

The Alberta Stroke Program Early CT score (ASPECTS): A predictor of mortality in acute ischemic stroke

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Abstract. Stroke is one of the leading causes of mortality globally and a main cause of disability. The objective of this study was to evaluate the importance and utility of the Alberta Stroke Program Early CT Score (ASPECTS) as a mortality predictor factor in diabetic vs. non-diabetic patients with acute ischemic stroke (AIS), correlated with age, monocyte values, and high-sensitivity cardiac troponin I (hs-cTnI). The prospective longitudinal observational study included 340 patients with AIS divided into two groups: diabetics and non-diabetics. ASPECTS was evaluated within the first 24 h after admission to the center. The ASPECTS was lower in the group of diabetic patients on average 4.9 vs. 6.05 ($P < 0.0001$). As the age of the patients increased, the lower the ASPECTS and the higher infarct size, indicating a statistically significant ($P < 0.0001$) result. The optimal correlation was observed between infarct size (ASPECTS) and hs-cTnI serum level [95% confidence interval (CI): -0.3216 to -0.1193; $P < 0.0001$]. Almost 94% of patients who had an ASPECTS higher than 3 points on admission survived, resulting in a favorable outcome and a very good predictability of the score (95% CI: 0.85 to 0.926, $P < 0.0001$). The ASPECTS is a mortality predictor, its value correlating inversely with the severity and evolution of patients, confirming

a good predictability with good specificity, sensitivity and area under the curve.

Introduction

Stroke is one of the leading causes of mortality worldwide and a main cause of disability in Western countries (1). The incidence of stroke is on the increase worldwide, as are the costs related to it (2). As traditional risk factors represent only a part of this increase, other factors that are not recognized (3) must be involved. Patients with type 2 diabetes present an increased risk of ischemic stroke and other cardiovascular diseases (4). It is estimated that 285 million individuals worldwide suffered from diabetes in 2010 and this number is due to increase to 439 million worldwide by 2030 (5). The risk of recurrent stroke and carotid artery stenosis in diabetic patients appears to be high (6). People with type 2 diabetes are frequently obese and have a higher risk of peripheral arterial disease, large vessel atherosclerosis and stroke (7,8).

Several possible mechanisms of stroke are involved in diabetic patients: vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation and thickening of the capillary basal membrane (9,10). Abnormalities in the early left ventricular diastolic filling are commonly observed in type 2 diabetes. The proposed mechanisms of congestive heart failure in type 2 diabetes include microvascular disease, metabolic derangements, interstitial fibrosis, hypertension and autonomic dysfunction. Vascular endothelial function is critical for maintaining structural and functional integrity of the vessel walls, as well as the vasomotor control (11). Nitric oxide (NO) mediates vasodilation, and its decreased availability can cause endothelial dysfunction and trigger a cascade of atherosclerosis. For example, NO-mediated vasodilation is impaired in individuals with diabetes, possibly due to increased inactivation of NO or decreased reactivity of the smooth muscle to NO. Individuals with type 2 diabetes have stiffer arteries and decreased elasticity compared with subjects having normal glucose levels. An increased inflammatory response is frequently observed in individuals with diabetes, inflammation playing an important role in the development of atherosclerotic plaque.

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C-reactive protein, cytokines and adiponectin are the main serum markers of inflammation (11).

The first vascular changes in the stroke area consist of swelling of the capillary endothelium and endocytosis of endothelial nuclei inside the vessel lumen. Similarly, changes inside the capillary lumen, hyalinization and sclerosis of the white matter arterioles appear. Secondary to plasmatic component release inside the ischemic stroke area, the swelling and breakdown of cell walls, and also perivascular edema are discernible. Vasogenic cerebral edema is markedly visible inside white matter. Newly formed vessels can be observed starting the third day after stroke. Mostly visible at the outskirts of the ischemic area, angiogenesis is also evident inside necrotic-associated areas (12).

Management of patients with acute ischemic stroke (AIS) is heavily dependent on an assessment of the extent of irreversible brain injury at baseline. Patients with extensive early ischemic changes at presentation are unlikely to benefit from thrombolysis or thrombectomy procedures (9). Moreover, such patients may also be at higher risk of developing complications of treatment, such as intracerebral hemorrhage (13). Rapid screening of patients for thrombectomy without the need for more advanced imaging modalities, such as computed tomography (CT) or magnetic resonance imaging-based perfusion, is the main advantage of using Alberta Stroke Program Early CT Score (ASPECTS) in clinical practice (14).

ASPECTS is a topographic scoring system that applies a quantitative approach, measuring the extent of early ischemic changes. It does not require physicians to evaluate volumes from two-dimensional images on pretreatment studies. The ASPECTS was developed to indicate the reliability and usefulness of a CT scan with a reproducible classification system to evaluate early ischemic changes (<3 h after the onset of symptoms) on CT studies prior to treatment in patients with ischemic stroke (15). More recently, the ASPECTS has been recognized as a key selection criterion in updated guidelines of the American Heart Association on acute stroke management, where endovascular therapy is recommended for patients with ASPECTS ≥ 6 at baseline (16).

Monocyte levels increase in patients with severe AIS or in those with associated infections and can be markers of brain damage. During the last decade, several studies aimed to establish prognostic algorithms in patients with stroke, by assessing correlations between biochemical markers and imaging findings. However, their results have not yet been applied in clinical practice. The objective of our study was to evaluate the importance of the ASPECTS as a mortality predictor correlated with clinical and biochemical data: age, values of monocytes and values of high-sensitivity cardiac troponin I (hs-cTnI), involved in the prognosis of AIS in diabetic vs. non-diabetic patients, as the profile of stroke may be different in diabetics.

Patients and methods

Study design. This is a prospective longitudinal observational study conducted at the Clinical County Emergency Hospital of Oradea, Oradea, Romania, from the 1st of January 2016 until 1st of January 2019. The study comprised 340 patients, 134 female and 236 male. The inclusion criteria were as follows: Diagnosis

of AIS, age between 40 and 90 years, imaging-confirmed ischemic stroke (CT scan), embolic production mechanism and thrombotic production mechanism. The exclusion criteria were represented by transient ischemic stroke, hemorrhagic stroke, hemorrhagic-transformed ischemic stroke, neoplastic patients, patients with autoimmune diseases, age <40 years or >90 years.

The patients were divided into two groups, diabetic (D) patients (n=101) and non-diabetic (ND) patients (n=239), for whom were analyzed the main ASPECTS as a predictive mortality factor correlated with age, monocyte values, and hs-cTnI. The ASPECTS was evaluated within the first 24 h of admission to the center, and the CT scan was performed within the first few hours of admission.

Statement of ethics approval. The entire study was conducted respecting the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) (17). The study was approved by the Ethics Committee of the Clinical County Emergency Hospital of Oradea, Bihor County, Romania (decision no. 30372/06.12.2018). All the patients signed an informed consent at the moment of their hospitalization, according to the hospital's protocol.

Methodology. ASPECTS is a 10-point quantitative topographic CT scan score used in patients with middle cerebral artery (MCA) stroke. It has also been adapted for the posterior cerebral circulation. Segmental assessment of the MCA vascular territory is made and 1 point is deducted from the initial score of 10 for every region involved: caudate, putamen, internal capsule, insular cortex, M1: 'anterior MCA cortex', corresponding to frontal operculum; M2: 'posterior MCA cortex', corresponding to posterior temporal lobe; M4: 'anterior MCA territory immediately superior to M1', M5: 'lateral MCA territory immediately superior to M2'; M6: 'posterior MCA territory immediately superior to M3'. An ASPECTS of ≤ 7 predicts a worse functional outcome at 3 months, as well as symptomatic hemorrhage (18). Variations of the ASPECT scoring system have been described for use in the posterior circulation and referred to as pc-ASPECTS. As it is the case for the anterior circulation, the pc-ASPECTS is a 10 point scale, where points are lost for each region affected. Unlike ASPECTS, the pons and the midbrain are worth 2 points each (regardless of whether or not the changes are bilateral; any involvement of the pons, for example, 2 points are deducted), thalami (1 point each), occipital lobes (1 point each), midbrain (2 points), pons (2 points), and cerebellar hemispheres (1 point each) (19).

Upon admission, the patients enrolled in the study underwent an imaging investigation consisting of a native CT scan, using the General Electric Optima 520 device with 16 turns (General Electric Co.). The images presented in the study were selected from diabetic and non-diabetic patients enrolled in the study, with the only criterion being the location of ischemic stroke in the affected territories, the images being processed by the Aycan Workstation 3.12,000 version 1.20 (Digitalsysteme GmbH).

The value of monocytes was determined from the whole blood, using the photometric impedance method (Cell Dyn Ruby analyzer), and the hs-cTnI value was determined via spectrophotometry, using an Architect ci4100 analyzer.

Table I. Main characteristics of the groups of patients with acute ischemic stroke.

Parameter	Patients		P-value	95% CI of difference	SE	Difference
	Diabetic (n=101)	Non-diabetic (n=239)				
Mean age (years)	64.78±0.85	63.42±0.6859	0.21	-3.518 to 0.8098	-	-
ASPECTS (points)	4.9307	6.0586	<0.0001	0.6213 to 1.6345	0.2575	1.1279
Monocyte level (%)	0.96	0.68	<0.0001	-0.3364 to -0.2111	0.03184	-0.2738
Hs-cTnI (pg/ml)	1,740.2584	88.7866	<0.0001	-2199.2928 to -1103.6508	278.5048	-1,651.4718
Glycosylated hemoglobin (%)	9.069±0.2082	5.656±0.05489	<0.0001	3.100 to 3.727	-	3.413±0.1593
Serum glucose (mg/dl)	276.9±7.864	84.56±0.6171	<0.0001	182.1 to 202.5	-	192.3±5.189

ASPECTS, Alberta Stroke Program Early CT Score; Hs-cTnI, high sensitivity cardiac troponin I; CI, confidence interval; SE, standard error.

Statistical analysis. The database was gathered in a Microsoft Excel document. For the analysis of correlations, the correlation tests available in the MedCalc program 14.1 were used. The correlation coefficient r (which can have values between -1 and 1) was analyzed. An inversely proportional correlation between the studied parameters was defined by an r value between -1 and 0. A value of 0, or close to it, shows the lack of any correlation, and the unilinear, directly proportional relationship is defined as a value between 0 and 1 of the correlation coefficients. For each analysis, the Gaussian distribution of the data was studied, to use the Pearson coefficient, if it is observed, and the Spearman coefficient if it is not observed. $P < 0.05$ were validated and considered to indicate statistical significance. These correlations were represented graphically by the graphical methods available in linear regression analyses.

The Gehan-Breslow-Wilcoxon test was used for the survival analysis of diabetic vs. nondiabetic patients. Receiver operating characteristic (ROC) curves were used to determine cut-off point values. This analysis also revealed the sensitivity and specificity of this value, as well as the area under the curve (AUC). The P-value, considered to be statistically significant, was a value below 0.05, which is obtained by comparing the area under the analyzed curves with an area under the curve of 0.5.

Results

Patient characteristics. The riskiest period for the development of an ischemic stroke is represented by the 6th and 7th decade, the most dangerous interval for diabetic patients being between 60 and 65 years, with a 95% confidence interval (CI) of 0.871 to 2.314. For non-diabetics, the interval was 65-70 years, with a 95% CI of 0.340 at 1,184; the difference between the two groups was not statistically significant. The main characteristics of the two groups of patients are presented in Table I.

Diabetic vs. non-diabetic groups. The ASPECTS was inferior in the group of diabetic patients (n=101 cases), 95% CI for the mean of 4.4692 to 5.3922, standard deviation (SD) 2.3378, compared to the non-diabetic control group (n=239 cases), 95% CI for the mean 5.7915 to 6.3256, SD 2.0956, arithmetic mean 4.9 vs. 6.05, the difference being statistically significant ($P < 0.0001$). The 95% CI difference was 0.6213 to 1.6345, from which it can be deduced that diabetic patients have more extensive strokes, and thus a lower ASPECTS (Fig. 1).

Age. The data obtained in this study related to the age of the patients with AIS was correlated with the size of the infarction. The data were quantified via the ASPECTS, and showed a directly proportional relationship; thus the older the age, the larger the infarct size, and consequently a lower ASPECTS. Following analysis of the lot of 340 patients with AIS, a correlation coefficient r of -0.4 was obtained, with a 95% CI of -0.5388 at -0.3704 and significance level $P < 0.0001$ (Fig. 2).

Value of monocytes. The value of monocytes in patients from the two groups recorded higher values in the group of diabetic patients, with an average value of 0.96%, with a 95% CI, of 0.8931 to 1.0289 vs. non-diabetic patients, 0.68% with a 95% CI, of 0.6580 to 0.7165, $P < 0.0001$. A correlation between the number of monocytes and the infarct size (ASPECTS) was obtained. Basically, the higher the number of monocytes, the lower the ASPECTS, resulting in a large cerebral infarction; thus, there was an inversely proportional relationship between the infarct size and the number of monocytes, $P = 0.0018$, 95% CI for r -0.2704 to -0.06340). The number of monocytes at diagnosis in the study group is generally between 0.6 and 0.9%, with an average of 0.76% with a 95% CI of 0.7372 to 0.8004 and a standard deviation of 0.29. The highest

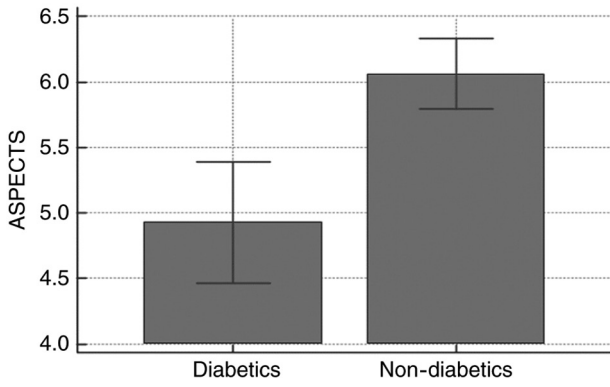


Figure 1. The Alberta Stroke Program Early CT Score (ASPECTS) in diabetic vs. non-diabetic patients.

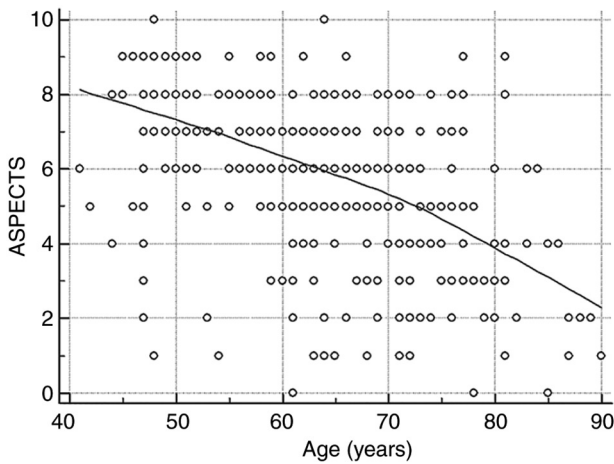


Figure 2. Correlation of the Alberta Stroke Program Early CT Score (ASPECTS) with age (years) at diagnosis.

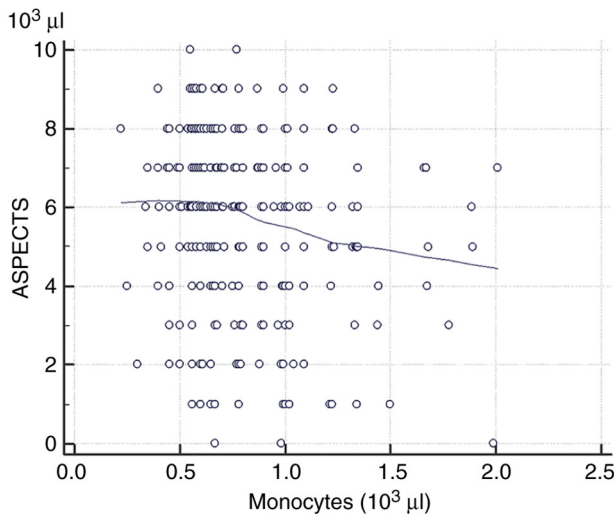


Figure 3. Correlation of the Alberta Stroke Program Early CT Score (ASPECTS) with the number of monocytes.

value of the number of monocytes was 2.01%, and the lowest was 0.22%. The correlation between the ASPECTS and the number of monocytes is presented in Fig. 3.

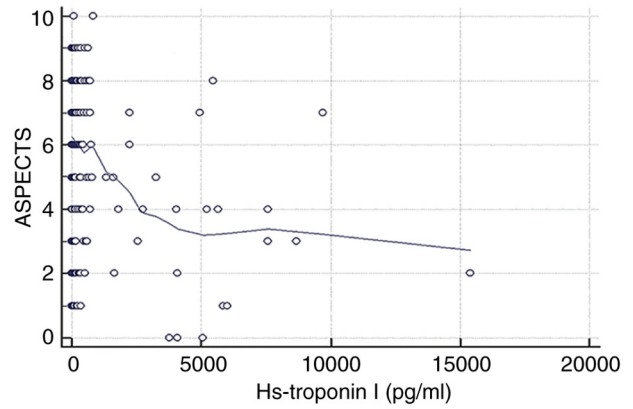


Figure 4. Correlation of the Alberta Stroke Program Early CT Score (ASPECTS) with the high-sensitivity cardiac troponin I (hs-cTnI) level.

hs-cTnI correlation with ASPECTS. The correlation of cardiac troponins with AIS was carefully researched. In the present study, regarding the level of hs-cTnI and the correlation with the ASPECTS, a directly proportional relationship was observed between the hs-cTnI level and the infarct size. Therefore, an inversely proportional relationship was noted with the ASPECTS, 95% CI -0.3216 to -0.1193. According to the statistical results, there was a statistically significant correlation with a P-value of <0.0001, between the studied parameters, i.e., hs-cTnI and ASPECTS. As shown in Fig. 4, the higher the level of hs-cTnI the lower the ASPECTS score.

Patient survival. The relationship of ASPECTS with the survival of patients with AIS was also studied. The ASPECTS was much lower in deceased patients, 95% CI of 2.1818 to 3.2467, compared to the group of surviving patients, 95% CI of 6.1136 to 6.5202, with an average of 2.7 v. 6.3, the difference being strongly statistically significant with $P < 0.0001$, 95% CI of 3.0897 to 4.1155. The ASPECTS in surviving patients vs. deceased patients is summarized in Fig. 5.

Elderly and survival. Old age seems to be a relevant factor when it comes to survival in patients who have suffered an ischemic stroke. The difference between the two groups is almost 7 years, being strongly statistically significant, $P < 0.0001$. In the first group of deceased patients, age was recorded as an average value of 69.4 years with a 95% CI of 66.6660 to 72.22983, the standard deviation being 10.5158; in the group of survivors, the mean age was 62.6 years, with a 95% CI of 61.4043 to 63.7999, the standard deviation being 10.2547. These results are summarized in Fig. 6.

AIS and survival. According to the results obtained after observing the group of 340 patients with AIS, divided into the two groups (the group of diabetic patients and the control group of non-diabetic patients), regarding survival, it can be observed that in the first 20 years from onset of stroke, survival showed a downward trend among the diabetic patients compared to non-diabetic patients, according to the Gehan-Breslow-Wilcoxon test, $P = 0.002$; after this period, the difference in survival became insignificant (Fig. 7).

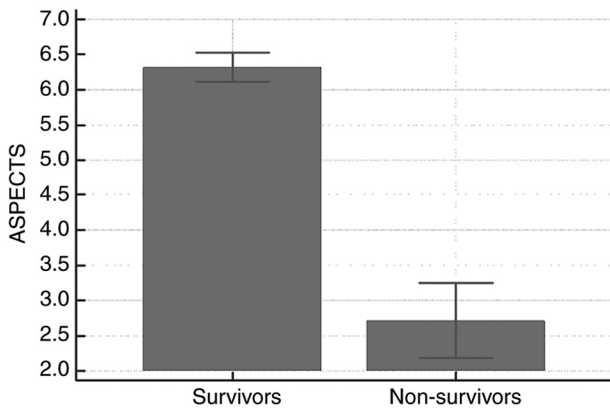


Figure 5. Alberta Stroke Program Early CT Score (ASPECTS) in surviving patients vs. deceased patients.

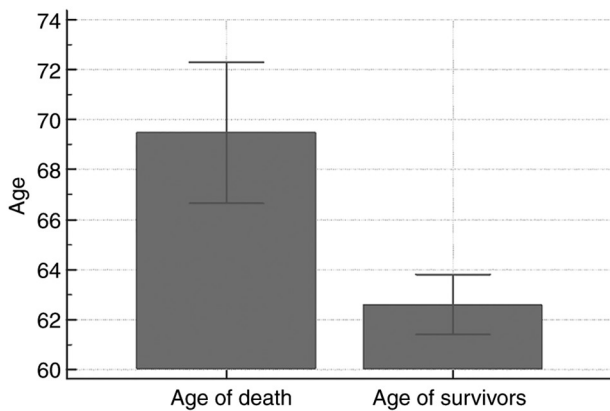


Figure 6. Age of deaths vs. age of survivors (years).

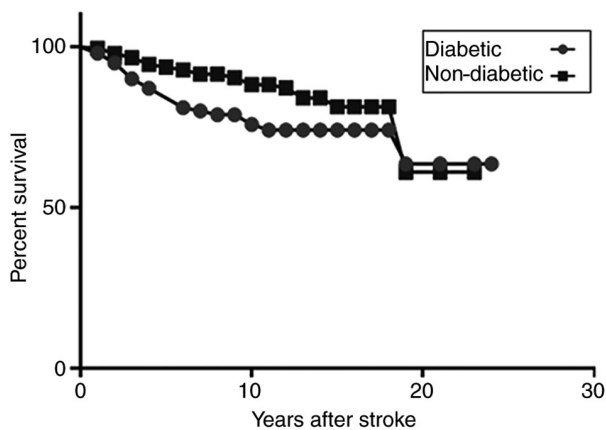


Figure 7. Survival of diabetic vs. nondiabetic patients.

ROC curves. According to the analysis of ROC curves, the ASPECTS proved to be of impressive utility. Almost 94% of patients who had ASPECTS >3 on admission survived, resulting in a favorable result and very good predictability of the score (95% CI: 0.85 to 0.926, $P < 0.0001$). The specificity with a value of 93.7% and the sensitivity with a value of 78.6% suggested that the ASPECTS is the parameter with the best specificity, sensitivity and area under the curve (AUC 0.896) (Fig. 8).

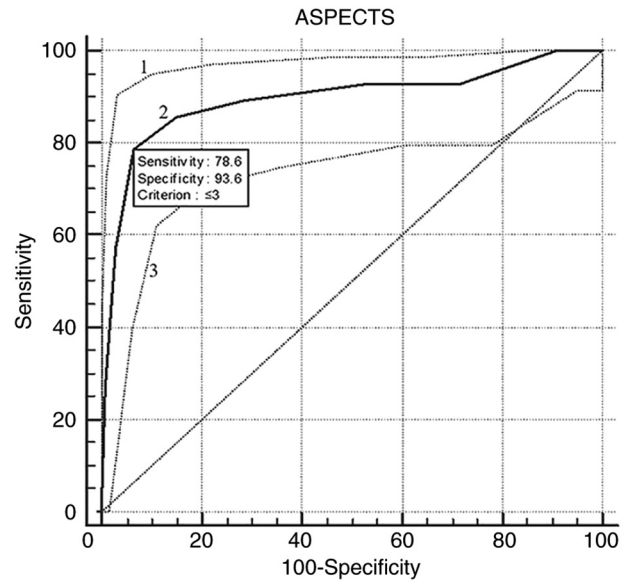


Figure 8. Alberta Stroke Program Early CT Score (ASPECTS) and Receiver operating characteristic curves, with a focus on sensitivity, and specificity. Line 1 represents the specificity, which is 93.7%. Line 2 represents the cut-off point, which corresponds with calculated specificity and sensitivity. Line 3 represents the sensitivity, which is 78.6%.

Discussion

The results obtained in the current research highlight the importance of the Alberta Stroke Program Early CT Score (ASPECTS), calculated at patients' admission, as a predictor of mortality correlated with other factors, in diabetic vs. non-diabetic patients who suffered an ischemic stroke. The most dangerous period for the development of an ischemic stroke is represented by the 6th and 7th decade. As other data also indicated, the incidence of stroke increases significantly with age, both in men and women, with incidence rates accelerating exponentially after 70 years (20). In the case of the elderly, the increased risk of stroke, as well as the higher risk of mortality and disability are strongly connected with poor physical activity, diet rich in fatty products, along with comorbidities such as arterial hypertension, diabetes or comorbidity factors including obesity, body fat distribution or hypercholesterolemia (21).

The number of monocytes at diagnosis in the study group was between 0.6 and 0.9%, with an average of 0.76%. The highest value of monocytes was 2.01%, and the lowest was 0.22%. The higher the number of monocytes, the lower the ASPECTS score, resulting in a large cerebral infarction; thus, there was an inversely proportional relationship between the infarct size and the number of monocytes, $P = 0.0018$, 95% CI for r -0.2704 to -0.06340. Monocytes are crucial in the prognosis after AIS, and are taken from the ischemic region (10). Thus, many functional differences between monocyte subtypes in AIS are highlighted. Moreover, AIS influences the peripheral immune response, determining characteristic immune responses of the brain, influencing the prognosis of AIS patients (22). In a study conducted by Kaito *et al* it was suggested that the number of the common monocyte subtype (CD14⁺⁺, CD16), that is the proinflammatory monocyte subtype in rodents, was significantly higher in peripheral blood flow,

while the number of the non-common monocyte subtype, the anti-inflammatory monocyte subtype in rodents, was significantly lower in the acute phase of AIS, strongly connected with the evolution and gravity of brain infarction (22). Clinical assays also revealed the connection of the higher number of classical monocytes, beginning to grow in the peripheral blood flow in the first 3 h after AIS onset, with the severity of brain damage (23). Thus, it is indicated that the prognosis of AIS patients with increased monocyte number at admission may be more difficult than in other patients, as indicated by the results of the present study. Previous findings revealed the multiple effects of HDL-cholesterol (antithrombotic, antioxidant and anti-inflammatory), which has a role of inhibiting the endothelial expression of adhesion molecules, impeding monocyte adherence to the arterial wall (24-26).

The best correlation was observed between infarct size (ASPECTS) and hs-cTnI serum level, 95% CI -0.3216 to -0.1193, $P < 0.0001$. The higher the level of serum hs-cTnI, the lower the ASPECTS score, resulting in a high-risk ischemic stroke. This result showed that the ASPECTS correlates very well with the highly sensitive (HS) I troponin, and is statistically significant with a P-value of < 0.0001 . A meta-analysis evaluated the increase of cardiac biomarkers after AIS and brain hemorrhage, revealing cardiac impairment and dysfunction due to stroke. In order to establish additional diagnosis and identify patients with increased risk of cardiac events, the biochemical analysis of brain natriuretic peptide (BNP), cTn and N-terminal BNP (NT-proBNP) (indicators revealing myocardial damage in stroke) was indicated. The cardiac biomarkers need to be attentively monitored, focusing on the therapy of cerebrovascular impairments, to offer immediate and proper treatment (24).

In the late 1970s, a study of cardiac enzymes released during the acute phase of ischemic stroke commenced (25). Further research correlated myocardial impairment after stroke, as well as acute cerebral lesions to increased levels of plasma catecholamines after the rapid increase of intracranial pressure (21). Currently, cardiac troponins are considered the most efficient biomarkers for myocardial injury available in the clinical setting. The first report associating the values of troponin with poor results in a group of patients with consecutive ischemic stroke considered a concentration of cTnT > 0.1 mg/l as highly increased troponin (26). Studies were conducted 12-72 h after admission, as well as after an undetermined delay from the stroke onset. For 70% of the patients, the values of troponin were high, troponin positivity being connected with a 3-fold increase of the risk of in-hospital death (27).

The data presented in the present study enhance understanding of the effects of troponin positivity in case of AIS. Since increased troponin levels have been associated with a higher risk of in-hospital cardiac events and death, adding the cTnI test to the admission analyses is indicated, given that myoglobin or CK-MB values, as well as ECG changes, have a less accuracy. Compared to the systematic screening strategy, it is preferable and cost effective to resume cTnI examination in patients with increased risk of stroke (28,29). Cardiac events and elevated troponin T levels have been used frequently in patients presenting severe ischemic strokes. Nevertheless, CT could not be associated with clinical results. The troponin T assay was used in this study to determine the incidence of

unsuspected cardiac events in patients who presented with ischemic stroke (30).

To sum up, the present study did not reveal pathologically elevated cTnI or cTnT concentrations for a significant subgroup of patients with acute cerebral ischemia. The regular diagnosis should not include measuring the levels of cTnI or cTnT, as it has no influence on the results (30). In many cases of patients with acute stroke, the serum hs-cTnT grows considerably, as several studies reveal. The therapy guidelines for AIS patients require troponin determination in acute phase (31). The relationship between the troponin growth after AIS and the disability and mortality rate in case of stroke patients is still arguable. Some studies show a connection between these factors, while other studies claim the opposite. There are data highlighting the relationship between increased troponin and low functional prognosis, with elevated troponin values being associated with increased risk of mortality (28,29,32,33). The pathophysiological action of troponin growth in AIS remains uncertain, generating confusion in diagnosis and therapy. A significant correlation of high hs-cTnT values with major disability or death risk, in the three months interval after AIS, was revealed after adjusting the data. These results showed that the association was independent of risk factors such as age and baseline NIHSS score, increased serum hs-cTnT levels being an independent risk factor for poor results, having prediction values for major disability and death in patients with AIS (34,35).

The limitation of our study derived from its monocentric type, with results that should be validated in other multicentric studies.

In conclusion, the ASPECTS proves to be of impressive utility. In the current study, almost 94% of patients who had ASPECTS > 3 on admission survived, resulting in a favorable result and very good predictability of the score (95% CI: 0.85 to 0.926, $P < 0.0001$). The specificity with a value of 93.7% and the sensitivity value of 78.6% proved that the ASPECTS is the parameter with the best specificity, sensitivity and area under the curve (AUC 0.896). As for the volume representation (semiquantitative method), the ASPECTS regions are unevenly evaluated, the particular ASPECTS regions having possible interindividual variability. The considerable variation of CT perfusion-derived ischemic core volumes in the same ASPECTS levels, as well as the absence of a powerful correlation between the methods, made the findings of the present study useful. Although elevated ASPECTS indicate positive outcomes, parts of infarcted tissue may remain undetected early after the infarction.

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Availability of data and materials

All data are registered at the Clinical County Emergency Hospital of Oradea, Oradea, Bihor County, Romania.

Authors' contributions

NOP, MAM, EEB and MS collected, analyzed and interpreted the patient data. DMT, CCD, MIP and SB made substantial contributions to the conception of the work and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript to be published. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Clinical County Emergency Hospital of Oradea, Bihor County, Romania (decision no. 30372/06.12.2018). All the patients signed informed consent at the moment of their hospitalization, according to the hospital's protocol.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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