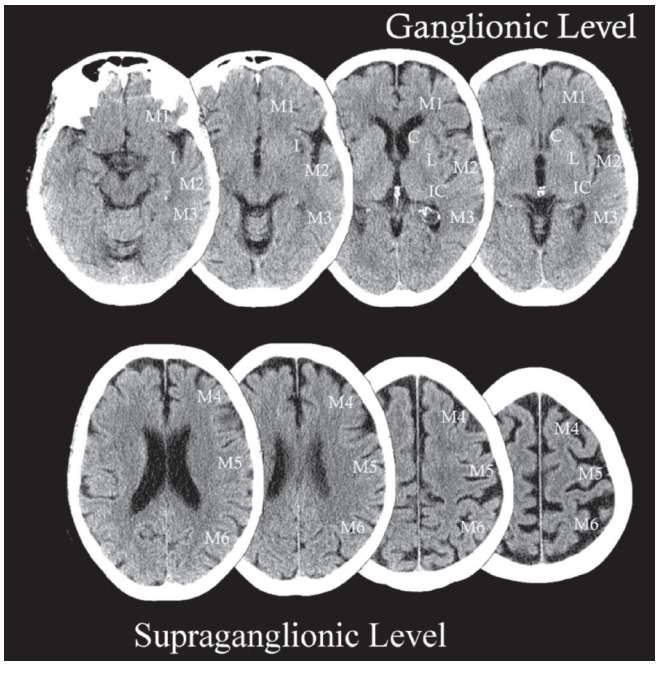

Fig. 3. Axial NCCT images showing the MCA territory regions as defined by ASPECTS. C – Caudate, I – Insular ribbon, IC – Internal Capsule, L – Lentiform nucleus, M1 – Anterior MCA cortex, M2 – MCA cortex lateral to the insular ribbon, M3 – Posterior MCA cortex, M4, M5, M6 are the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, rostral to basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5and M6).

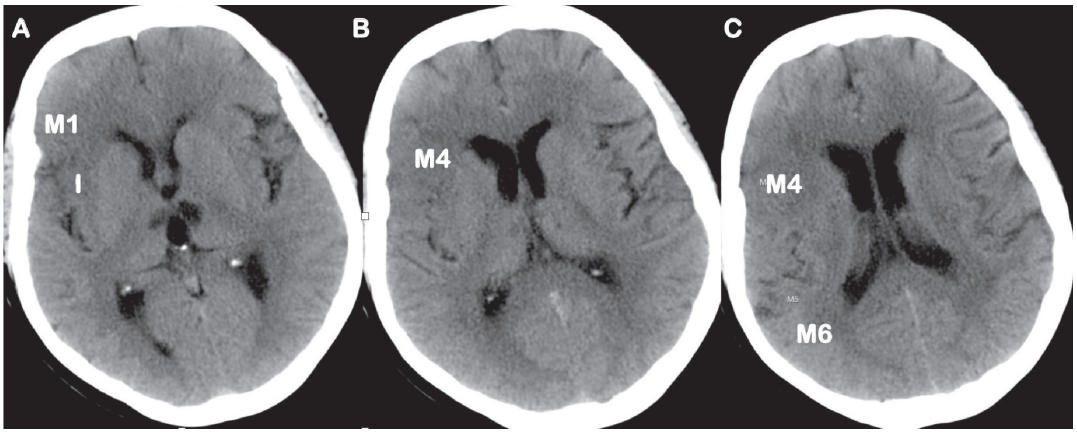

Fig. 4. Female, 55 years. NCCT in hyperacute phase of stroke (2 hours of symptoms onset – left hemiparesis, right pyramidal insufficiency, visual disorders, aphasia).
A, B – ganglionic level. C – supraganglionic level. Early signs of stroke in right MCA, ASPECTS = 6 (M1, M4, M6, I). Chronic bilateral lacunar infarct in thalamus.

ASPECTS is determined from evaluation of two standardized regions of the MCA territory: the basal ganglia level, where the thalamus, basal ganglia, and caudate are visible, and the supraganglionic level, which includes the corona radiata and centrum semiovale (fig. 3). All cuts with basal ganglionic or supraganglionic structures visible are required to determine if an area is involved. The abnormality should be visible on at least two consecutive cuts to ensure that it is truly abnormal rather than a volume averaging effect (fig. 4).

The ECASS I and ECASS II studies have shown that the presence of early CT signs occupying more than one-third of the MCA territory is accompanied by an increase in the hemorrhagic transformation risk (especially of PH- 2 type in the ECASS II study) and poor clinical outcome [11]. The multicenter analysis of 1205 patients routinely treated by intravenous tPA within 3 h shows that the symptomatic HT rate is multiplied by more than 4 in patients with early signs in >1/3 of the MCA territory [47]. In the MAST-E study, the presence of early signs was also a strong predictor of hemorrhagic transformation and symptomatic ICH [29]. In contrast, other thrombolysis studies have shown that the presence of early signs was related to stroke severity but was not independently associated with the occurrence of side effects [14, 15]. The ASK (Australian Streptokinase Trial) study, evaluating treatment with intravenous streptokinase within the first 4 h of ischemic stroke, did not show a significant association between the presence of early signs and the occurrence of a major PH.

Hyperdense middle cerebral artery sign. It has been shown that the presence of an arterial hyperdensity on the pre-therapeutic brain CT scan is an independent predictive factor of any tPA related to HT [46]. It was previously demonstrated that this sign was frequently observed in patients developing an asymptomatic HT after thrombolysis by intravenous tPA within the first 3 h. In other study, the presence of an arterial hyperdensity on brain CT scan is associated with MCA or internal carotid artery occlusion in most cases and with a specific MRI pattern consisting of a large pretreatment diffusion and perfusion abnormality volume [48]. The presence of a proximal arterial hyperdensity, as the severity of perfusion reduction suggests, is probably associated with a limited collateral blood supply. The maximal haemodynamic consequence lies in the territory of the perforating lenticulostriate arteries and the severity of the ischemic injury in this territory probably induces the hemorrhagic transformation [14].

Leukoaraiosis (LA). Originally noted as diffuse, nonspecific subcortical white matter lesions on CT, leukoaraiosis is a common finding among patients with ischemic stroke and has been associated with poor post-stroke outcomes as well as increased risk for HT [51-52]. LA represents cerebral white matter changes that are frequently observed on CT and MRI scans of elderly individuals, are seen as bilateral, patchy, or diffuse areas of hypodensity on CT involving the periventricular and centrum semiovale white matter. These lesions have irregular margins and do not follow specific vascular territories [53].

The largest visual scales used for assessment of LA on CT are: 1) Van Swieten et al., (score 0-4). The severity of LA is graded separately for the regions anterior and posterior to the central sulcus added together: 0 – no lesion, 1 – partial involvement of the white matter, and 2 – extending up to the subcortical region [54]. 2) Blennow et al., (score 0-3). The final score is the mean value between the extension and severity scores. Extent of LA: 0 – no decrease in the attenuation of white matter; 1-decreased attenuation of white matter at the margins at the frontal and occipital horns of the lateral ventricles; 2-decreased attenuation of white matter around the frontal and occipital horns of the lateral ventricles with some extension toward the centrum semiovale; and 3-decreased attenuation of white matter extending around the whole lateral ventricles and coalescing in the centrum semiovale. Severity of LA: 0-none, 1-mild, 2-moderate, and 3-marked decrease in the attenuation of white matter [55].

A recent retrospective multicenter study showed, that leukoaraiosis is a risk factor for symptomatic HT in 449 patients

treated with thrombolysis for anterior circulation stroke less than 6 h after symptom onset [49]. For the analysis, leukoaraiosis in the deep white matter was dichotomized into absent or mild versus moderate or severe. The rate of symptomatic HT was significantly higher in patients with moderate to severe leukoaraiosis of the deep white matter (n = 12 of 114; 10.5%) than in patients without relevant leukoaraiosis (n=13 of 335; 3.8%). In a logistic regression analysis (including age, NIHSS score on admission and type of thrombolytic treatment), leukoaraiosis remained an independent risk factor (p = 0.03). Other large study of 1,153 consecutive patients with imaging-confirmed ischemic stroke concluded, that presence of coexisting severe leukoaraiosis predicts poor functional 90-day outcome (modified Rankin Scale) in patients with acute intracranial large artery occlusion in anterior circulation independent of other known important outcome predictors (70% of patients in this subgroup were either severely disabled or died at 90 days) [50].

Computed Tomography Angiography (CTA). CTA provides excellent imaging of intra- and extra-cranial vasculature, which is essential in diagnosis of every type of cerebrovascular disease, especially acute ischemic stroke. Recent studies show that CTA is a safe and accurate technique for imaging most extracranial and intracranial vessels for stenosis/occlusions with the sensitivity and specificity equal to or superior to that of MRA (Magnetic Resonance Angiography) in most circumstances, and in some cases, its overall accuracy approaches or exceeds that of DSA [56, 57]. For the acute stroke patient, vascular imaging plays several roles: 1) differentiation of real occlusion from transient ischemic attack, or other cerebrovascular disease and establishing the mechanism of ischemia to prevent subsequent episodes, 2) visualization of the localization of the site of vascular occlusion, extent and morphology of thrombus, 3) assessment of collaterals status and 4) analysis of cerebral parenchyma on CTA source images (CTA-SI).

A recent retrospective multi-center study of 263 patients showed, that the quantification of intracranial thrombus extent predicts functional outcome, final infarct size and risk of HT [58]. This study group developed the clot burden score (CBS) -a semiquantitative CTA grading system in acute anterior circulation ischemic stroke to quantify the extent of ipsilateral intracranial thrombus, allotting major arteries 10 points for the presence of contrast opacification on CTA. 2 points each were subtracted for absence of contrast opacification in the complete cross-section of any part of the proximal M1 segment, distal M1 segment or supraclinoid ICA and 1 point each for M2 branches, A1 segment and infraclinoid ICA (Fig 5, A). A score of 10 indicates absence of a visible occlusion on CTA, a score of 0 indicates occlusion of all major intracranial anterior circulation arteries. Study group found, that patients with lower CBS were more likely to have hemorrhagic infarct transformation (P = 0,003) and parenchymal hematoma (P = 0,008) on follow-up scans [58].

Collateral flow. Next extremely important CTA parameter is the development grade of **collateralls** in the infarcted hemisphere (fig. 5, B, C, D)**.** The presence of robust collateral flow is associated with rapid recanalization in acute ischemic stroke and reduction of infarct size [60]. The PROACT II trial investigators semiquantitatively analyzed pial collateral formation on angiography and categorized them as full, partial, or none and found that presence of good collaterals influences NIHSS score at initial presentation, infarct volume and HT rate on 24-hour CT scan in patients with MCA occlusion. The presence of collaterals has also been associated with better outcomes, reduced infarct size, and faster recanalization [15]. In the study Lin K. et al., 2012, the CTA collateral score was graded using a 4-point scale from 0 to 3 ("0"–absent collateral supply; "1"– collateral supply filling >0 but ≤ 50%; "2"– collateral supply filling >50 but <100%; and "3"– collateral supply filling 100% of the occluded MCA territory compared to the contralateral side) and compared with HT rate. Data analysis revealed significant associations between symptomatic HT and proximal occlusion (p = 0.049) and collateral score (p = 0.017) [59].

Computed tomography angiogram-source images (CTA-SI). The source images of the brain during CTA acquisition make a focus of hypoperfusion much more detectable than does the NCCT (Fig 6). Lev et al., [32] demonstrated the very high correlation between size of the infarct on CTA-SI and that which was demonstrated on follow-up CT studies. Hypoattenuation on brain CTA source images is attributable to early ischemic edema and a diminished con-

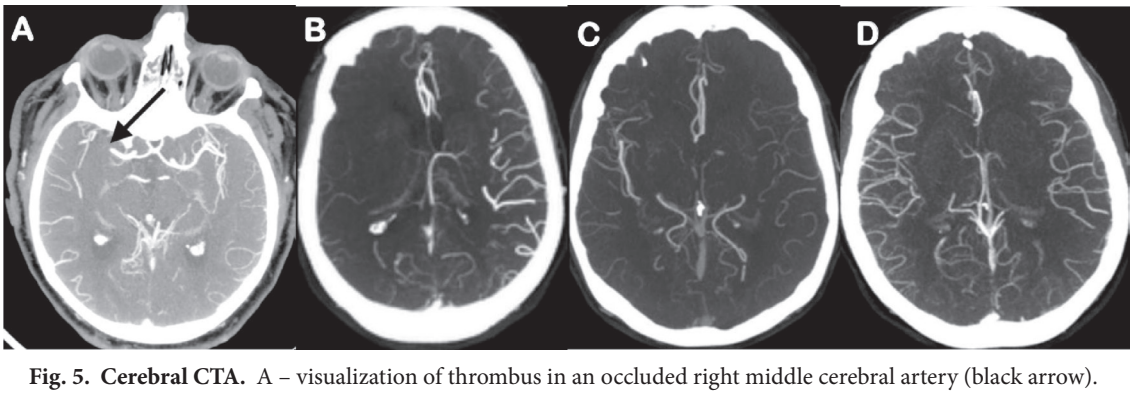

Fig. 5. Cerebral CTA. A – visualization of thrombus in an occluded right middle cerebral artery (black arrow). 3 grades of collaterals development: B – poor collaterals in right ischemic hemisphere, C – intermediate collaterals in the left MCA territory, D – good collaterals in left MCA ischemic circulation.

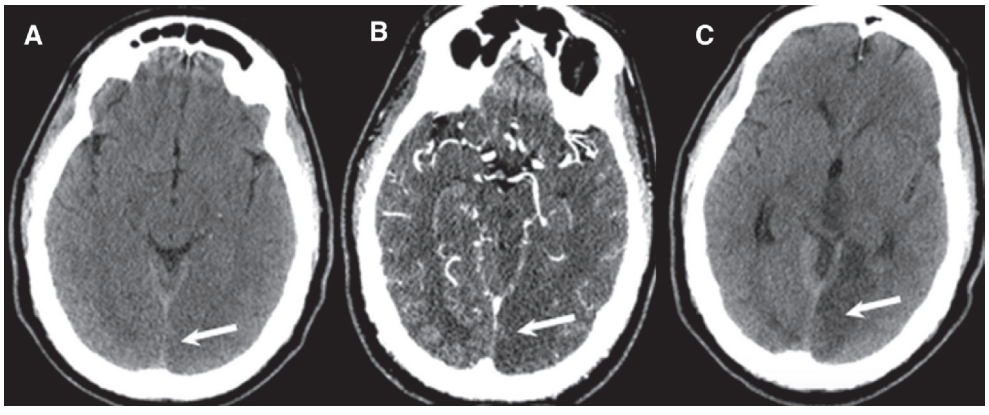

Fig. 6. Hyper-acute ischemic stroke in the left posterior cerebral artery circulation territory (arrow). A – NCCT, very difficult detectable early CT signs of ischemic lesion. B – CTA-SI, clearly detectable hypo-attenuation zone in the projection of left occipital lobe. C – follow up CT in subacute phase, confirming CTA-SI findings.

trast agent–exchanging blood pool. Results of pilot studies have suggested that hypoattenuation on CTA source images delineates ischemic tissue likely to be irreversibly infarcted and that lesion volume is seen on CTA source images. Focal hypoattenuation on CTA source images may reflect a profound degree of ischemia- induced endothelial injury with increased risk of reperfusion hemorrhage or inadequate leptomeningeal collateral blood flow. Data suggested that axial source images provide a visually detectable threshold of hypoattenuation without post-processing that is a powerful independent predictor of both HT and poor outcome [61]. Regions of abnormality on the NCCT usually cannot be segmented prospectively because of their ill-defined borders; areas of abnormality are more conspicuous on CTA source images. ASPECTS calculated on the CTA-SI have shown that CTA-SI is better at depicting early ischemic change than NCCT and therefore offers a more accurate score [59]. Investigators found that threshold at ASPECTS ≤5 on CTA-SI had high sensitivity (75.0%) and specificity (85.5%) for symptomatic HT [59]. Comparing CTA-SI and NCCT images Aviv et al., found that CTA-SI improved trainee accuracy by 9%, but had little impact on more experienced readers. The accuracy and sensitivity of stroke extent assessment was increased for all readers, but was greatest for the trainee (17% and 12%, respectively). Clinical history contributed little to CTA-SI accuracy. Observer resolution was higher for CTA-SI. NCCT could have resulted in the misclassification of more patients than CTA-SI [62].

Computed Tomography Perfusion (CTP). CT perfusion imaging uses dynamic contrast- enhanced data to produce parametric color overlay maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to local peak enhancement (TTP) (fig. 7). These standard perfusion metrics are used to detect an acute ischemic stroke and the presence of "penumbra," the hypoperfused but potentially salvageable tissue at risk of infarction [63-65]. CTP, can not only provide the diagnostic information about ischemic region, but and the functional brain data about blood-brain barrier (BBB) physiology, especially its permeability. HT is generally thought to arise from ischemic damage to the blood-brain barrier (BBB), expressed in elevated permeability. Microvascular permeability (expressed as the transendothelial transfer of constant or permeability surface area product [PS]) is a metric of BBB integrity. Increased blood–brain barrier permeability, one of the pathological changes following ischemic stroke, is believed to predispose to complications such as hemorrhagic transformation [79], massive vasogenic edema, infarct expansion [80] and poor clinical outcome [81, 78]. Like the standard perfusion metrics, PS can also be calculated using dynamic imaging by measuring the leakage of an intravascular tracer (contrast agent) into the extravascular (interstitial) space [66, 67]. BBB permeability imaging provides a physiologic individualized measurement intimately connected to the underlying pathophysiology of PH-2 (ischemia-induced vascular damage followed by reperfusion) and may, therefore, offer excellent sensitivity and specificity (fig. 8).

Recent study [68] showed, that there was complete separation of PS in HT group and PS and in non-HT group measurements; any PS between 6.0 and 9.8 mL/100 mg per minute can be used as a threshold value to predict HT with a sensitivity and specificity of 100%. Investigators showed that elevated PS can be detected during hyper-acute period using first-pass dynamic CT data. Patients with high PS who were not treated with recombinant tissue plasminogen activator (rtPA) tended to develop smaller petechial hemorrhagic infarctions that were asymptomatic. Christopher D. d'Esterre (2013) demonstrated, that the patients with HT had a significantly higher PS than did those without haemorrhage. A PS threshold of 0.23 $ml^{-1} \bullet min^{-1} \bullet (100g)^{-1}$ also enabled the differentiation of patients with HT from those without [69]. Results showed that besides the PS parameter and ASPECT score, no other factors (age, sex, or baseline NIHSS score) were associated with HT. Hom J et al., investigated the opportunities of perfusion CT in prediction of HT and malignant edema in patients with acute ischemic stroke [76]. They reported that using admission BBB perfusion imaging above a volume threshold as the sole predictor yields a sen-

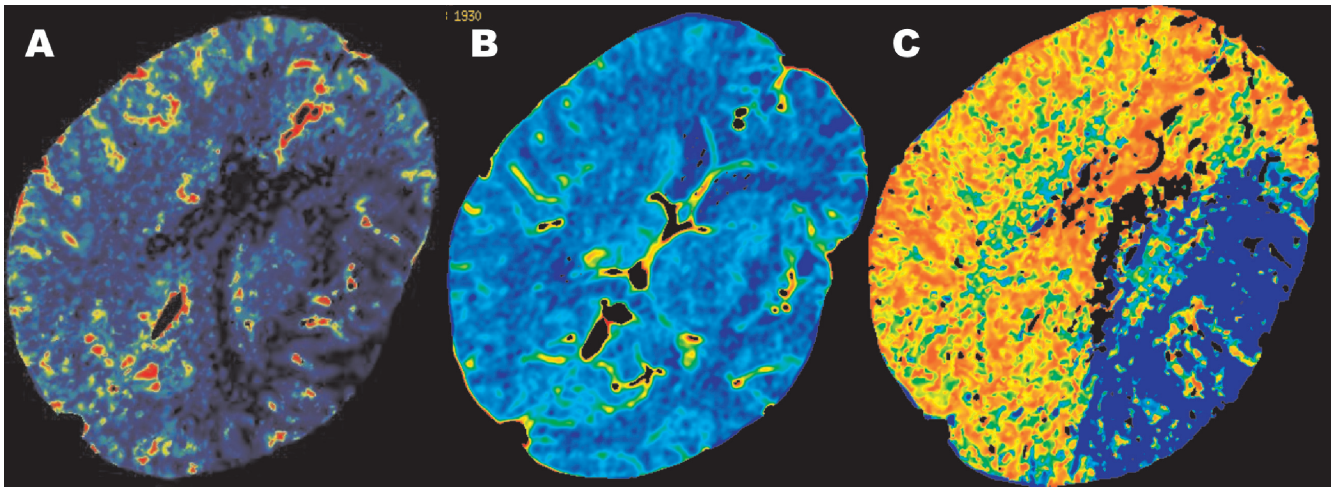

Fig. 7. Female, 84 years, acute (1 hour from the symptoms onset) ischemic stroke in left middle cerebral artery circulation territory. Standard CT perfusion maps. A – CBF. B – CBV. C – MTT.

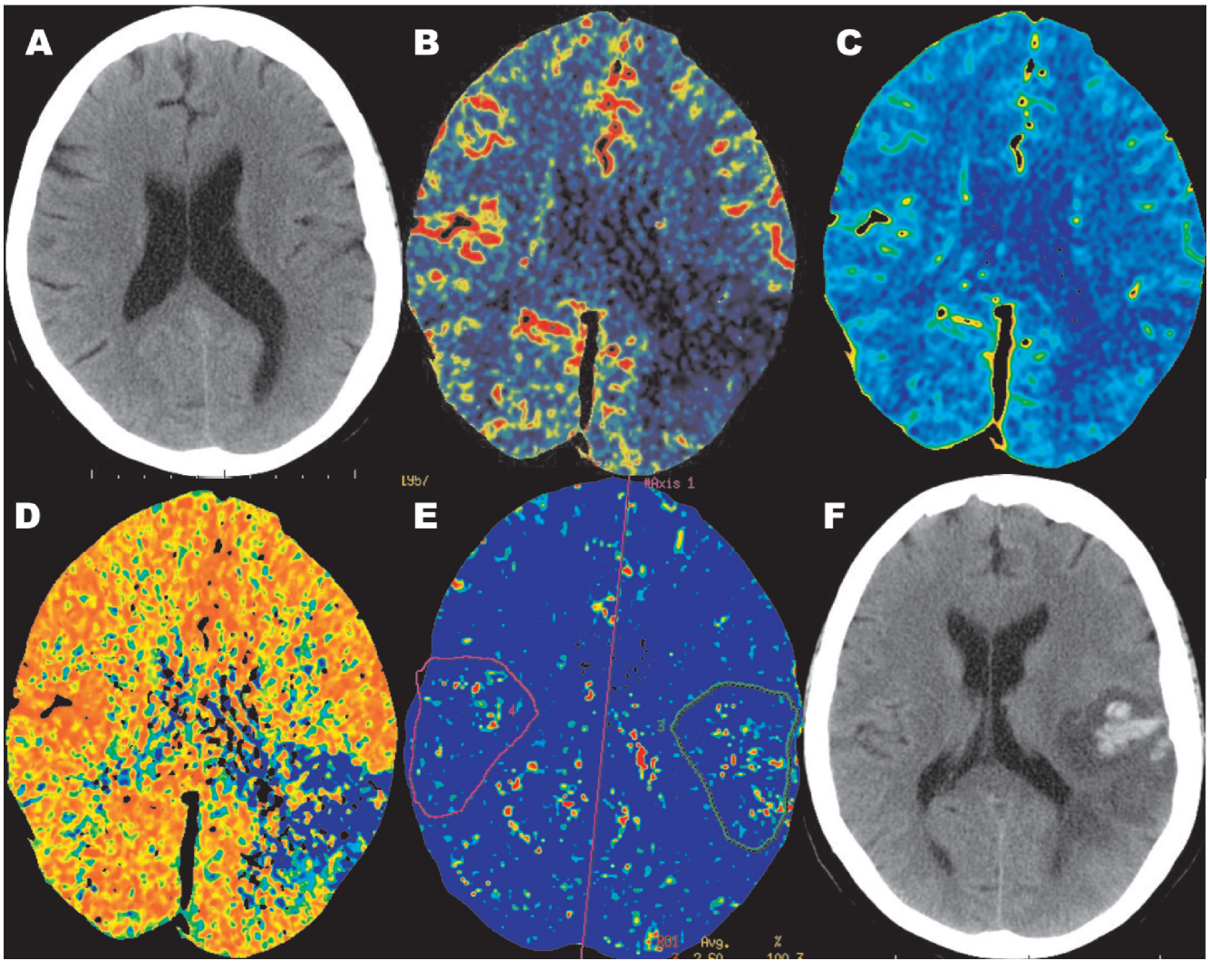

Fig. 8. Female, 57 years, acute (2 hour from the symptoms onset) ischemic stroke in left middle cerebral artery circulation territory. CT perfusion functional maps. A – non-contrast CT, there is no evidence of abnormalities, B – CBF, C – CBV, D – MTT, E – permeability surface area product (PS), F – non-contrast CT 26 hours after symptoms onset, hemorrhagic transformation, parenchymatous hematoma type 2.

sitivity of 100% and specificity of 79% (5 false-positives from 32). Reperfusion was a statistically significant predictor of SHT in the univariate analysis, but the reperfusion scores in patients with SHT were lower than those in other patients, not higher as we would have expected on the basis of the role of reperfusion in SHT [77].

Other (not PS) functional Perfusion CT parameters were studied to determine their correlation with HT and results failed to show any difference with statistical importance, with only exception for the relative cerebral blood volume (rCBV) map. Patients with HT had higher median total volume at risk of ischemia, longer median relative mean transit time (rMTT), and lower median relative cerebral blood flow (rCBF) compared with controls, though this did not reach statistical significance. Cases with HT did have a significantly lower median rCBV compared with controls (p = 0.01). For each 0.1-U decrease in rCBV, the odds of developing an HT increases by 14% [70]. Prediction of HT by reduced pretherapeutic CBF, an inherent characteristic of the stroke itself, was first suggested by Ueda et al., by using SPECT [71]. A reduction in CBF to <50% of normal was considered as the critical value for developing HT [72]. Gupta et al., in their study of 23 patients with symptomatic stroke or carotid stenosis concluded that mean ipsilateral CBF <13 mL/100 g per minute was the cutoff for developing HT [73]. They found that rCBV rather than rCBF was the strongest predictor of HT. This is similar to reports of rCBV (rather than rCBF) being a stronger predictor of penumbra viability in patients with acute ischemic stroke [74], with similar [75] or even lower [59] values reported by authors for rCBV in patients with HT. In other words, indicators of penumbra viability may also indirectly predict HT, which would be expected to occur more frequently in infarcted core rather than salvageable penumbra regions. Jain et al., found that a cutoff rCBV of at least 0.98 could predict development of HT in patients with AIS with 72% specificity [70].

Multimodality Computed Tomography. Different CT modalities showed different accuracy in prediction of hemorrhagic transformation, but most of studies reported better sensitivity and specificity for the Perfusion CT. Darius G. Nabavi et al., published a novel imaging CT algorithm using all 3 CT methods and developed a new scoring system – MOSAIC: Multimodal Stroke Assessment Using Computed Tomography [82]. With 3 main CT modalities (NCCT, CTA, PCT), profound knowledge about brain anatomy, vessel status, and tissue hemodynamics can be acquired in acute stroke patients within several minutes. The calculation is made by adding scores from every CT modality: 1) Early signs of infarction on NCCT: 0 = No infarction signs, 1 = 1–3 ASPECTS regions infarcted, 2 = >4 ASPECTS regions infarcted. 2) Ipsilateral pathology on CTA: 0= Normal or stenosis <50%, 1= ICA/MCA stenosis >50%, 2= ICA/MCA occlusion. 3) PCT_{CBF} slice-1: 0 = No perfusion deficit, 1= Perfusion deficit <20%, 2= Perfusion deficit > 20%. 4) PCT_{CBF} slice-2: 0= No perfusion deficit, 1= Perfusion deficit <20%, 2= Perfusion deficit >20%. The range of possible points consists from 0 to 8, with the lowest MOSAIC score of 0 representing normal findings in all 3 modalities. Linear regression analysis between CT results and outcome measures revealed consistent differences among the 4 CT components for all target parameters: of the 3 single CT components, the ASPECTS score on NCCT showed the lowest correlation coefficients (r =0.42 to 0.58), whereas PCT_{CBF} consistently showed the highest values (r =0.52 to 0.75) with respect to clinical status and infarction size. With respect to the correlation coefficients on linear regression analysis, MOSAIC was superior to all single CT components (r=0.59 to 0.78): sensitivity values were the lowest for NCCT (58.9%), followed by CTA (66.7%) and PCT_{CBF} (71.8%), whereas the MOSAIC score showed the highest values (87.1%); the specificity with respect to occurrence of infarction was 100% for all parameters. The combination of 3 CT modalities was superior to all single CT components with respect to the various outcome measures and showed a strong correlation to the size of infarction (r=0.78) [82].

Conclusions

Hemorrhagic transformation (HT), which refers to a spectrum of ischemia-related brain hemorrhage, is a frequent spontaneous complication of ischemic stroke and still represents the most feared complication. HT is a complex and multifactorial phenomenon and it is important to understand its underlying mechanism and identify its predictors. Different CT modalities are largely used worldwide for the ischemic stroke diagnosis and evaluation of their possibilities in HT prediction has been intensely studied in recent years. Non-contrast CT standard investigation showed high sensitivity and specificity values in assessment of early ischemic signs (dense MCA, loss of basal ganglia outline, loss of insular ribbon, hypodensity, effacement of sulci or ventricles, dense cortical sulci, loss of gray and white matter differentiation) in correlation with HT prediction. The most useful methods in HT prediction on CT were reported to be low The Alberta Stroke Program Early CT score (ASPECTS), presence of dense MCA, leukoaraiosis and early CT signs in 1/3 of middle cerebral artery territory. Another application of NCCT in relation to HT – is timely diagnosis and classification of its various types (hemorrhagic infarction type 1 and 2, parenchymal hematoma type 1 and 2) and dynamics of low-up. Next CT modality is Angiography, which showed the potential in HT prediction by the assessment of the collateral flow grade; presence, localization and extent of intra-arterial occlusion and ASPECTS score calculated from the ACT source images. Last CT modality is dynamic functional Perfusion imaging, which includes large spectrum of quantitative parameters (cerebral blood flow, cerebral blood volume, mean transit time, time to peak enhancement and permeability surface area product). Microvascular permeability (expressed as the transendothelial transfer of constant agent) expressed in color PS (permeability surface) map calculated from the Perfusion CT data showed the best results in HT prediction. The combination of 3 CT modalities

(MOSAIC scoring system: Multimodal Stroke Assessment Using Computed Tomography) was superior to all single CT components and showed a strong correlation to the size of infarction, clinical outcome and HT prediction.

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