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DIAGNOSIS AND EARLY PROGNOSIS OF ACUTE ISCHEMIC STROKE EVOLUTION

312.02 - NEUROSCIENCES

Summary of the doctoral thesis in medical sciences

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The thesis was elaborated at the Department of Neurology no. 1 of the Public Institution State University of Medicine and Pharmacy "Nicolae Testemitanu" and the Public Medical Institute of Neurology and Neurosurgery Institute "Diomid Gherman"

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CONTENT

INTRODUCTION

Actuality and importance of the research problem. Stroke is the second leading cause of death in the 60+ age group, the fifth leading cause of death in the 15-59 age group, and the leading cause of permanent disability in adults in industrialized countries worldwide [1, 2, 3]. Acute ischemic stroke (AIS) accounts for about 85-90% of all strokes, about 10% are intracranial hemorrhages, and about 3% are strokes with subarachnoid hemorrhage. Posterior AIS represents 18-20% of all acute ischemic strokes [1, 2, 4, 5, 6]. Over 70% of stroke survivors and over 50% of stroke deaths are attributed to acute brain ischemia [6].

Thanks to the advantages (availability, speed and ability to present intracranial hemorrhage) that CT, compared to other imaging investigations, offers for the examination of stroke patients, a comprehensive three-component imaging protocol was developed – NCCT (non-contrast computed tomography), followed by ACT (angiography computed tomography) and PCT (perfusion computed tomography). Multimodal CT imaging in acute stroke can provide all the necessary information about the anatomy of the brain, the state of the cerebral vessels, the characteristics of the thrombus and the cerebral tissue hemodynamics before the administration of reperfusion treatment, thus avoiding an additional imaging study [3, 7].

Predicting long-term clinical outcomes in AIS is important, but it is not easy when we rely solely on patient symptoms, clinical signs, and NCCT. The results of recently published investigations on dynamic Perfusion CT exam found the feasibility and perspective of this method for rapid assessment of patients with AIS. PCT imaging, being a faster, accessible, more widely available diagnostic tool, relatively inexpensive and with proven benefits, offers practical advantages. PCT provides important parameters that significantly increase the accuracy of stroke diagnosis, regardless of the location (anterior or posterior circulation), predict disease outcome, present information on the blood–brain barrier (BBB) permeability and Hemorrhagic transformation (HT) riak, allow correct selection of patients for reperfusion treatment [7].

The aim of the research was to determine the possibilities of computed tomography perfusion examination in establishing early diagnosis and prognosis of patients with clinical-anamnestic data suggestive of acute ischemic stroke.

In order to achieve the goal, the following exploration **objectives** were stipulated:

1. Study of the parameters of cerebral perfusion by CT in patients with acute ischemic stroke during the therapeutic window and up to 24 hours after the onset of clinical manifestations.
2. Analysis of the correlation between Perfusion CT indices and the volume of cerebral infarction determined by native CT with respect to clinical manifestations and result at discharge in patients with acute ischemic stroke.
3. To identify imaging changes susceptible to the haemorrhagic transformation risk of stroke and to study the change in blood–brain barrier permeability in patients with acute ischemic stroke examined by Perfusion CT.
4. Evaluation of the accuracy of Perfusion CT indices in acute ischemic stroke at admision and in the subacute phase in correlation with clinical-anamnestic data and functional outcome in patients with significant internal carotid artery stenosis.
5. Analysis of cerebral microcirculation parameters in different evolutionary phases of acute ischemic stroke by Perfusion CT in follow-up.

The general methodology of the research was developed based on the publications of local [8, 9] and abroad [4, 10] authors. For the research and solution of the problems addressed

in the thesis we used the methods: analytical epidemiology, history, clinical, anamnestic, paraclinical, statistical, mathematical, monitoring and evaluation.

The research is a prospective controlled clinical study that includes analysis of methods of emergency clinical diagnosis, non-contrast computed tomography and perfusion by computed tomography in patients with acute ischemic stroke. The main clinical-anamnestic indicators were compared prospectively and the model of the risk of HT of the cerebral infarction core was determined.

The research was performed in the clinical departments and the imaging department of the Public Medico-Sanitary Institution Institute of Neurology and Neurosurgery "Diomid Gherman". Brain CT imaging was performed and analyzed by the author, a neuroradiologist with 12 years of experience, including 8 years in stroke imaging.

Scientific innovation of the obtained results.

1. For the first time in the Republic of Moldova, were determined the emergency indications for performing the CT Perfusion examination in patients with acute ischemic stroke, which have exceeded the therapeutic window with clinical application of the method.
2. For the first time, imaging factors susceptible to predict the risk of hemorrhagic transformation of cerebral ischemic infarction have been identified, not only in the blood-brain barrier permeability map, but also in other pathophysiological parameters (MTT-mean transit time, PEI-positive enhancement integral, MSI - mean slope of increase).
3. Based on the evaluation of the imaging parameters in correlation with the clinical manifestations, the volume of the ischemic parenchymal lesion was predicted and imaging factors with prognostic value for the clinical outcome at discharge were highlighted. The “benign” evolution of CT Perfusion parametres in patients with acute ischemic stroke and significant internal carotid artery stenosis has been demonstrated for the first time.
4. For the first time worldwide, “non-standard” parameters of cerebral microcirculation (MTT-mean transit time, PEI- positive enhancement integral, MSI- mean slope of increase) were analyzed together with basic perfusion indices in the area of ischemia. - 233 quantitative parameters.
5. The relative and absolute perfusion values outside the ischemic area (in the whole affected hemisphere, infra / supratentorial areas analyzed as a whole) were analyzed in order to predict the risk of hemorrhagic transformation, assessment of correlations with clinical outcome, highlighting differences in macro- and microcirculation in patients with and without severe carotid stenosis in different stages of acute ischemic stroke (being a possible factor in the phenomenon of cerebral ischemic preconditioning). Very few studies have analyzed absolute perfusion values, most use only relative values (% of healthy hemisphere).
6. The method of calculating the volume of lesions according to the brain areas in the ASPECTS (Alberta Stroke Program Early Computed Tomography Score) region and the whole brain method were developed. Within the research project, a new method of analysis of radiological investigations was developed - "Standard radiological report for the description of ischemic stroke in MRI or CT". New methods were approved at the meeting of the Department of Radiology and Imaging, have been received Certificates of Innovator, Implementation Acts, Certificates of Copyright AGEPI.
7. For the first time, 4 types of micro-circulation in the cerebral parenchyma have been identified, which develop in different proportions and combinations in the subacute phase of acute ischemic stroke: 1) the final lesion (perfusion values correspond to the infarct core), 2) moderate hypoperfusion or cerebral hibernation (perfusion values correspond to persistent

hypoperfusion), 3) hyperperfusion, 4) normal perfusion. Penumbra areas persist in the regions adjacent to the final lesion: in Control CT perfusion were significantly more common and their volume was higher in patients with internal carotid artery stenosis ≥70%, compared to patients without stenosis (for the affected vascular pelvis .06 ± 3.0% and 7.84 ± 1.6%, respectively; p = 0.039 and for the whole brain - whole brain score - 19.39 ± 4.4% and 10.06 ± 1.9%, respectively; p = 0.028).

8. We have identified that the deterioration of the blood-brain barrier correlates statistically significantly with the clinical outcome at discharge, especially with the risk of death and the unfavorable mRS score. This is characteristic not only for one parameter, but for all indices measured in the permeability of the blood-brain barrier - absolute (ml / 100g / min) and relative (% versus healthy hemisphere) perfusion map PS (Permeability Surface) in the penumbra and throughout the hemisphere affected, regardless of the presence of the hemorrhagic transformation. Thus, not only the hemorrhagic transformation contributed to the impairment of the clinical condition, but also the deterioration of the blood-brain barrier on its own, which can be easily calculated by CT Perfusion from the first hours of cerebral arterial occlusion.

For future medical practice, these data may contribute to the more active development and application of possible blood-brain barrier protection or stabilizing agents with the potential to reduce mortality or deep functional neurological deficit, and not only by reducing the hemorrhagic transformation rate of stroke, but also by preventing other pathological molecular pathways in the blood-brain barrier.

The applicative significance of the study. Perfusion CT provides important parameters that significantly increase the accuracy of acute ischemic stroke diagnosis, regardless of the location (anterior or posterior circulation), predicts disease outcome, presents information about blood-brain barrier permeability and hemorrhagic transformation risc, allows correct selection of patients for reperfusion treatment.

Approval of research results. The results of the study were presented and discussed in the following national and international scientific forums: 3rd Congress of the European Academy of Neurology. June 24-27, 2017, Netherlands Amsterdam, The Netherlands; Scientific-practical neurological conference on "Topics in contemporary minimally invasive treatment in Neurology and Neurosurgery". July 14, 2017, Chisinau, Republic of Moldova; VI Congress of Neurologists and Neurosurgeons of the Republic of Moldova. October 2-5, 2017, Chisinau, Republic of Moldova; Scientific Conference of Radiologists of the Republic of Moldova "Contemporary Imaging Techniques and Interventional Radiology". November 10, 2017, Chisinau, Republic of Moldova; The regional conference entitled “Stroke. Staged neurological and neurosurgical treatment”. February 28, 2018, Chisinau, Republic of Moldova; Days of the State University of Medicine and Pharmacy "Nicolae Testemitanu" and the Annual Scientific Conference. October 15-19, 2018, Chisinau, Republic of Moldova; International Symposium on Cerebrovascular Pathology. November 27-30, 2019, Chisinau, Republic of Moldova; Medespera 2018 - the 7th International Congress for students and young doctors. May 3-5, 2018, Chisinau, Republic of Moldova.

During the research have been developed new methods for radiology exams analysis "Score whole brain" and "Standard radiological report for the description of ischemic stroke in MRI or CT" and approved at the meeting of the Department of Radiology and Imaging - 2 methods (excerpt No. 9 of 4.11.2021).

Innovator Certificates – No. 5 of 4.11.2021: No. 16/11.21/01 "Standard Radiological Report for the Description of Ischemic Stroke in Imaging Magnetic Resonance Imaging or

Computed Tomography", No. 16/11.21/02 "Permeability Surface area product in Computed Tomography Neuroperfusion", No. 16/11.21/03 "Whole brain score. Analysis of cerebral arterial areas of vascularization in sectional imaging", No. 16/11.21/04 "CT Neuroperfusion: Dynamic Imaging Investigation of Patients with Acute Ischemic Stroke ", No. 16/11.21/05 "Tissue Classification - automatic method of dynamic imaging data post-processing in Perfusion CT"

Acts of implementation - No. 10 (No. 01-08/387 of 28.08.2019 INN, No. 01-08/388 of 28.08.2019 INN, No. 01-08/386 of 28.08.2019 INN, No. 01-08/408 of 12.10.2021 INN, No. 01-08/407 of 12.10.2021 INN, No. 1000-21 of 13.10.2021, No. 1001-21 of 13.10.2021, No. 1002-21 of 13.10.2021, No. 1003-21 of 13.10 .2021, No. 1004-21 of 13.10.2021).

AGEPI (The State Agency on Intellectual Property) Copyright Certificate – No. 4 certificates (No.1874 /O / 7096, 1876/ O/ 7098, 1877/ O/ 7099, 1878 / O/ 7100).

Keywords: acute ischemic stroke, computed tomography, hemorrhagic transformation, ischemic preconditioning, penumbra, core.

Approval of the Research Ethics Committee for the study - Protocol no. 60 on no. 55 from 03.06.2016.

1. ACUTE ISCHEMIC STROKE - DIAGNOSIS AND PROGNOSIS

1.1. Perfusion computed tomography in acute stroke management

Computed Tomography (CT) imaging in acute stroke consists of three protocols - non-contrast CT, followed by CT Angiography (CTA) and Perfusion CT (PCT) - which provide sufficient information about the anatomy of the brain, the cerebral vessels and tissue hemodynamics [7]. Non-contrast CT is used to differentiate hemorrhagic stroke from ischemic stroke, to detect stroke-mimicking conditions, to assess early signs of ischemia and thrombus characteristics, and limits of stroke core. Non-contrast CT is followed by CTA, used to determine the exact location and extent of arterial occlusion, finding proximal occlusions of large vessels that may be suitable for intra-arterial thrombolysis or endovascular thrombectomy, identification of collateral blood circulation. PCT, a method that increases especially the imaging sensitivity in the early stages of acute ischemic stroke, is applied to assess the extent and severity of hypoperfusion, to differentiate potentially salvageble brain tissue (penumbra) from irreversibly damaged brain tissue (infarction core), to select and initiate reperfusion treatment – IVT (intravenouss thrombolisis) and / or ET (endovascular treatment), based on patient-specific data from physiological images and not on an arbitrary time interval. Post-treatment CT and PCT are used to rule out HT, including caused by reperfusion therapy [3, 7].

1.2. Hemorrhagic transformation in patients with acute ischemic stroke

The HT (hemorrhagic transformation) rates of acute ischemic stroke differ greatly between studies, but in general, more than half of all strokes at one time develop a hemorrhagic component. In clinical trials, the incidence rate of HT in acute ischemic stroke was 2.2-68.0% [5, 11, 12] depending on various factors: rates of selected patients, time of initiation of treatment, thrombolytic agent used, and route of administration, definition of hemorrhagic transformation and the follow-up period [12].

The ongoing effort to determine hemorrhagic transformation predictors in patients with acute ischemic stroke found a set of clinical factors needed to be correlated with imaging examination indices. The higher severity of acute ischemic stroke (NIHSS score), the location and the larger size of the stroke area, especially the massive cerebral infarction, are the factors that best correlate with HT. Decreased ASPECTS (Alberta Stroke Program Early Computed Tomography Score), increased time from stroke to reperfusion treatment, increased BBB

permeability on Perfusion CT, poor collateral performance, anticoagulant or antiplatelet therapy, reperfusion treatment (IVT and / or ET), diabetes mellitus, atrial fibrillation, and cerebral embolism, a range of serum biomarkers (low total cholesterol, low-density lipoprotein and platelet counts, elevated blood glucose levels, matrix metalloproteinases 9 and globulins) and advanced age are associated with an increased risk of HT [5, 7, 11, 12].

1.3. Ischemic conditioning in patients with acute ischemic stroke

Ischemic conditioning, also known as ischemic tolerance, is a robust neuroprotective phenomenon that involves the repeated application of a short, transient episode of non-lethal cellular ischemia followed by reperfusion. By regulating endogenous protective mechanisms, it increases tissue resistance and global neuroprotection. Thus, the pathophysiological consequences are attenuated in the affected tissue and the overall extent of the subsequent more severe lesion of ischemia and / or reperfusion is reduced [1, 8, 9, 13].

The concept of ischemic conditioning includes ischemic **pre-conditioning** (until the development of ischemia), ischemic **per-conditioning** (during the ischemic event, until confirmation of the final diagnosis of acute ischemic stroke and reperfusion treatment) and ischemic **post-conditioning** (after ischemia or during reperfusion) [1, 6, 14, 15].

Experimental animal studies have clearly defined and confirmed the efficacy of neuroprotection by ischemic conditioning (ischemic preconditioning, ischemic per-conditioning and ischemic post-conditioning) after focal or global ischemic stroke. Although there is little evidence to support the existence of ischemic conditioning in human stroke, clinical trials in humans have confirmed the effectiveness of ischemic conditioning in acute ischemic stroke [1]. Both studies found a significant reduction in the size of the infarct core, cerebral edema and neurological dysfunction [14, 15], prevention of neuronal apoptosis and recurrent stroke, preservation of BBB integrity, increased recovery rate in patients with intracranial arterial stenosis [1, 13].

2. STUDY MATERIAL AND METHODS

2.1. General features of the research

In order to achieve the purpose and objectives of the research, we made a prospective controlled non-randomized clinical trial study that includes the analysis of emergency diagnostic methods (neurological, imaging, Perfusion CT) and the prediction of the evolution of pathology in patients with acute ischemic stroke. We prospectively compared the main indicators and determined the spectrum of CT imaging factors, susceptible to the early prediction of the haemorrhagic transformation (HT) of the infarction core. We analyzed perfusion parameters in correlation with pre-existing HT and cerebral IPC (ischemic preconditioning) in patients with significant carotid stenosis.

The onset of acute ischemic wake-up stroke was estimated as the average point of sleep duration (the time between the time patient went to bed and the time of waking up with symptoms). Acute ischemic stroke with unknown onset has been reported in patients who have been seen without pathology for less than 24 hours until the onset of clinical manifestations.

After confirming eligibility and obtaining informed consent, until the initiation of the investigation, the patients included in the study or their legal representative were fully informed of the purpose of the study, the clinical requirements, the benefits and risks of the investigations and the treatment administered.

The study protocol was approved by the Ethics Committee of the "Nicolae Testemitanu" State University of Medicine and Pharmacy - Protocol no. 60 on no. 55 from 03.06.2016.

The study included 100 patients with acute ischemic stroke: 54 (54.0%) men and 46 (46.0%) women with a mean age of 67.05 ± 1.09 years (from 21 years to 91 years old). From the urban area came 57 (57.0%) patients and from the rural area 43 (43.0%) patients. About ¾ (75 - 75.0%) of the patients had a certain degree of disability or were retired, 20 (20.0%) of the patients were employed and 5 (5.0%) patients had a stable occupation.

2.2. Investigation methods

All patients included in the study were examined in accordance with the National Clinical Protocol "Ischemic Stroke" and the institutional Stroke Protocol, which included the following research methods:

1. General clinical research methods with the following variables: age, sex, medical history, concomitant pathologies, known vascular risk factors, stroke etiology, neurological clinical manifestations, including time of onset of symptoms, time of arrival at hospital, time of onset of the disease until the imaging examination, the severity of the stroke according to the NIHSS scale, the evaluation of the functional result according to the mRS scale.

2. Special study methods:

• Cerebral NCCT (non-contrast computed tomography) - cerebral atrophy, supported cerebral infarction, ASPECTS score, brain damage score proposed by the author "whole brain score", early HT visualization.

• Perfusion CT was performed on a 64-line helical scan CT scanner - VCT select (General Electric Healthcare, USA, 2009) by the Cine Mode dynamic scanning method with contrast agent administration, after native non-contrast axial scanning and exclusion of hemorrhagic stroke. The post-processing of the acquired primary data was performed by the CT Perfusion 4D application based on the deconvolution algorithm. Perfusion maps were evaluated – CBV- cerebral blood volume, CBF - cerebral blood flow, MTT - mean transit time, Tmax, TTP - time to peak, PS - permeability surface, MSI- mean slope of increase, PEI - positive enhancement integral. The infarct core and penumbra were calculated automatically, using the combination of the most accurate Tmax and CBF threshold values, reported in the literature. The volume of the hypoperfusion zone corresponded to the Tmax value> 6 seconds, and the infarct core volume to the CBF value <30%.

• Perfusion CT-derived dynamic angiography: location and extent of arterial occlusion, thrombus severity score (Puetz), collateral status (Miteff), revascularization, and cerebral reperfusion according to the TICI classification.

• Ultrasonography of the intra-extracranial arteries according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) classification with the allocation of patients in groups with and without ischemic pre-conditioning.

• Control PCT was performed in the subacute phase of ischemic infarction, approximately on day 4-7 after the onset of clinical manifestations. The imaging pattern recorded in the Perfusion CT control investigation included the following spectrum of findings: final lesion, persistent penumbra, hyperperfusion, normal perfusion, and perfusion maps for each type of finding.

Method of assessing the affected area. The affected brain area was assessed visually quantitative: 10 areas in the anterior ASPECTS region (MCA - middle cerebral artery pool) or posterior (VB - vertebro-basilar pool) are considered equal to 100% (100) of the arterial pool,

each ASPECTS area = 10 % (10). If an entire ASPECTS area is affected, it is considered that 10% of the vascularity pool is affected, compared to the final lesion in the control investigation: true- and false- negative / positive areas. If a region is partially affected, the percentage affected by all areas in an affected pool is added together. For example: M1 = 0, M2 = 0, M3 = 0, I = 5, C = 10, L = 5, IC = 3, M4 = 3, M5 = 10, M6 = 0, means that a third of inner capsule (IC = 3) and area M4, half of the island (I = 5) and lenticular core (L = 5), total caudate core (C = 10) and area M5 (M = 10), areas not affected M1, M2, M3 and M6, the summary area affected by the DHW basin is equal to 0 + 0 + 0 + 5 + 10 + 5 + 3 + 3 + 10 + 0 = 36 areas (36%) out of 100%.

The “whole brain” method developed by the author. We propose to assess the brain lesion not only in a single vascular pool but to include the entire surface of the infra- and supratentorial cerebral parenchyma by including all pools of cerebral vascularization: MCA (10 classic ASPECTS zones) + vertebro-basilar pool (10 zones "posterior circulation ASPECTS”-pcASPECTS) includes the bilateral infratentorial brain + the ACA pool (1 area in a hemisphere). The author developed and analytically validated this method (figure 1). This methodology and schematic representation was approved by the University Radiology Department – protocol No. 9 from 4.11.2021, Certificate of innovation – No. 16/11.21/03 from 4.11.2021, Acts of implementations – No. 01-08/408 from 12.10.2021 Institute of Neurology and Neurosurgery and Nr 1000-21 from 13.10.2021 Medpark, AGEPI (The State Agency on Intellectual Property) Copyright Certificate – No. 1878 – Seria O / Nr 7100.

Therefore, the whole brain arteries score covers the full region of cerebral arterial vascularization, 32 areas in total bilateral, which provides comprehensive information on the actual volume of impaired blood circulation. During our study and practical experience, we found that ischemic injury is very often more complex than only 1 vascular area: blood circulation disorders extend into the areas adjacent to the primary lesion, often are affected "watershed zones" between different arterial regions even in the contralateral hemisphere to the lesion may be affected (for example, in anatomical variations of the Willis circle, hypoperfusion extends into the contralateral frontal lobe when both ACAs feed from a carotid artery due to aplasia of the contralateral A1 arterial segment).

For the whole brain score, all pools of cerebral vascularization were considered at once all together: middle cerebral artery (in one hemisphere = 10 points ASPECTS = 100%), anterior cerebral artery (in one hemisphere = 1 point = 1 vascular area = 10% of the cerebral surface), vertebro-basilar pool (integral infratentorial brain = 10 points = 100%, left or right side = 5 points = 50%). Therefore, the right or left half of the infratentorial + supratentorial brain = 16 areas of vascularization, 160 areas of surface (figure 2).

Brain perfusion scanning protocol by computed tomography and post-processing of acquired data. Brain perfusion by computed tomography was performed in the Radiology and Medical Imaging department of IMSP INN in the Republic of Moldova at 64-slices helical scanner - VCT select (General Electric Healthcare, USA) by dynamic scanning method Cine Mode with contrast enhancement, after non-contrast axial scanning and exclusion of hemorrhagic stroke [16]. Scanning parameters (according to the recommendations of the manufacturer General Electric Healthcare for VCT Select 64 rows): tube rotation time - 1.0 second, slice thickness of 5 mm, scanning time - 40 seconds, gentry inclination - parallel to the orbito-meatal line, voltage X-ray current = 80 kV, current intensity - constant 100 mA, total number of primary images obtained - 792. Enhancement- 50 ml of the non-ionic contrast agent Visipaque (iodixanol), 320 mg/ml of iodine, introduced through the antecubital vein at a flow rate of 5-6 ml/s, followed by the administration of 40 ml of physiological solution at a rate of 5-6

ml/s [10, 16]. Irradiation dose during the investigation Perfusion CT - DLP (dose-length product) 388 mGy, the summary dose for 2 investigations - 776 mGy, which is much less than the FDA (Food and Drug Administration) recommendations. According to FDA recommendations, the scan parameters should not exceed 80 kVp and 200 mAs.

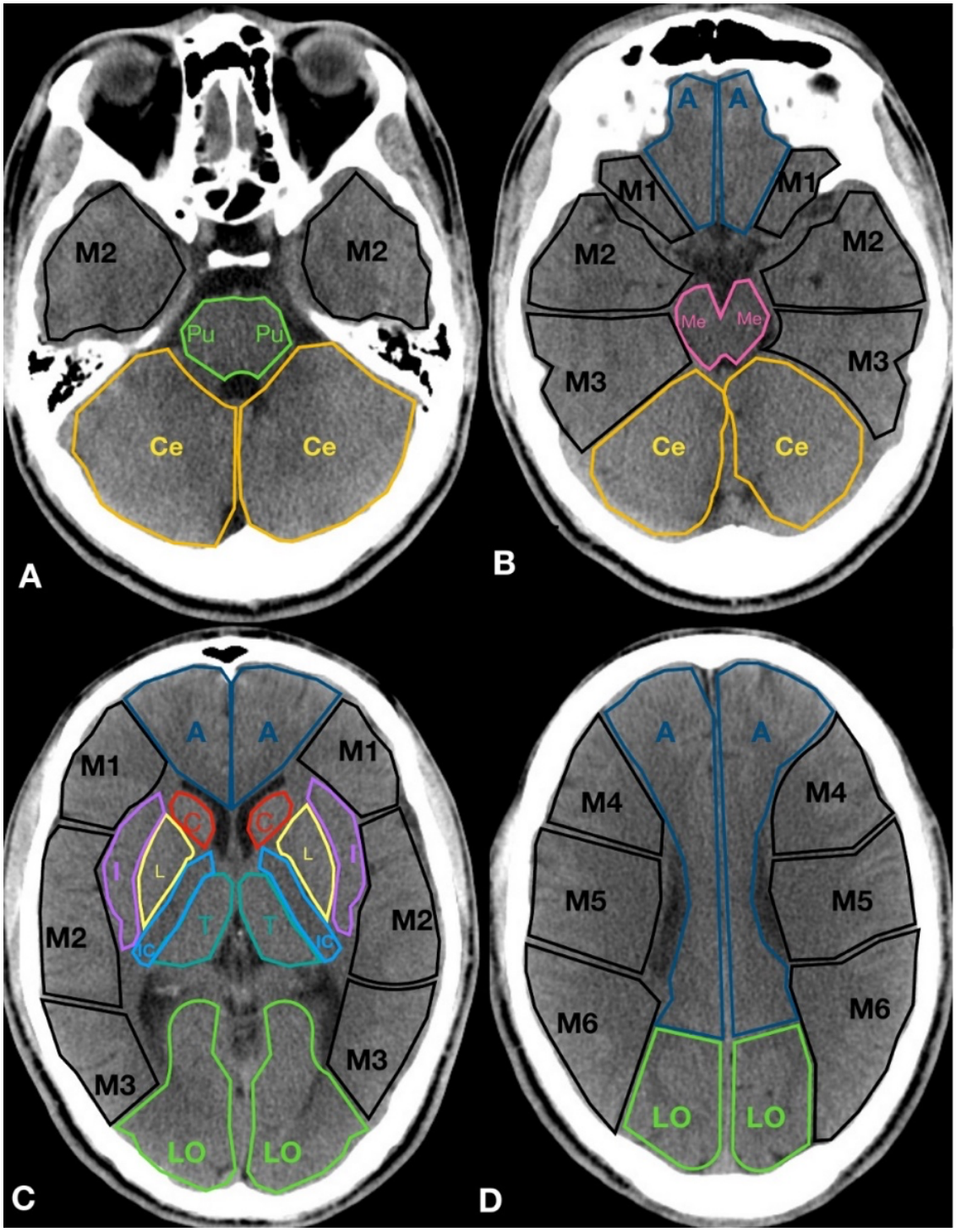


Figure 1. "**Whole brain" - ASPECTS score for the whole brain.**

Note. A, B - non-contrast computed tomography at the level of the cranial base, areas of arterial vascularization: Ce - cerebellar hemispheres, Pu – pons Varolio, Me - midbrain, A - ACA area, M1 / M2 / M3 - MCA pool; C - supratentorial section at the level of the basal ganglia: C - caudate head, L - lenticular nucleus, I - island, IC - internal capsule, T - thalamus, LO - occipital lobe, A - ACA area, M1 / M2 / M3 – MCA pool; D - supratentorial section at the supraventricular supraganglionic level: LO - occipital lobe, M4 / M5 / M6 - MCA pool, A - ACA pool. The vertebro-basilar system (Pu, Ce, Me, LO, T), MCA (M1, M2, M3, M4, M5, M6, I, L, C, IC), ACA (A). ASPECTS - Alberta Stroke Program Early Computed Tomography Score. ACA - anterior cerebral artery. MCA - middle cerebral artery

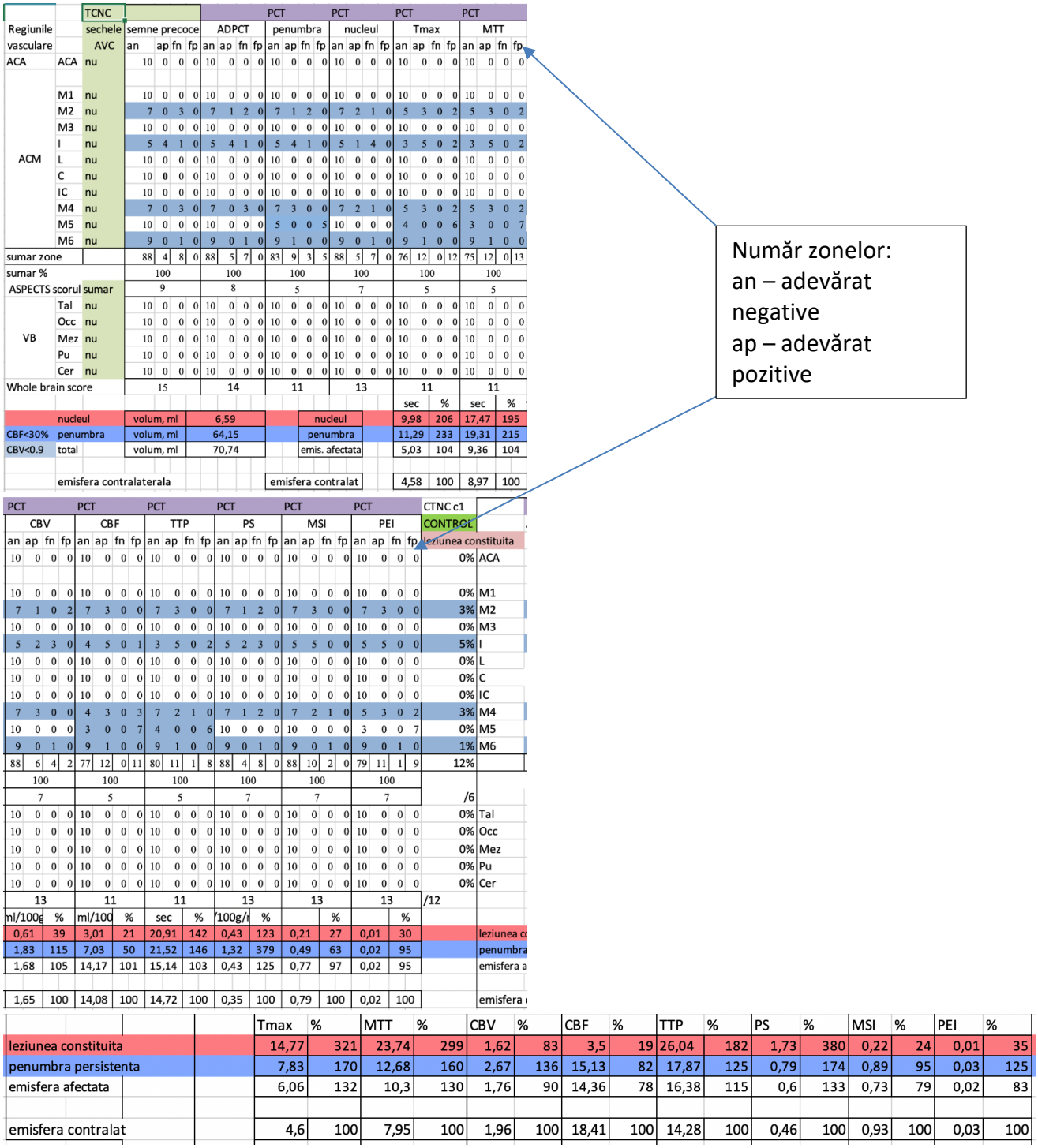


Figure 2. **Example of tables, completed for each patient.**

Note. Table above - example of calculation (case 1) of visible areas with cerebral ischemic damage on admission in non-contrast computed tomography imaging, brain perfusion by CT with time-invariant images - dynamic angiography derived from Perfusion CT, automatic tissue classification map (core and penumbra), perfusion maps. Table below - non-contrast CT, control PCT in the subacute phase with the calculation of the areas of ischemic final lesion, persistent penumbra or hyperperfusion. Absolute and relative perfusion parameters were recorded in the lesion, persistent penumbra / hyperperfusion, affected hemisphere and contralateral hemisphere.

The study included adult patients (lower age limit - 18 years, upper age limit not specified) with suspected acute ischemic stroke, admisssed consecutively in IMSP INN "Diomid Gherman" with good quality Perfusion CT performed within 24 hours of symptoms onset.

PCT shows the type, age, and extent of the ischemic stroke. The infarction core and penumbra were calculated automatically by the CT Perfusion 4D application based on the deconvolution algorithm, using the combination of the most accurate Tmax and CBF threshold values, reported in the literature. The volume of the hypoperfusion zone corresponded to the Tmax value> 6 seconds, and the infarct core volume to the CBF value <30%.

From the images of time-invariable angiography derived from PCT, the following parameters were calculated: 1) place and length of arterial occlusion in acute ischemic stroke, 2) degree of collateral development and 3) revascularisation state. Patients were classified as having large vessel occlusion (ICA, MCA-M1 and AB) and medium vessel occlusion (MCA-M2, MCA-M3, ACA and PCA). To quantify thrombus characteristics, at PCT we studied thrombus location, thrombus permeability, thrombus severity score, and degree of residual flow.

2.3. Methods of statistical processing of results

Primary data processing was performed using the functions and modules of the "Statistical Package for the Social Science" (SPSS) version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and Microsoft Office Excel 2019 on the personal computer through procedures of descriptive and inferential statistics. The normality testing of interval scale variables was performed using the Kolmogorov-Smirnov test and the appropriate application of parametric or non-parametric tests. The t test for independent samples or the non-parametric Mann-Whitney U test was used to estimate significant differences between the means of two groups. The dynamics of the group mean values were assessed by the t test for sample-pairs or by the Wilcoxon test. Contingency table data were analyzed by the method of variational statistics (χ^2 and Fisher's exact method). The assessment of the degree of intensity of the statistical links was performed by the correlation procedure: the coefficients r Pearson, ρ Spearman or τ Kendall. The calculation of the diagnostic accuracy indicators (sensitivity, specificity, positive predictive value, negative predictive value) was performed based on the 2x2 contingency table. Statistically significant we considered the differences with the bilateral value $p < 0.05$.

3. CLINICAL VALUE OF MULTIMODAL COMPUTER TOMOGRAPHY IN THE DIAGNOSIS, MONITORING OF TREATMENT AND PROGNOSIS OF ACUTE ISCHEMIC STROKE

3.1. Evaluation of cerebral perfusion parameters by computed tomography at patients with acute and subacute ischemic stroke

The study included 100 acute ischemic stroke patients: 54 (54.0%) men and 46 (46.0%) women with a mean age of 67.05 ± 1.09 years (from 21 years to 91 years). Pathology assessment found hypertension in 98 (98.0%) patients, coronary artery disease or other cardiovascular disease in 86 (86.0%) patients, atrial fibrillation in 46 (46.0%) patients, diabetes mellitus in 25 (25.0%) patients, obesity of varying degrees in 21 (21.0%) patients, hyperlipidemia in 20 (20.0%) patients, transient ischemic attack in 9 (9.0%) patients and current smoking in 8 (8.0%) patients.

The assessment of the time from onset of symptoms to CT scan found that in 0-3 hours CT scan was performed in 59 (59.0%) patients, in 3-6 hours - in 15 (15.0%) patients, in 6-12 hours - in 14 (14.0%) patients, in 12-24 hours - in 1 (1.0%) patient, wake-up - in 8 (8.0%)

patients and the onset was unknown in 3 (3.0%) patients. The mean time to onset of symptoms was 210.93 ± 22.4 minutes (10 minutes to 1200 minutes).

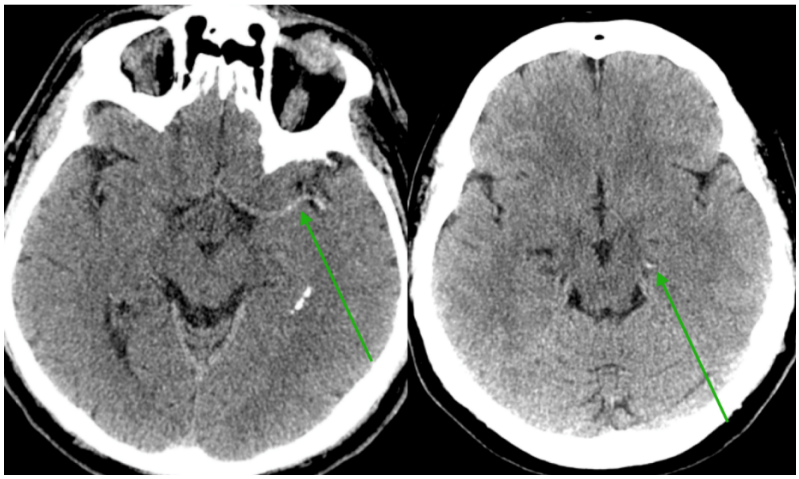
At admission, the mean NIHSS value was 11.88 ± 0.7 points (0 points to 26 points) and the mean mRS value was 3.33 ± 0.1 points (1 point to 5 points).

Non-contrast computed tomography on admission revealed: global cortical atrophy in 84 (84.0%) patients, parietal atrophy (Koedam) in 82 (82.0%) patients, global temporal medial lobe atrophy in 80 (80,0%) of patients, hydrocephalus (Evan's index) in 48 (48.0%) of patients, sequelae of non-lacunar stroke in 34 (34.0%) of patients, sequelae of lacunar stroke in 60 (60, 0%) of patients, hypodensity in the deep brain white matter (Fazekas) in 82 (82.0%) patients, the mean value of the ASPECTS score 9.14 ± 0.2 points and the mean value of the "whole brain" score 15, 09 ± 0.2 points.

The sign of hyperdense artery was determined in 56 (56.0%) patients, including ICA in 16 (16.0%) cases, MCA-M1 in 33 (33.0%) cases, basilar artery in 2 (2.0%) cases, MCA-M2 in 23 (23.0%) cases, MCA-M3 in 6 (6.0%) cases and PCA in 4 (4.0%) cases (figure 3).

Table 1 shows the diagnostic accuracy indicators of the non-contrast CT and Perfusion CT parameters in patients with acute ischemic stroke.

Dynamic angiography, derived from cerebral perfusion by computed tomography at admition, showed: the visibility of the arterial occlusion point in 74 (74.0%) patients, the location of the arterial occlusion was visualized in 74 (74.0%) patients (at ICA in 24 (24.0%) cases, at MCA-M1 in 42 (42.0%) cases, at the basilar artery in 3 (3.0%) cases, at MCA-M2 in 31 (31.0%)), in MCA-M3 in 11 (11.0%) cases, in ACA in 1 (1.0%) case, in PCA in 7 (7.0%) cases, 43 (43.0%) patients, moderately developed collaterals in 25 (25.0%) patients and undeveloped collaterals in 32 (32.0%) patients, mean score value for thrombus severity 7.64 ± 0, 3 points.



A B

Figure 3. **Sign of the hyperdense cerebral artery.**

Note. A - Case 11, a 63-year-old man came to the neurologist's consultation, lost his consciousness, aphasia with right hemiparesis, non-contrast computed tomography 20 minutes after the onset of clinical symptoms, Hyperdense middle cerebral artery on the left (arrow); B - Case N3, woman, 57 years old, right hemisensitive syndrome, hemianopia, NIHSS 2, non-contrast tomography 35 minutes after the onset of clinical manifestations, hyperdense posterior cerebral artery sign on the left (arrow).

Table 1. **Diagnostic accuracy indicators (%) in patients with acute ischemic stroke**

Indicator	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Early signs of non-contrast computed tomography	22,1	99,9	99,1	79,6	80,6
Postcontrast hypodense areas at computed tomography perfusion, primary imaging	47,8	99,0	94,3	84,9	86,1
Penumbra	94,1	77,8	58,4	97,6	81,9
Core	46,2	99,7	98,3	85,0	86,6
Tmax	96,8	75,0	56,0	98,6	80,4
MTT- mean transit time	96,7	71,6	52,8	98,5	77,8
CBV- cerebral blood volume	48,2	99,5	96,7	85,4	86,8
CBF- cerebral blood flow	86,0	88,4	70,8	95,1	87,8
TTP- time to peak	91,7	73,8	54,1	96,4	78,3
PS- permeability surface	48,2	98,0	88,8	85,2	85,7
MSI- mean slope of increase	61,8	97,0	87,3	88,5	88,3
PEI- positive enhance integral	60,5	97,3	88,3	88,1	88,1

The analysis according to the arterial vessel involved in acute ischemic stroke found ICA in 29 (29.0%) patients, MCA-M1 proximal in 30 (30.0%) patients, MCA-M1 distal in 33 (33.0%) of patients, MCA-M2 greater than 31 (31.0%) of patients, MCA-M2 less than 17 (17.0%) patients, ACA-A1 of 1 (1.0%) patient and ICA infraclinoid of 1 (1.0%) patient. Only one artery was involved in 21 (34.4%) cases, and in the vast majority of cases (40 - 65.6%) 2 and more vessels were involved: 2 vessels in 15 (24.6%) patients, 3 vessels in 14 (23.0%) patients, 4 vessels in 6 (9.8%) patients and 5 vessels in 5 (8.2%) patients.

Brain perfusion by computed tomography on admission (mapping). For penumbra in the affected hemisphere, the mean value of the ASPECTS score was 4.91 ± 0.3 points (0 points to 10 points) and the mean value of the whole brain score (early signs ischemic) - 10.41 ± 0.4 points (0 points to 16 points). For the core in the affected hemisphere, the mean value of the ASPECTS score was 7.79 ± 0.2 points (from 2 points to 10 points) and the mean value of the whole brain score (early ischemic signs) was 13.71 ± 0.3 points (8 points to 16 points). The following volumes were found: ischemic core - 21.9 ± 2.9 ml (0.12 ml to 94.99 ml), penumbra - 66.51 ± 5.8 ml (1.67 ml to at 263.0 ml) and hypoperfusion - 84.51 ± 7.2 ml (from 1.67 ml to 279.35 ml) (Figure 4, 5).

The correlation analysis revealed that with the increase in the size of the core and penumbra, the values of the NIHSS score at admission, the mRS score at admission, the number of stroke areas in the MCA lesion, the number of stroke areas in the brain lesion, the period of hospitalization, the NIHSS discharge score and the mRS discharge score.

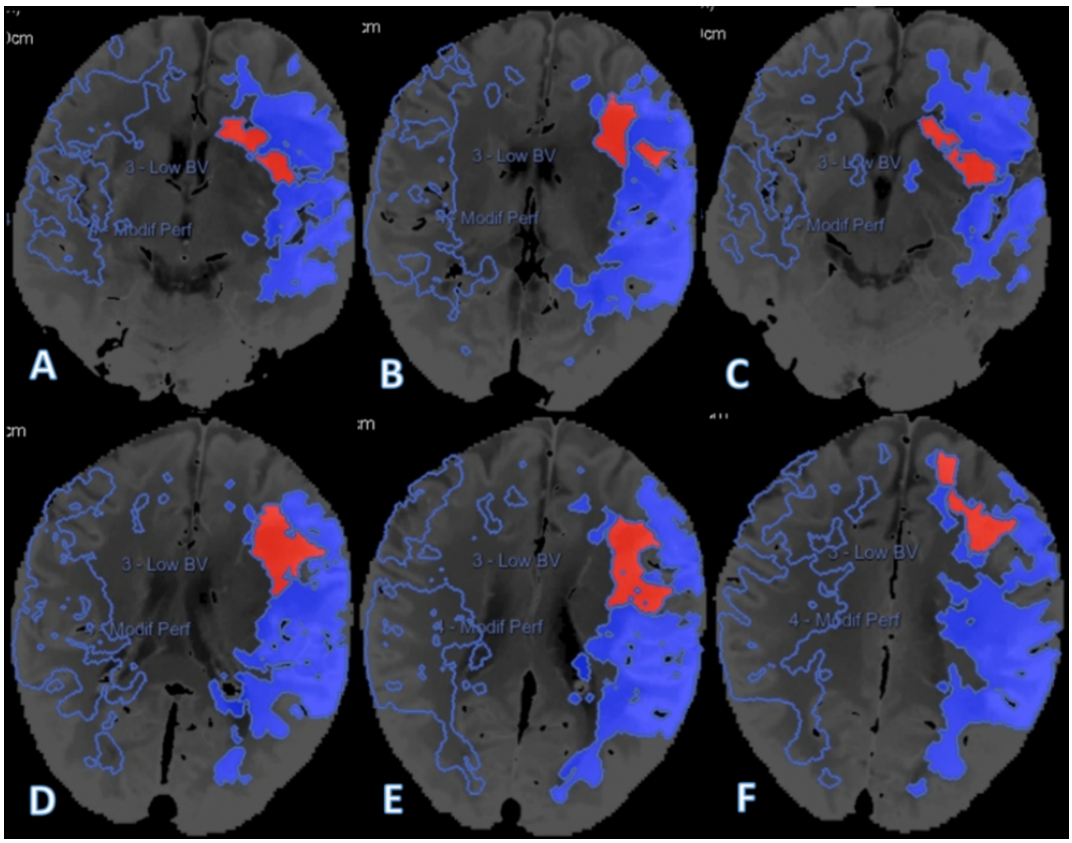


Figure 4. **Automatic "tissue classification" perfusion map.**

Note. Case 25, 68-year-old man, one hour after the onset of aphasia, right hemiparesis, visual field disorders. A, B, C, D, E, F - automatic map "tissue classification", the ischemic core is presented in red, penumbra - in blue with the calculation of the absolute values of the core and penumbra, the reflection of symmetrical areas in the healthy hemisphere and the calculation of values relative perfusion rates (compared to values in the healthy hemisphere - 100%). Low BV (low blood volume) - core, Modif Perf (modified perfusion) - penumbra.

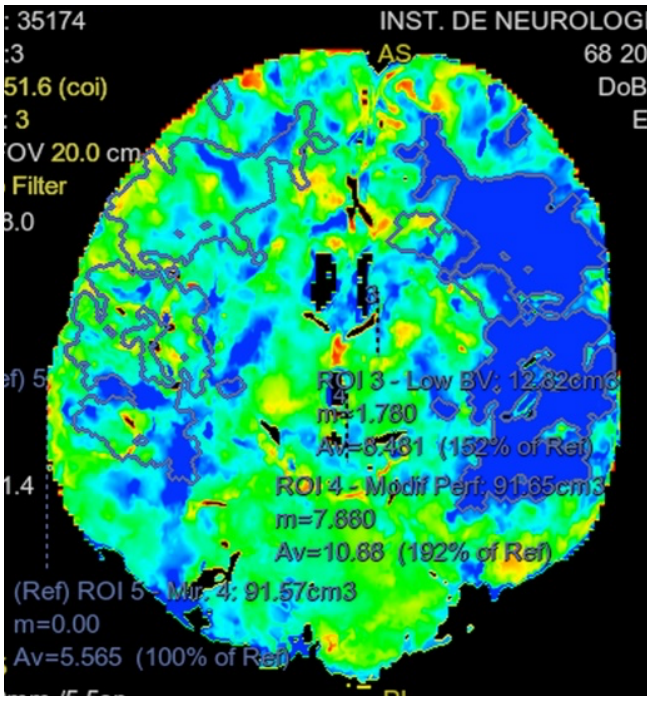


Figure 5. **Analysis of perfusion maps - detection of absolute and relative perfusion parameters in the penumbra and core and compared to identical contralateral areas.**

Note. Case 25, 68-year-old man, one hour after the onset of aphasia, right hemiparesis, visual field disorders. Map Tmax, Region of Interest - ROI 3= low blood volume (low BV): core volume = 12.82 cm3, mean Tmax in core = 8.48 seconds (152% compared to the same region in the contralateral hemisphere - ROI 5 with Tmax 5.65 seconds in the right hemisphere); region 4 (ROI 4) = penumbra with decreased. Tmax, penumbra volume = 91.65 cm3, average Tmax in penumbra = 10.68 seconds (192% compared to the same region in the contralateral hemisphere - ROI 5 with Tmax 5.65 seconds in right hemisphere).

The NIHSS discharge score correlates: inversely proportional to the absolute perfusion values at admission in the ischemic core CBF ($\rho = -0.31$, $p < 0.05$) and PEI ($\rho = -0.29$, $p < 0.05$), directly proportional to the absolute perfusion values at admission in the ischemic core TTP ($\rho = 0.25$, $p < 0.05$) and PS ($\rho = 0.39$, $p < 0.01$), directly proportional to the absolute perfusion values at admission in the penumbra Tmax ($\rho = 0.39$, $p < 0.001$), MTT ($\rho = 0.32$, $p < 0.01$), TTP ($\rho = 0.41$, $p < 0.001$) and PS ($\rho = 0.34$, $p < 0.01$).

MRS score at discharge correlates: inversely proportional to absolute perfusion values at admission in the ischemic core CBV ($\rho = -0.27$, $p < 0.05$), CBF ($\rho = -0.30$, $p < 0.01$) and PEI ($\rho = -0.27$, $p < 0.05$), directly proportional to the absolute perfusion values at admission in the ischemic core PS ($\rho = 0.23$, $p < 0.05$), directly proportional to the absolute perfusion values at admission in penumbra Tmax ($\rho = 0.34$, $p < 0.01$), MTT ($\rho = 0.21$, $p < 0.05$), TTP ($\rho = 0.39$, $p < 0.001$) and PS ($\rho = 0, 42$, $p < 0.001$).

The following values of the previously analyzed parameters were determined in the deceased patients: NIHSS score at admission ≥8 points, mRS score at admission ≥3 points, ischemic core volume ≥0.63 cm3, penumbra volume ≥2.18 cm3, absolute Tmax in the hemisphere affected ≥5.12 sec, relative CBV in core ≥9%, relative CBV in affected hemisphere ≥66%, relative CBF in affected hemisphere ≥40%, absolute TTP in affected hemisphere ≥9.33 sec, absolute PS in penumbra ≥0 , 46 ml / 100g / min, relative PEI in penumbra ≥14%, relative PEI in affected hemisphere ≥52%, number of areas with stroke in MCA lesion ≥0, number of areas with stroke in total brain injury ≥0, mRS discharge score ≥0.

Ultrasonography of extracerebral vessels. Ipsilateral stroke ICA stenosis, determined according to the NASCET method, was insignificant in 34 (34.0%) patients, up to 70% in 33 (33.0%) patients and 70% or more in 33 (33.0) %) of patients. ICA contralateral stroke stenosis was insignificant in 45 (45.0%) patients, up to 70% in 48 (48.0%) patients and 70% or more in 7 (7.0%) patients. Local hemodynamic changes were present in 80 (80.0%) patients and pathological deformities in 71 (71.0%) patients.

Non-contrast control computed tomography. Hemorrhagic transformation was diagnosed in 25 (25.0%) patients, including hemorrhagic infarction type 1 (HI1) in 3 (3.0%) cases, hemorrhagic infarction type 2 (HI2) in 6 (6.0%) cases, parenchymal hematoma type 1 (PH1) in 9 (9.0%) cases and parenchymal hematoma 2 (PH2) in 7 (7.0%) cases (Figure 6, 7).

Brain perfusion by control computed tomography (angiographic sections). No reperfusion was found in 18 (18.0%) patients. The TICI reperfusion score 2b-3 (successful reperfusion) was revealed in 42 (42.0%) patients and the TICI score 0-2a (insufficient reperfusion) - in 40 (40.0%) patients.

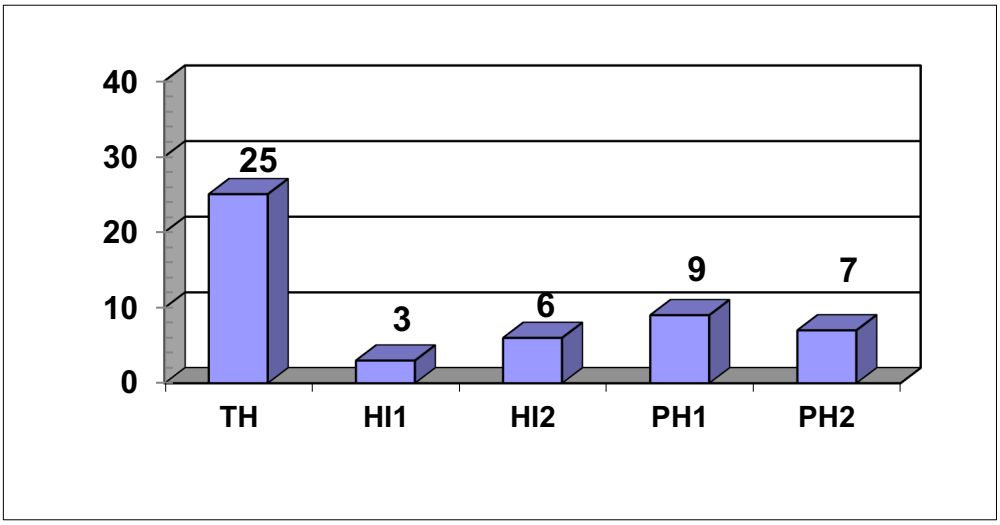


Figure 6. **Frequency of hemorrhagic transformation in patients with acute ischemic stroke (%).**

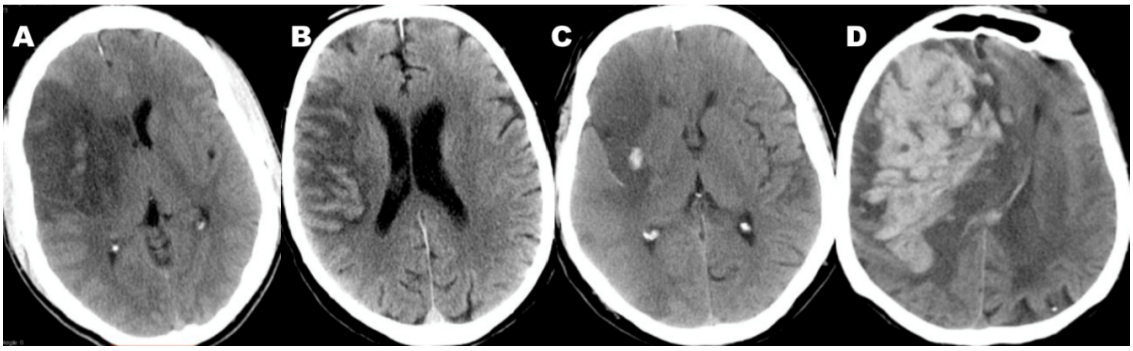


Figure 7. **Types of hemorrhagic transformation**

Note. Non-contrast control computed tomography in the subacute phase, hemorrhagic transformation (HT) types. A - patient B., 51 years old, 3 days after the onset of left hemiplegia. HI1 (hemorrhagic infarction 1) - small petechial hyperdensities in the center of the right MCA ischemia, extended frontal-parietal hypodense area and in the basal ganglia, contralateral displacement of the median structures. B - Case 6, 76-year-old woman, wake-up stroke, 10 days after the onset of symptoms, HI2 - fronto-parietal confluent hyperdensities in ischemic stroke in the right MCA pool. Death over 19 days in the intensive care unit. C - case 44, male 60 years old, 2 days after the onset of left hemiplegia, sopor. PH1 (parecymal hematoma 1) - homogeneous hyperdensity of 5 mm in the projection of the right putamen on the median contour of the ischemia in the right MCA, in the lenticulostriate arteries pool. D - case 82, 85-year-old woman, blood clotting disorders, PH2 - massive hematoma hemorrhagic transformation that subtotally occupies the ischemia in the right MCA. Death in 2 days in the intensive care unit.

Brain perfusion by computed tomography control (mapping). The control examination found the following visible areas of varying degrees of perfusionof brain tissue in the phase subacute cerebral ischemia compared to the perfusionimaging picture at admission: critical ischemic lesion hypoperfusion in 16 (16.0%) patients, persistent penumbral hypoperfusion in 2 (2.0%) patients, hyperperfusion in 8 (8,0%) patients, total normalization of perfusionin 4 (4.0%) patients, mixt final ischemic lesion with persistence of penumbral regions in 54 (54.0%) patients, final ischemia with hyperperfusion sectors in 7 (7.0%) patients, lesion with partial normalization (an area of primary ischemia restored perfusion parameters) in 1

(1.0%) patient, hypoperfusion (persistent penumbra) with partial normalization of perfusion in 3 (3.0%) patients, hyperperfusion with partial normalization of perfusion in 3 (3.0%) patients, mixt areas of persistent penumbra and normalization perfusion in 1 (1.0%) patient , persistent penumbra with hyperperfusion and normal perfusion in 1 (1.0%) patient.

The following clinical results were obtained: death - 17 (17.0%) patients, mean NIHSS at discharge - 6.11 ± 0.6 points (0 to 22 points), mean mRS at discharge - 2.53 ± 0.2 points (0 points to 6 points). The mRS discharge score was favorable (0-2 points) in 54 (54.0%) cases and unfavorable (3-6 points) in 46 (46.0%) cases. Of the patients who survived, at discharge 45 (54.2%) were independent without care, 20 (24.1%) were indipendent with care, and 18 (21.7%) were dependent from constant care.

3.2. Determining the spectrum of imaging factors susceptible to forecasting early onset of hemorrhagic transformation of ischemic stroke

In the general study group 25 (25.0%) of patients with acute ischemic stroke developed HT. At admission, patients with acute ischemic stroke with and without HT were similar in gender, age, risc factors, history of treatment, onset of symptoms, main clinical manifestations, cerebral atrophy, type of hydrocephalus, hydrocephalus-atrophic changes, non-lacunar and lacunar supported stroke.

However, patients with acute ischemic stroke with HT were statistically significantly higher: the frequency of concomitant presence of 4-6 risk factors (52.0% and 26.6%; $p < 0.05$), the frequency of aphasia / dysphasia (96.0% and 74.7%; $p < 0.05$), mean NIHSS score (16.28 ± 1.2 and 10.41 ± 0.8 points; $p < 0.001$), mean mRS score (3.84 ± 0.1 and 3.16 ± 0.1 points; $p < 0.01$), frequency of hyperdense artery sign on ICA (40.0% and 8.0%; $p < 0.01$), on MCA-M1 (64.0% and 22.7%; $p < 0.001$) and on MCA-M2 (40.0% and 17.3%; $p < 0.05$), visualization of the arterial occlusion point (100.0% and 65 , 3%; $p < 0.001$), large vessel occlusion: on ICA (56.0% and 13.3%; $p < 0.001$) and on MCA-M1 (76.0% and 30.7%; $p < 0.001$) , the frequency of undeveloped collateral (64.0% and 21.3%; $p < 0.001$) and the frequency of insufficient revascularization (68.0% and 30.7%; $p < 0.001$).

Patients with acute ischemic stroke with HT at admission were statistically significantly lower: frequency of concomitant presence of 1-3 risc factors (48.0% and 73.4%; $p < 0.05$), mean value of non-contrast CT ASPECTS score (7.84 ± 0.6 and 9.57 ± 0.1; $p < 0.01$), moderately developed collateral frequency (8.0% and 30.7%; $p < 0.01$), strongly developed collateral frequency (32.0%) and 54.7%; $p < 0.05$) and mean thrombus severity score (5.44 ± 0.5 and 8.37 ± 0.2 points; $p < 0.001$).

The mean perfusion values in the core, penumbra, and affected hemisphere with statistically significant difference in patients with acute ischemic stroke with and without HT are shown in Table 2.

Table 2. **Mean perfusion values at admission in the core, penumbra, and affected hemisphere with statistically significant difference in patients with acute ischemic stroke with and without haemorrhagic transformation.**

Indicator	Stroke with HT	Stroke without HT	p
Absolute PS in core (ml/100g/min)	1,98±0,3	0,34±0,03	0,000

Relative Tmax in core (%)	239,04±12,3	202,52±9,7	0,030
Relative MTT in core (%)	196,96±11,4	164,00±8,9	0,033
Relative CBF in core (%)	22,16±2,0	29,07±2,0	0,017
Relative PS in core (%)	388,64±70,1	92,72±13,8	0,000
Absolute Tmax in penumbra (sec)	12,04±0,2	10,35±0,2	0,000
Absolute MTT in penumbra (sec)	18,20±0,5	16,57±0,4	0,027
Absolute TTP in penumbra (sec)	21,66±0,6	19,26±0,4	0,002
Absolute PS in penumbra (ml/100g/min)	2,86±0,2	0,72±0,05	0,000
Relative Tmax in penumbra (%)	270,24±13,1	224,75±13,1	0,004
Relative MTT in penumbra (%)	235,72±10,4	208,04±6,8	0,036
Relative TTP in penumbra (%)	152,92±4,4	137,17±2,6	0,003
Relative PS in penumbra (%)	566,36±55,0	185,34±14,5	0,000
Absolute Tmax in affected hemisphere (sec)	7,95±0,3	6,75±0,2	0,001
Absolute MTT in pathologic hemisphere (sec)	12,44±0,4	10,91±0,3	0,015
Absolute TTP in pathologic hemisphere (sec)	15,85±0,5	16,26±0,4	0,021

The correlation analysis revealed that with the increase of absolute perfusion values (core and penumbra Tmax, core and penumbra MTT, core and penumbra TTP, core and penumbra PS) and relative perfusion values (core and penile Tmax penumbra, MTT in the core and penumbra, TTP in the penumbra, PS in the core and penumbra) at admission, increases the risk of HT in patients with acute ischemic stroke. Only the relative value of CBF in the core was inversely associated with the risk of HT in acute ischemic stroke patients.

In patients with acute ischemic stroke and HT, the following absolute perfusion values were determined upon admission in the core: Tmax ≥6.06 sec, MTT ≥6.18 sec, CBV ≥0.21 ml / 100g, CBF ≥1.98 ml / 100g / min, TTP ≥13.16 sec, PS ≥0.03 ml / 100g / min, MSI ≥0.13 and PEI ≥0.01. For the penumbra these parameters were: Tmax ≥9.48 sec, MTT ≥11.18 sec, CBV ≥0.92 ml / 100g, CBF ≥3.74 ml / 100g / min, TTP ≥17.03 sec, PS ≥ 0.57 ml / 100g / min, MSI ≥0.31 and PEI ≥0.01.

Patients with acute ischemic stroke and HT had the following relative perfusion values at hospital admission: Tmax ≥138%, MTT ≥74%, CBV ≥9%, CBF ≥11%, TTP ≥98%, PS ≥7%, MSI ≥13% and PEI ≥6%. For the penumbra these parameters consisted of: Tmax ≥186%, MTT ≥136%, CBV ≥52%, CBF ≥29%, TTP ≥112%, PS ≥139%, MSI ≥32% and PEI ≥27%.

3.3. Clinical and imaging results in patients with acute ischemic stroke with ischemic preconditioning

In the general study group, 36 (36.0%) of patients with acute ischemic stroke on the same side were considered with brain IPC (ischemic preconditioning) where ICA (internal carotid artery) stenosis was diagnosed ≥70% by ultrasonography and CT Angiography methods.

Patients with acute ischemic stroke and IPC were statistically significantly higher: mean value of the time from simptoms onset to admission (299.27 ± 48.2 and 166.02 ± 21.3 minutes; $p < 0.05$), grade 2 frequency Koedam score (55.6% and 25.0%; $p < 0.01$), frequency of grade 2 medial temporal lobe atrophy (32.2% and 12.5%; $p < 0.05$), frequency of local changes in carotid artery hemodynamics (97.2% and 70.3%; $p < 0.01$).

In patients with acute ischemic stroke and IPC were statistically significantly lower: the frequency of onset of symptoms in the first 3 hours (38.9% and 70.3%; p <0.01), the frequency of grade 1 of the Koedam score (30.6% and 51.6%; p <0.05) and the frequency of impaired posterior circulation (2.8% and 14.1%; p <0.05).

Statistical mean Perfusion CT values with statistically significant difference in patients with acute ischemic stroke with and without ipsilateral severe internal carotid artery stenosis (probable source of cerebral ischemic preconditioning) are presented in Table 3.

Table 3. **Mean values of the control Perfusion CT with statistically significant difference in acute ischemic stroke patients with and without severe internal carotid artery stenosis**

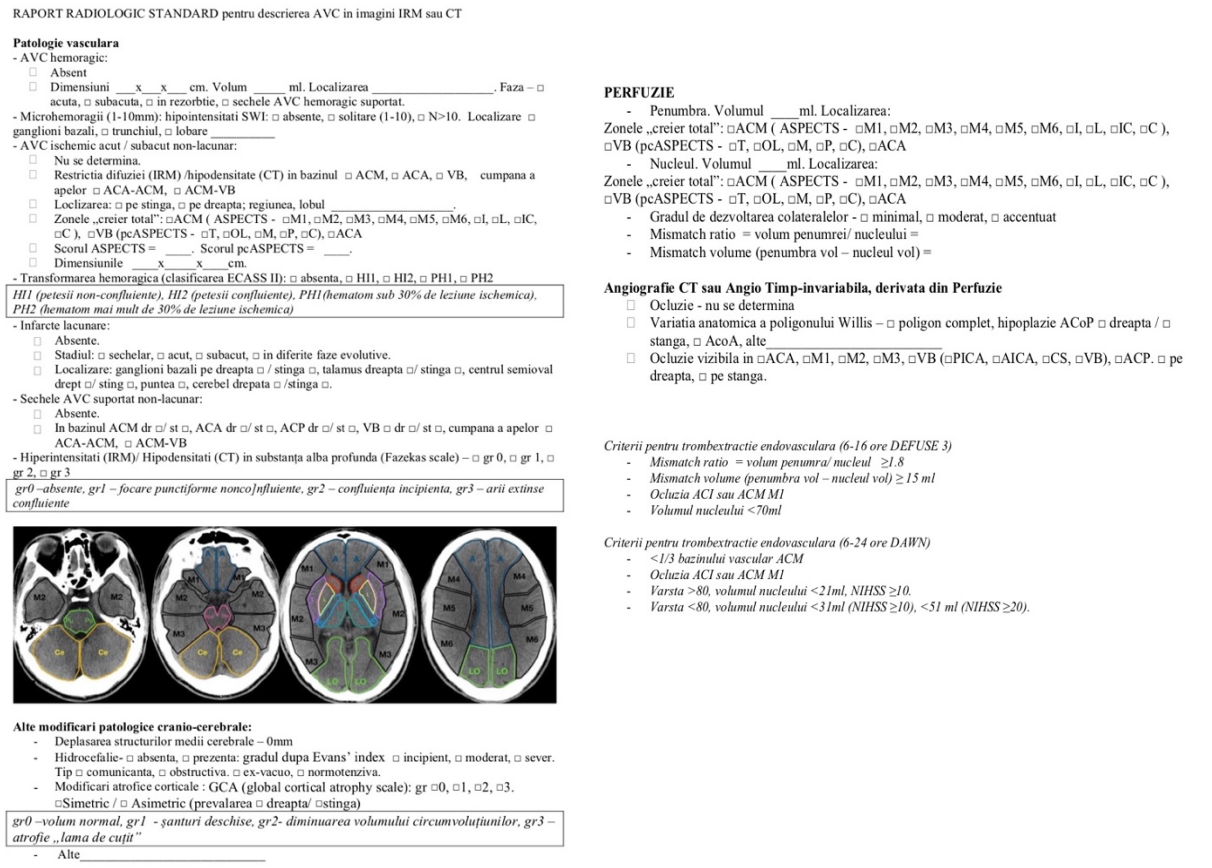
Indicator	Patients with stroke and severe stenosis	Patients with stroke without stenosis	**p**
Persistent penumbra	15,06±3,0	7,84±1,6	0,039
Persistent penumbra in the affected hemisphere	19,39±4,4	10,06±1,9	0,028
Absolute MSI (mean slope of increase*)* in hyperperfusion	1,71±0,3	1,10±0,1	0,032
Persistent CBV (cerebral blood volume) in the affected hemisphere (ml/100g)	1,65±0,1	1,87±0,1	0,011

4. SUMMARY OF THE RESULTS

The results of recently published investigations on dynamic Perfusion Computed Tomography (PCT) scanning have demonstrated the feasibility and perspective of this method for rapid assessment of patients with acute ischemic stroke. Compared to other imaging methods for assessing brain perfusion, PCT offers a number of practical advantages: (a) it can be easily introduced into the activity of stroke units, (b) it can be performed immediately after excluding a bleeding stroke by the non-contrast CT method, (c) the results can be obtained quickly (acquisition time is less than 1 minute) and (d) all Perfusion CT protocols (pre-contrast scan, perfusion contrast enhanced source images, time-invariant angiography derived from perfusion set of data) are performed on the same CT device and do not require other equipment.

Perfusion CT, a method that increases especially the imaging sensitivity in the early stages of acute ischemic stroke, is applied to assess the extent and severity of hypoperfusion, to differentiate potentially salvage brain tissue (penumbra) from irreversibly damaged brain tissue (infarction core), to select and initiate reperfusion treatment (intravenous thrombolisis and / or endovascular treatment), based on patient-specific data from physiological images and not on an arbitrary time interval. Post-treatment CT and Perfusion CT are used to exclude heamorrhagic transformation, including caused by reperfusion therapy, to assess reperfusion rate and to appreciate ischemic damage and possible complications.

As a result of the research, the author developed a new method - Standard radiological report to describe ischemic stroke on brain imaging - computed tomography or magnetic resonance imaging, which represents the applicative value of the study (Figure 8).



RAPORT RADIOLOGIC STANDARD pentru descrierea AVC in imagini IRM sau CT

Patologie vasculara

- AVC hemoragic:
  - ☐ Absent
  - ☐ Dimensiuni ___x___x___ cm. Volum _____ ml. Localizarea _____. Faza – ☐ acuta, ☐ subacuta, ☐ in rezorbtie, ☐ sechele AVC hemoragic suportat.
- Microhemoragii (1-10mm): hipointensitati SWI: ☐ absente, ☐ solitare (1-10), ☐ N>10. Localizare ☐ ganglioni bazali, ☐ trunchiul, ☐ lobare _____
- AVC ischemic acut / subacut non-lacunar:
  - ☐ Nu se determina.
  - ☐ Restrictia difuziei (IRM) /hipodensitate (CT) in bazinul ☐ ACM, ☐ ACA, ☐ VB, cumpana a apelor ☐ ACA-ACM, ☐ ACM-VB
  - ☐ Loclizarea: ☐ pe stinga, ☐ pe dreapta; regiunea, lobul _____.
  - ☐ Zonele „creier total": ☐ACM (ASPECTS - ☐M1, ☐M2, ☐M3, ☐M4, ☐M5, ☐M6, ☐I, ☐L, ☐IC, ☐C), ☐VB (pcASPECTS - ☐T, ☐OL, ☐M, ☐P, ☐C), ☐ACA
  - ☐ Scorul ASPECTS = ____. Scorul pcASPECTS = ____.
  - ☐ Dimensiunile ____x_____x____cm.
- Transformarea hemoragica (clasificarea ECASS II): ☐ absenta, ☐ HI1, ☐ HI2, ☐ PH1, ☐ PH2

HI1 (petesii non-confluiente), HI2 (petesii confluiente), PH1(hematom sub 30% de leziune ischemica), PH2 (hematom mai mult de 30% de leziune ischemica)

- Infarcte lacunare:
  - ☐ Absente.
  - ☐ Stadiul: ☐ sechelar, ☐ acut, ☐ subacut, ☐ in diferite faze evolutive.
  - ☐ Localizare: ganglioni bazali pe dreapta ☐ / stinga ☐, talamus dreapta ☐/ stinga ☐, centrul semioval drept ☐/ sting ☐, puntea ☐, cerebel drepata ☐ /stinga ☐.
- Sechele AVC suportat non-lacunar:
  - ☐ Absente.
  - ☐ In bazinul ACM dr ☐/ st ☐, ACA dr ☐/ st ☐, ACP dr ☐/ st ☐, VB ☐ dr ☐/ st ☐, cumpana a apelor ☐ ACA-ACM, ☐ ACM-VB
- Hiperintensitati (IRM)/ Hipodensitati (CT) in substanța alba profunda (Fazekas scale) – ☐ gr 0, ☐ gr 1, ☐ gr 2, ☐ gr 3

gr0 –absente, gr1 – focare punctiforme nonco]nfluiente, gr2 – confluiența incipienta, gr3 – arii extinse confluiente

Alte modificari patologice cranio-cerebrale:

- Deplasarea structurilor medii cerebrale – 0mm
- Hidrocefalie- ☐ absenta, ☐ prezenta: gradul dupa Evans' index ☐ incipient, ☐ moderat, ☐ sever. Tip ☐ comunicanta, ☐ obstructiva. ☐ ex-vacuo, ☐ normotenziva.
- Modificari atrofice corticale : GCA (global cortical atrophy scale): gr ☐0, ☐1, ☐2, ☐3. ☐Simetric / ☐ Asimetric (prevalarea ☐ dreapta/ ☐stinga)

gr0 –volum normal, gr1 - șanturi deschise, gr2- diminuarea volumului circumvoluțiunilor, gr3 – atrofie „lama de cuțit"

- Alte_____

PERFUZIE

- Penumbra. Volumul ____ml. Localizarea:

Zonele „creier total": ☐ACM (ASPECTS - ☐M1, ☐M2, ☐M3, ☐M4, ☐M5, ☐M6, ☐I, ☐L, ☐IC, ☐C), ☐VB (pcASPECTS - ☐T, ☐OL, ☐M, ☐P, ☐C), ☐ACA

- Nucleul. Volumul ____ml. Localizarea:

Zonele „creier total": ☐ACM (ASPECTS - ☐M1, ☐M2, ☐M3, ☐M4, ☐M5, ☐M6, ☐I, ☐L, ☐IC, ☐C), ☐VB (pcASPECTS - ☐T, ☐OL, ☐M, ☐P, ☐C), ☐ACA

- Gradul de dezvoltarea colateralelor - ☐ minimal, ☐ moderat, ☐ accentuat
- Mismatch ratio = volum penumrei/ nucleului =
- Mismatch volume (penumbra vol – nucleul vol) =

Angiografie CT sau Angio Timp-invariabila, derivata din Perfuzie

- ☐ Ocluzie - nu se determina
- ☐ Variatia anatomica a poligonului Willis – ☐ poligon complet, hipoplazie ACoP ☐ dreapta / ☐ stanga, ☐ AcoA, alte_____
- ☐ Ocluzie vizibila in ☐ACA, ☐M1, ☐M2, ☐M3, ☐VB (☐PICA, ☐AICA, ☐CS, ☐VB), ☐ACP. ☐ pe dreapta, ☐ pe stanga.

Criterii pentru trombextractie endovasculara (6-16 ore DEFUSE 3)

- *Mismatch ratio = volum penumra/ nucleul ≥1.8*
- *Mismatch volume (penumbra vol – nucleul vol) ≥ 15 ml*
- *Ocluzia ACI sau ACM M1*
- *Volumul nucleului <70ml*

Criterii pentru trombextractie endovasculara (6-24 ore DAWN)

- *<1/3 bazinului vascular ACM*
- *Ocluzia ACI sau ACM M1*
- *Varsta >80, volumul nucleului <21ml, NIHSS ≥10.*
- *Varsta <80, volumul nucleului <31ml (NIHSS ≥10), <51 ml (NIHSS ≥20).*

Figure 8. **Standard radiological report for assessment of stroke on examination by computed tomography or magnetic resonance imaging.**

The standardized report is a universal tool for analyzing brain imaging and can be applied to both computed tomography and magnetic resonance imaging. The report is very simple to perform by the radiologist, because it contains all necessary information to describe possible brain pathological changes and only those that are present in the patient with stroke need to be checked. The analysis by a standardized method saves significantly the time of the analysis of hundreds of images and the mass of three-dimensional volumetric data (such as the angiography of the intra-extracerebral vessels, perfusion sourse images), of the quantitative data in the perfusion maps. The progress of radiology is huge and extremely fast, with new protocols, released on the commercial market almost annually by different manufacturers, which induces the need for in-depth overspecialized education to correctly interpret investigations and causes difficulties for novice imagists. The report helps young doctors to understand in a short time the concept of multimodal, complex investigations, which provide not only structural but also functional data (neuroperfusion). The calculation formulas are included: penumbra / core mismatch ratio and mismatch volume.

The report is very clear and useful for interpretation by non-radiologists (neurologists, neurosurgeons, endovascular interventions) because it contains important information for decision making in the selection of treatment tactics, for example: volume / location / age of hemorrhagic stroke, age / arterial pool / localization according to the ASPECTS score of the ischemic lesion, "whole brain" diagram with all vascular pools where the territories affected by the ischemic lesion will be marked by radiologist, hemorrhagic transformation according to ECASS II (European Co-operative Acute Stroke Study II), microangiopathy according to

Fazekas scale, vascular pool and dimensions of the previous cerebral infarctions (lacunar, non-lacunar), global. cortical atrophy scale (GCA), type and severity of hydrocephalus according to Evan's index, core and penumbra volume with mismatch ratio and mismatch volumes, the degree of collateral flow development (Miteff classification), the site of arterial occlusion. The report also contains imaging criteria for endovascular thromboextraction, developed in the trials DAWN (Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) trials, which guide the specialist in choosing treatment tactics.

The "standard radiological report" method developed by the author was approved by the University Radiology Department – protocol No. 9 from 4.11.2021, Certificate of innovation – No. 16/11.21/01 from 4.11.2021, Acts of implementations – No. 01-08/407 from 12.10.2021 Institute of Neurology and Neurosurgery and Nr 1001-21 from 13.10.2021 Medpark, AGEPI (The State Agency on Intellectual Property) Copyright Certificate – No. 1878 – Seria O / Nr 7100.

GENERAL CONCLUSIONS

1. Absolute and relative perfusion parameters were identified (% compared to healthy hemisphere) in patients with acute ischemic stroke within the first 24 hours of clinical manifestations, characteristic of the ischemic nucleus and penumbra (confirming the hypothesis of tissue window of application of the recanalization treatment, which significantly extends the duration of the therapeutic window used in contemporary clinical protocols for the diagnosis and treatment of stroke):

Ischemic core - Tmax (10.0 ± 0.3 sec, 214.08 ± 7.9%), MTT (14.16 ± 0.5 sec, 174.43 ± 7.2%), CBV (0.6 ± 0.2 ml / 100g, 32.85 ± 1.4%), CBF (4.23 ± 0.2 ml / 100g / min, 26.89 ± 1.5%), TTP (20.22 ± 0%), 4 sec, 144.46 ± 3.9%), MSI (0.45 ± 0.06, 47.47 ± 4.8%) and PEI (0.02 ± 0.005, 32.37 ± 2.05%).

Penumbra - Tmax (10.79 ± 0.2 sec, 236.59 ± 7.0%), MTT (16.99 ± 0.3 sec, 215.25 ± 5.8%), CBV (3.9 ± 2.1 ml / 100g, 97.47 ± 2.5%), CBF (8.41 ± 0.3 ml / 100g / min, 49.82 ± 2.0%), TTP (19.89 ± 0%) 3 sec, 141.27 ± 2.3%), MSI (0.63 ± 0.04, 70.16 ± 5.3%) and PEI (0.03 ± 0.008, 79.0 ± 2.07%).

2. The clinical-imaging correlation found that the deceased patients compared to the surviving patients had statistically significantly higher values of the NIHSS admission score, ischemic nucleus volume and penumbra, absolute and relative PS in the penumbra, absolute Tmax and TTP in the affected hemisphere, CBV relatively in the core, PEI relatively in the penumbra, the volume of the final lesion. Favorable discharge result correlates with lower values of absolute and relative Tmax in the penumbra and in the affected hemisphere, MTT and TTP absolute and relative in the affected hemisphere, relative TTP in the penumbra, absolute PS in the core and in the penumbra, relative PS in the penumbra, PS absolute and relative in the affected hemisphere, absolute and relative MSI in the core and statistically significantly higher values of absolute and relative in the core CBV, relative CBV in the affected hemisphere, absolute and relatively CBF in the core, relative CBF in the affected hemisphere, absolute and relative PEI in thecore, PEI relatively in the penumbra and in the affected hemisphere.

3. a. The risk of hemorrhagic transformation in patients with acute ischemic stroke is reflected by the increase in the volume of the acute lesion visible on the perfusion maps (Tmax, MTT, CBV, CBF, TTP, MSI and PEI), the increase in absolute perfusion values at admission in the core and penumbra (Tmax, MTT, TTP), increased relative values in the core (Tmax, MTT)

and in the penumbra (Tmax, MTT, TTP), which were statistically significantly higher in patients with hemorrhagic transformation compared to patients without transformation. In the group of patients with hemorrhagic transformation, the sign of hyperdense artery, occlusion in the large vessel, bad collaterals and insufficient revascularization were significantly more frequently visualized (TICI score 0-2a).

b. The perfusion map for measuring the permeability of the blood-brain barrier PS (permeability surface) showed a statistically significant difference in all measured parameters - absolute and relative PS in the core and penumbra in patients with and without hemorrhagic transformation of cerebral ischemic stroke. Overall, PS is an important neurophysiological imaging index in assessing the evolution of acute ischemic stroke, the risk of hemorrhagic transformation in the first hours of arterial occlusion, and the risk of an unfavorable clinical outcome.

4. The parameters of cerebral perfusion by computed tomography at hospitalization of patients did not find statistically significant differences in patients with and without severe internal carotid artery stenosis (which possibly contributes to the formation of ischemic preconditioning), apart from CBV and MSI. Repeated indices and clinical manifestations at discharge are certainly better.

5. The analysis of the parameters of the cerebral microcirculation by PCT in the subacute phase of the evolution of acute ischemic stroke in dynamics on the 4th-7th day highlighted the following spectrum of findings: 1) ischemic lesion, 2) persistent penumbra, 3) hyperperfusion (significant increase in perfusion rates compared to the healthy hemisphere), 4) normalization of cerebral perfusion. The assessment of the evolution in dynamics confirms the hypothesis of "tissue window" and "individualized window" with the persistence of areas of significant hypoperfusion for much longer than 24 hours - up to 7 days and probably more.

PRACTICAL RECOMMENDATIONS

1. To use the perfusionby computed tomography within 3-24 hours of the onset of clinical manifestations in patients with acute ischemic stroke, in the case of unknown onset or cerebral infarction on waking, after excluding other causes (hematoma, TIA, tumor, etc.) by computed tomography or brain magnetic resonance imaging.
2. Until the analysis of the CT perfusionto be verified in each patient the correctness of the selection of the main inlet artery and the large exit vein of the postprocessing program, in case of incorrect or suboptimal selection, it is recommended to switch to the manual method and correctly identify the vessels. necessary.
3. In the analysis of perfusion by CT in stroke patients to perform segmentation of the penumbra and core with the calculation of "mistCTAh ratio" and "mistCTAh volume".
4. Routine use “Standard radiological report for description of ischemic stroke on computed tomography or magnetic resonance imaging examination.
5. To assess and report cerebral perfusion changes not only in the affected arterial pool but also in the entire brain parenchyma, using the whole brain method.
6. To calculate in routine practice the permeability of the blood-brain barrier in patients with acute ischemic stroke.

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la care au fost prezentate rezultatele cercetărilor la teza de doctor în științe medicale cu tema „Diagnosticul și prognozarea precoce a evoluției accidentului vascular cerebral ischemic acut”, realizată în cadrul Catedrei de neurologie nr. 1 a Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”, a dnei **Pleșcan Tatiana**

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LIST OF ABBREVIATIONS

ACA	-	the anterior cerebral artery
ICA	-	internal carotid artery
MCA	-	middle cerebral artery
PCA	-	posterior cerebral artery
ASPECTS	-	Alberta Stroke Program Early Computed Tomography Score
CTA	-	computed tomography angiography
AIS	-	acute ischemic stroke
BBB	-	blood-brain barrier
CBF	-	cerebral blood flow
CBV	-	cerebral blood volume
RF	-	risk factors
mRS	-	modified Rankin scale
MSI	-	mean slope of increase
MTT	-	mean transit time
NIHSS	-	National Institutes of Health Stroke Scale
IPC	-	ischemic preconditioning
PEI		positive enhancement integral
PS	-	permeability surface
PCT	-	perfusion by computed tomography
CT	-	computed tomography
NCCT	-	non-contrast computed tomography
ET	-	endovascular treatment
HT	-	hemorrhagic transformation
TICI	-	Thrombolysis in Cerebral Infarction
IVT	-	intravenous thrombolysis
Tmax	-	blood transit time to the peak of the impulse response
TTP	-	time to peak

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