

# Current data about localization of acute ischemic stroke and prognostic factors in diabetic and non-diabetic patients

Nicolae Ovidiu POP<sup>1,2</sup>, Petru Aurel BABEȘ<sup>3</sup>, Larisa Bianca HOLHOȘ<sup>4</sup>, Eugenia GAVRILUȚ<sup>3</sup>, Gabriel Mihai MEKEREȘ<sup>5</sup>, Mariana MEKERES-RACOVIȚĂ<sup>6</sup>, Voiță Nuțu CRISTIAN<sup>6</sup>, Alina Oana IACOB-CUCIAN<sup>7</sup>

<sup>1</sup> Intensive Care Anesthesia Clinic, County Emergency Clinical Hospital, Oradea, Romania.

<sup>2</sup> Department of Surgical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Romania

<sup>3</sup> Faculty of Medicine and Pharmacy, University of Oradea, Romania

<sup>4</sup> Department of Morphological Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410073, Romania.

<sup>5</sup> Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Romania

<sup>6</sup> Faculty of Medicine and Pharmacy, University of Oradea, Romania

<sup>7</sup> County Emergency Clinical Hospital, Tg. Mures, Romania

## ABSTRACT

**Introduction.** Ischemic stroke accounts for approximately 85% of all vascular accidents and has a high number of identified risk factors, including transient ischemic attack, smoking, metabolic syndrome, alcohol consumption, elevated cholesterol levels and artery stenosis carotid. Diabetes mellitus (DM) is a well-established risk factor for ischemic stroke.

**Material and method.** This prospective longitudinal observational study highlights the importance of localization of ischemic stroke, including 340 patients with acute ischemic stroke with / without diabetes mellitus. The database was collected in a Microsoft Excel document. The correlation analysis was processed in the MedCalc 14.1 program where correlation tests included in the program were used.

**Results.** The predominant localization of ischemic stroke in diabetic patients was the middle cerebral artery followed by the posterior cerebral artery and the double localization compared to the group witness where the same trend is maintained ( $p = 0.22$ ). The correlation between the localization of the acute ischemic stroke with the age 64.5 for MCA, 64.6 for PCA, and 73.57 for DL (CI 95%,  $p = 0.02$ ). The correlation of the NIHSS severity score with the location of ischemic strokes was also obtained: average NIHSS score 18.9 points for MCA, 18.5 for PCA, 24 for DL (CI 95,  $p < 0.0001$ ). The data obtained from the Kaplan-Meier analysis on the survival rate of the patients (divided by the vascular territory involved), provided an expected result difference (statistically significant,  $p < 0.0001$ ).

**Conclusions.** There is no statistically significant difference between diabetic vs. non-diabetic patients regarding the localization correlated with DM, the double location being statistically insignificant between the two batches. The double location having a higher frequency in elderly patients.

**Keywords:** diabetes, non-diabetes, ischemic stroke, prognosis

Corresponding author:

Nicolae Ovidiu Pop

E-mail: pop\_ovidiu212@yahoo.com

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## INTRODUCTION

In developed countries, stroke is the third cause of mortality, followed by neoplastic and cardiovascular diseases. Increased risk is often seen in people with diabetes and is associated with weaker clinical outcomes (including higher mortality), so, the evaluation of the risk factors and prognosis for stroke are of utmost importance in patients' evolution.

Ischemic stroke accounts for approximately 85% of all vascular accidents [1] and has a high number of identified risk factors, including transient ischemic attack, smoking, metabolic syndrome, alcohol consumption, elevated cholesterol levels and artery stenosis carotid [2]. Also, diabetes mellitus (DM) is a well-established risk factor for ischemic stroke [3]. In addition, diabetes is considered a cerebrovascular risk factor, associated with increased mortality in the hospital, in patients with ischemic stroke [4-7]. Despite the improvement in primary prevention and acute treatment over the past decades, the stroke is still a devastating disease. At the beginning of the 21st century, the incidence of strokes in Europe ranged from 95 to 290 / 100,000 inhabitants / year, with a mortality rates / month of 13-35% [8]. Approximately 1.1 million Europeans have suffered a stroke in each year, 80% of being of ischemic type. Although the incidence of stroke worldwide is in decline, the incidence of vascular accident in young people is increasing. Due to the aging population the number of strokes is expected to increase drastically in the next few years to 2025, 1.5 million Europeans will suffer an annual stroke [9,10]. Managing the risk factors of stroke should prolong or prevent the incident of acute thrombotic stroke since most of the patients with type 2 diabetes mellitus came to the hospital with a condition of hyperglycemia and hypertension [11].

Anterior and posterior circulation ischemic stroke have different natural histories, these regional differences in the prevalence of individual risk factors might also affect the case fatality rates for ischemic stroke. Furthermore, targeting individual risk factor modification at a population level (e.g. DM or atrial fibrillation) may exact both a quantitative and qualitative effect on stroke incidence [12]. Intracranial atherosclerosis of the anterior circulation and intracranial atherosclerosis of the posterior circulation are thought to involve different pathogeneses and risk factors [13,14].

Stroke mechanisms differ according to the location of cerebral atherosclerosis. Because perforators are directly branched out of intracranial atherosclerosis, it is understandable that intracranial atherosclerosis produces strokes more often by way of local branch occlusion. In addition, in situ thrombo-occlusion is more common in patients with intracranial atherosclerosis,

probably because of relatively sufficient collateral circulation through the posterior communicating artery, anterior communicating artery, and external carotid artery in patients with extracranial atherosclerosis. However, artery-to-artery embolism was the dominant stroke mechanism in extracranial atherosclerosis, both in patients with anterior (proximal internal carotid artery) and posterior (proximal vertebral artery) circulation diseases. Nevertheless, stroke mechanisms still differed in apparently similar intracranial vessels. For instance, although artery to artery embolism was the most frequent stroke mechanism in patients with middle cerebral artery disease, local branch occlusion was the most important mechanism associated with basilar artery disease. In general, artery to artery embolism was more prevalent in anterior circulation intracranial atherosclerosis, whereas local branch occlusion was more common in posterior circulation intracranial atherosclerosis. This difference may be attributable to smaller and shorter perforating vessels arising from posterior circulation arteries that may be more vulnerable to occlusion in the presence of parental artery atherothrombosis. Alternatively, because posterior circulation intracranial atherosclerosis is more closely associated with metabolic risk factors, such as hypertension and diabetes ready may be atherosclerotic and thus more vulnerable to occlusion in the presence of parental artery disease [12,15,16].

## AIM

The main aim of this study is to present the importance of localization of ischemic stroke in the diabetic patient, as well as the to evaluate the prognostic factors compared to acute ischemic stroke at nondiabetic patients.

## MATERIALS AND METHODS

### Study design

A prospective longitudinal observational study was conducted within the Clinical County Emergency Clinical Hospital of Oradea, Romania, from 1st of January 2016 until 1st of January 2019. In the study, were enrolled 340 patients, both females and males.

The inclusion criteria were as follows: age between 40 and 90 years, imaging-confirmed ischemic stroke diagnosis (CT scan). The exclusion criteria were represented by transient ischemic stroke, hemorrhagic stroke, hemorrhagic-transformed ischemic stroke, neoplastic patients, patients with autoimmune diseases, age over 90 years or under 40 years.

Upon admission, the patients enrolled in the study underwent an imaging investigation consisting of a na-

tive CT scan. Depending on the arterial location of the ischemic stroke were divided into 3 groups MCA, PCA and DL and was analyzed the localization of the stroke in the arteries, respectively the MCA, PCA and DL, correlated with age, NIHSS scale, number of days of hospitalization, survival rate and has been studied comparative the localization of the stroke in the arteries at diabetic patients and nondiabetic patients.

### Ethical statement

The entire research study was conducted respecting the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). 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).

### Methodology

For quantification of the stroke-related neurologic deficit, it was used the National Institutes of Health Stroke Scale (NIHSS), a clinical assessment tool that estimate the acuity of stroke patients, determine the treatment, and suggest outcome prediction for the patient [17]. NIHSS is a quantitative measure of stroke-related neurologic deficit that has proven intra- and inter-rater reliability and has predictive validity for long-term stroke outcome [18-24]. Evaluation of the NIHSS in the first 24 hours after stroke onset could predict the next level of care after acute hospitalization [25].

The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. Ratings for each item are scored on a 3- to 5-point scale, with 0 as normal, and there is an allowance for untestable items. Scores range from 0 to 42, with higher scores indicating greater severity.

Stroke severity may be stratified on the basis of NIHSS scores as follows: very severe <25, severe 15-24, mild to moderately severe 5-14, mild 1-5 [23,25].

Imaging investigation consisting of a native CT scan, it was done with the General Electric Optima 520 device with 16 turns (General Electric Company, USA). The images presented in the paper are selected from diabetic and non-diabetic patients enrolled in the study, having as criterion the location of ischemic stroke in the affected territories, the images being processed by the Aycan Workstation 3.12,000 version 1.20.

### Statistical analysis

The database was collected in a Microsoft Excel document. The correlation analysis was processed in

the MedCalc 14.1 program where correlation tests included in the program were used. The correlation coefficient  $r$ , which can take values between -1 and 1 was analyzed. An inversely proportional correlation between the studied parameters is defined by a value  $r$  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 coefficient. For each analysis, the Gaussian distribution of the data was studied, so as to use the Pearson coefficient, if it is observed, and the Spearman coefficient if it is not observed. Results with a  $p$  value less than 0.05 were validated and considered statistically significant. These correlations were represented graphically by the graphical methods available in linear regression analyzes.

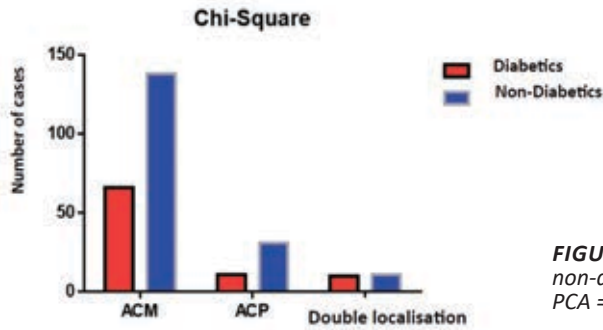
The use of ROC curves was performed to determine the limit of cut-off-point values. The result of this analysis denotes the sensitivity, the specificity of these values, but also the area under the curve (AUC). The  $p$  value, considered to be statistically significant, is a value below 0.05, which is obtained by comparing the area under the analyzed curves with an area under the curve of 0.5.

## RESULTS

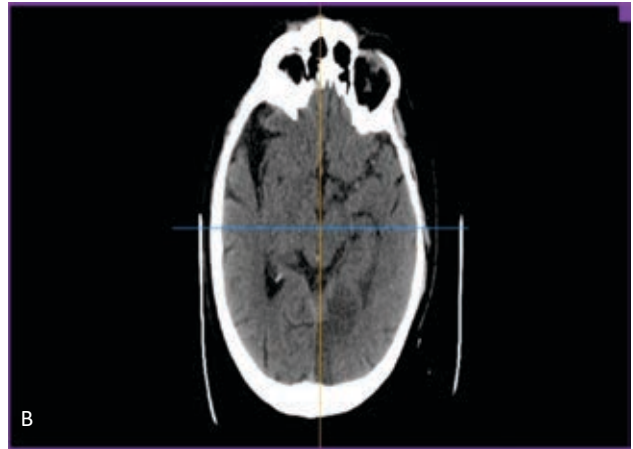
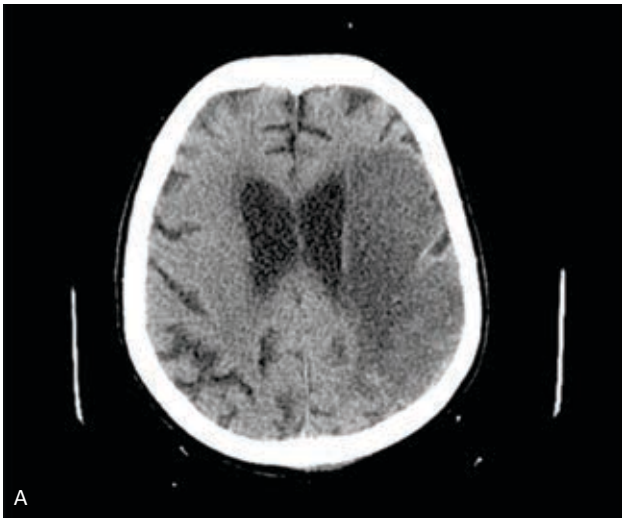
The predominant localization of ischemic stroke in diabetic patients was the middle cerebral artery followed by the posterior cerebral artery and the double localization compared to the group witness where the same trend is maintained. For patients where the localization was double their proportion was almost equal to a percentage of 48% of diabetic patients versus 52% of non-diabetic patients, the difference between the frequency of distribution of diabetes versus the other groups was not statistically significant ( $p = 0.22$ ) (Figure 1). The ischemic stroke-computer tomography localization is exposed in Figure 2.

The correlation between the localization of the acute ischemic stroke studied on the three groups (middle cerebral artery, posterior cerebral artery, double localization) with age, patients have obtained the following data: there is some trend for older patients with an average value of age of 73 years to have more frequent locations of the arteries involved in the ischemic stroke (Figure 3).

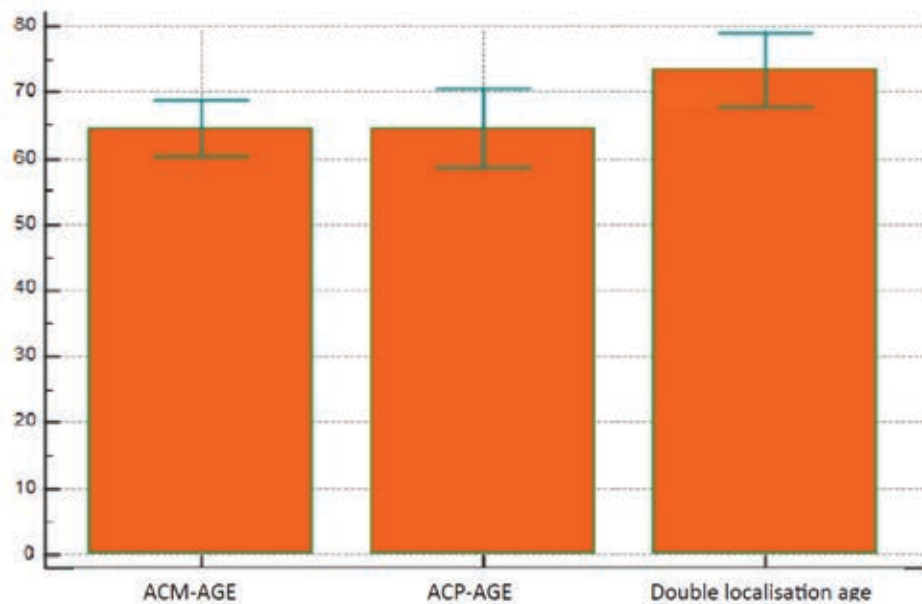
The difference from patients who had an acute ischemic stroke in which it was involved only one vascular territory is almost 10 years (64.5 years for middle cerebral artery versus 64.6 years for posterior cerebral artery versus 73.57 double localization). The difference is statistically significant  $p = 0.02$  (table 1).



**FIGURE 1.** Localization of ischemic stroke between diabetic and non-diabetic patients. (MCA = middle cerebral artery, PCA = posterior cerebral artery)



**FIGURE 2.** Stroke in the territory of a) the middle cerebral artery – hyper density in the territory of the middle cerebral artery, ectasic ventricular system, normally positioned, cerebral atrophy; b) the posterior cerebral artery – spontaneous hypodense beaches extending in the right cerebellar hemisphere and vermis respectively right parieto-occipital which compresses the fourth ventricle, mild supratentorial hydrocephalus



**FIGURE 3.** Localization of ischemic stroke and age (MCA = middle cerebral artery, PCA = posterior cerebral artery)

**TABLE 1.** Correlation between localization of stroke and age, CI 95%

Vascular territory	Average age (years)
Middle cerebral artery	64.5 (60.3832 to 68.7596)
Posterior cerebral artery	646 (58.5794 to 70.6587)
Double localization	73.57 (67.9991 to 79.1437)

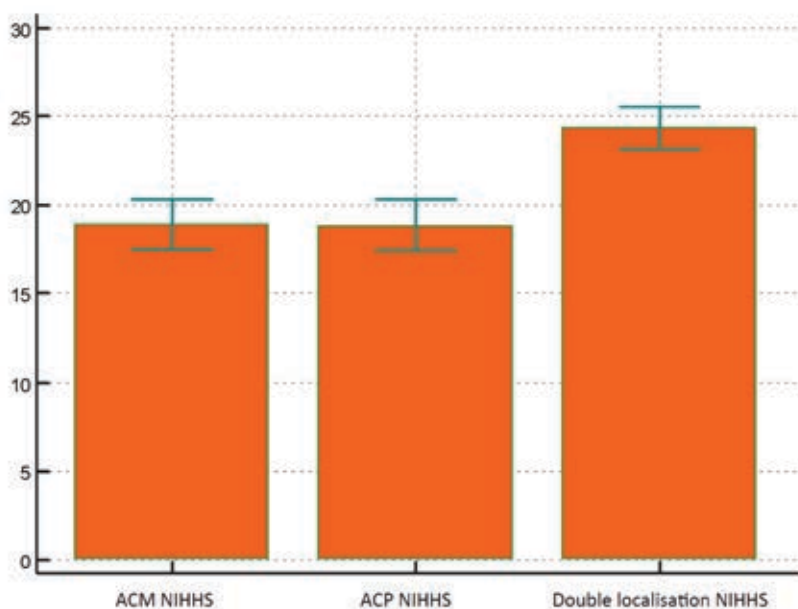
Following the correlation of the NIHSS severity score with the location of ischemic strokes we obtained an NIHSS score on average of 18-19 points in case of localization on the middle cerebral artery and the posterior cerebral artery, the double location of an affect-

ed area greatly increases the score severity to an average of 24 points (Figure 4).

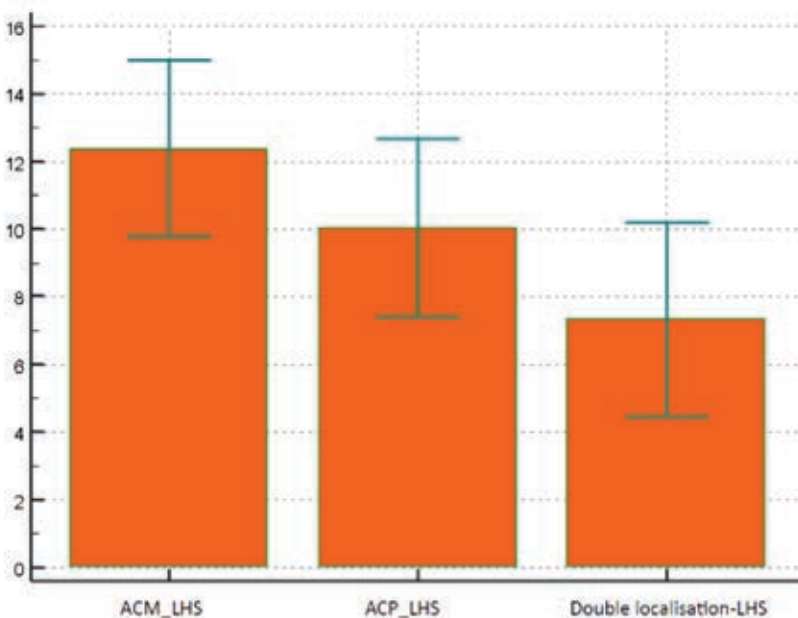
The difference is strongly statistically significant between both averages and linear trend analysis quadratic ( $p < 0.0001$ ), as it is shown in Table 2.

**TABLE 2.** Correlation between localization of ischemic stroke and NIHSS scale, CI 95%

Vascular territory	NIHSS points
Middle cerebral artery	18.9 (17.4660 to 20.3435)
Posterior cerebral artery	18.5 (17.3942 to 20.3201)
Double localization	24 (23.2073 to 25.554)



**FIGURE 4.** Localization of ischemic stroke and NIHSS (MCA – middle cerebral artery, PCA – posterior cerebral artery)



**FIGURE 5.** Localization of ischemic stroke and number of hospitalization days



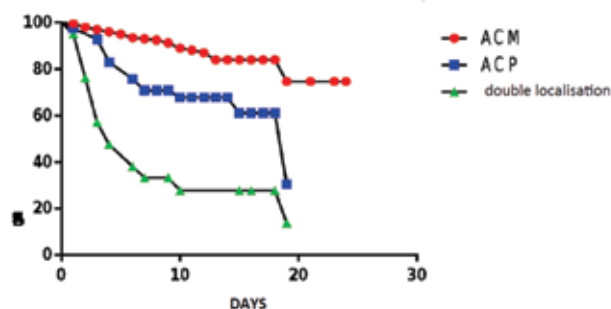
Patients with acute ischemic stroke in the territory of the median cerebral artery have the longest average hospitalization being (n = 12 days) followed by those whose location was the posterior cerebral artery (n = 10 days). The shortest days of hospitalization are the patients with double location with an average (n = 7 days), p < 0.0117 (Figure 5).

The difference from patients who had an acute ischemic stroke in which involved only one vascular territory is like middle cerebral artery with 12.38 days of length of hospitalization days, posterior cerebral artery with 10.04 days of length of hospitalization days and double localization with 7.33 days, p < 0.0017 (Table 3).

**TABLE 3.** Correlation between localization of ischemic stroke and number of hospitalization days, CI 95%

Vascular territory	Average days of hospitalization
Middle cerebral artery	12.38 (9.7801 to 14.9818)
Posterior cerebral artery	10.04 (7.4111 to 12.6841)
Double localization	7.33 (4.4822 to 10.1845)

The data obtained from the Kaplan-Meier analysis on the survival of patients (divided by the vascular territory involved), provided an expected result. Patients with vascular accident in the territory of the median cerebral artery have the highest survival rate, with an average of 22 days, followed by those whose territory was the posterior cerebral artery, with an average of 19 days, and, regarding the double location, the lowest survival rate was obtained with an average of 4 days (Figure 5).



**FIGURE 6.** Survival according to localization of ischemic stroke

This difference is statistically significant (p < 0.0001) and systematic time goes on, as can be seen in the Table 4.

**TABLE 4.** Survival proportion according to localization of ischemic stroke

Days	MCA	PCA	Double localization
0.000	100.000	100.000	100.000
1.000	99.5098	97.61905	95.2381
2.000	98.03194	-	76.19048

Days	MCA	PCA	Double localization
3.000	97.04669	92.85714	57.14286
4.000	96.06145	83.08271	47.61905
5.000	95.0762	-	-
6.000	93.58286	75.75188	38.09524
7.000	93.07425	70.86466	33.33333
8.000	92.51692	70.86466	-
9.000	91.28336	70.86466	33.33333
10.000	89.00128	67.91196	27.77778
11.000	88.08374	67.91196	-
12.000	87.03513	67.91196	-
13.000	84.03391	67.91196	-
14.000	84.03391	67.91196	-
15.000	84.03391	61.12077	27.77778
16.000	84.03391	61.12077	27.77778
17.000	84.03391	61.12077	-
18.000	84.03391	61.12077	27.77778
19.000	74.69681	30.56038	13.88889
21.000	74.69681		
23.000	74.69681		
24.000	74.69681		

## DISCUSSIONS

Diabetes patients have a higher risk of developing complications in hospitalization, with greater discharge disability, higher incidence of recurrent stroke, and increased mortality at 90 days from onset of ischemic stroke [26]. Considering the data obtained in this study, diabetes is not an independent risk factor for a particular localization in acute ischemic stroke. Advanced age was found also as another risk factor, correlated with mortality and disability [27,28-31].

The results of Zafar study did not show any statistically significant differences in age and gender distribution between the 2 groups [32]. No significant age difference was identified between the two groups in other studies as well. [33,34]. In the present research, the difference between the frequency of distribution of diabetes vs. the other group was not statistically significant (p = 0.22).

In one study [35] diabetics were relatively older than non-diabetics and in a recent multinational study diabetes mellitus was independently associated with a slightly younger age [36]. Our data revealed that the difference from patients who has an acute ischemic stroke (in which it was involved only one vascular territory) is almost 10 years; there is some trend for older patients with an average value of age of 73 years to have more frequent locations of the arteries involved in the ischemic stroke (p = 0.02) to an average of 24, the difference being strong statistically significant p < 0.0001.

Microangiopathic category and lacunar infarction were more common in the diabetic group than non-di-

abetic as mentioned in other prospective studies describing the patterns of stroke in diabetic patients [34,35,37]. A large prospective European multicenter study conducted by Megherbi et al. [34] characterizing stroke pattern in diabetic patients found that the frequency of intracerebral hemorrhage was lower, the rate of lacunar infarction was higher, and recovery was worse in diabetic patients.

Higher frequencies of lacunar infarction can be explained by the hypothesis that diabetes mellitus can lead to small vessel arteriopathy in various organs of the body, especially in the retina, kidneys and brain [38]. Diabetes is not only a risk factor for ischemic stroke but can lead to more insidious brain damage represented by lacunar infarction and hence increases the risk of dementia as well [39].

The sub-types and topography of ischaemic stroke are presumed to differ between diabetic and non-diabetic individuals according to the type of angiopathy induced by diabetes mellitus. Lacunar (small, less than 15 mm in diameter infarction, cyst like, frequently multiple) is the typical type of stroke in diabetic subjects [40]. Lacunar infarcts are typically found in the distribution of deep perforating arteries [41].

Zafar study [33] found significant differences in subtypes of ischaemic stroke in diabetics and non-diabetics. Cortical infarct was the commonest subtype in both groups and subcortical infarct were more frequent in diabetics than non-diabetics. As far as the aetiology of ischaemic stroke is concerned, large artery disease was more common than small vessel disease in diabetic group. Similar result was described in one more study [35].

In Bamford et al. study diabetic group, the distribution of the pathological subtypes of stroke [42] was slightly different, with more posterior circulation infarct and lacunar infarct syndromes. The Arboix et al. study observe more lacunar infarct syndromes in diabetic patients has not been reported in other study [43], which raises the problem of biases induced by small series, the definition of diabetes, and other methodological aspects [6,43].

The type and topography of diabetes-related cerebral infarction are believed to differ from brain infarcts in nondiabetic individuals [44]. Diabetes has been thought to be a risk factor for small and lacunar infarcts [45,46]. The study of Jørgensen et al. could not confirm this association. They found no significant differences between the groups regarding infarct size, site, and initial stroke severity. The symptomatic infarct seems therefore to be similar in patients with and without diabetes [6].

The study of Karapanayiotides et al. [35] revealed differences in the topography of ischemic stroke between patients with diabetes mellitus and non-diabetic

patients: subcortical infarcts were more frequent in diabetes mellitus, whereas complete middle cerebral artery territory infarcts were less frequent posterior cerebral infarction was higher in patients with diabetes mellitus in accordance with an MRI study [47], which suggested a greater vulnerability to posterior circulation ischemia in diabetics.

The NIH Stroke Scale (NIHSS) is a neurologic severity scale that is valid, reliable, and reproducible [48]; it is commonly used in many clinical trials dealing with medical therapy for acute stroke [49]. Baseline NIHSS scores on admission are associated with chronic functional outcome [49], hospital disposition after stroke [50], infarct volume, and angiographic findings [51]. In the trial of ORG 10172 in Acute Stroke Treatment (TOAST), the baseline NIHSS score was lower in patients with posterior circulation (PC) stroke than in patients with anterior circulation (AC) stroke [52].

Fink et al. [53] reported a significant correlation between diffusion-weighted MR imaging lesion volume and NIHSS score. Several studies examined relationships between initial NIHSS score and vascular imaging techniques such as CT angiography [54], and MR angiography [55], reporting that a higher NIHSS score was associated with more severe vascular lesions in patients with acute stroke. However, vascular imaging methods have limitations in clearly displaying occlusion or stenosis of the main stem and branches of the middle cerebral artery (MCA) and anterior cerebral artery (ACA). Relationships between NIHSS score and site of arterial occlusion during the hyperacute phase of stroke, therefore, have yet to be accurately determined. From the data of this study, the NIHSS correlation with the location of ischemic strokes, it was obtained an average NIHSS score of 18-19, in the case of localization on the middle cerebral artery or on the posterior cerebral artery, the double location of an affected area greatly increasing the score severity.

Some studies have reported no significant differences in NIHSS scores between patients with middle cerebral artery trunk occlusion and internal carotid artery/middle cerebral artery tandem occlusion, a result that is compatible with the present results [56]. When the internal carotid artery is occluded, the severity of neurologic deficit is contingent on collateral blood flow through the anterior communicating or leptomeningeal arteries from the anterior cerebral artery or posterior cerebral artery [56].

This NIHSS score at baseline was indeed lower among posterior circulation patients, although this may in part be an artifact of the elements of the scale, which are more highly weighted towards anterior circulation deficits, e.g. aphasia, neglect and motor function. Thus, the NIHSS does not fully 'capture' the spectrum of posterior circulation-related deficits [57]. The

NIHSS has been used as an outcome in many randomized trials of stroke. A difference of one point in the total NIHSS score (e.g. between mild versus moderate limb weakness) is associated with greater length of stay, increased mortality, and increased costs of care [58-60].

In study of Chang for patients with mild or moderate neurological impairments 1 point increase of NIHSS scale correspond to an increase in length of stay, also when patient had severe neurological impairment correspond to a decrease in hospitalization [61].

The decreased length of hospitalization in patients with more severe stroke was largely related to the mortality rate, fact confirmed in the present research by the less days of hospitalization of the patients with double location (with an average ( $n = 7$  days)), the most probably in the context of stroke severity and early death ( $p < 0.0117$ ).

Stroke subtype was also a strong predictor of length of hospital stay, with small-vessel occlusion stroke associated with an approximately 1.5-day shorter length of hospital stay than the other subtypes ( $p 0.001$ ) [61].

Initial stroke severity, but not age or comorbidity, was shown to be one of the significant predictors of length of hospital stay, we may postulate the hypothesis that initially reducing stroke severity in first-ever ischemic stroke patients with mild or moderately severe stroke might be a wiser way to reduce length of hospital stay after acute care hospitalization [61].

The total anterior cerebral infarction. group had a higher mortality, longer length of stay, more severe disability, and a higher incidence of complications than the other 3 subgroups (partial anterior cerebral infarction, posterior cerebral infarction, and lacunar cerebral infarction) who were similar at the different time points apart from rate of stroke recurrence within the first 6 months, which was significantly higher in the posterior cerebral infarction group compared to the other groups [62]. In our study, Kaplan-Meier analysis showed that patients with vascular accident in the territory of the middle cerebral artery have the highest survival rate, with an average of 22 days, followed by those whose territory was the posterior cerebral artery (with an average of 19 days); regarding the double location, the lowest survival rate was obtained with an average of 4 days, difference is statistically significant ( $p < 0.0001$ ).

The study by Gattringer et al. showed that the location of the cerebral infarction in the posterior territory has a higher mortality rate than the anterior territory, most likely due to the mass effect exerted on the brainstem [60].

In the literature is no consensus regarding progression of stroke in terms of lesion topography, than posterior circulation infarctions were found to be significantly more frequent in the patients with neurological

worsening. Similar findings were reported in other studies of literature [63,64].

The initial severity of neurological deficit was considered as an independent risk factor for outcomes in most studies [27,28-31].

DeGraba et al. found no difference in lesion topography between the patients with or without neurological worsening [65], while others reported frequently progression in the anterior circulation infarcts [66,67]. A lower rate of cardioembolic infarcts in the posterior circulation compared with anterior circulation might explain this finding [68]. However, infarct topography was found to be an independent factor for neurological progression in this study.

Diabetes is an independent risk factor of death from stroke. Tuomilehto et al. [69] calculated that 16% of all stroke mortality in men and 33% in women could be directly attributed to diabetes. However, one local study could not show much difference in the outcome in the diabetics versus non-diabetics [70]. One large prospective European multicentre study [34] calculated that stroke in diabetic patients was different from stroke in non-diabetics from several perspectives.

The study of Sumer et al. shows that progressing stroke severely affects the prognosis of patients, increases mortality more than four times and leads to poor functional outcome scores. The frequency of deterioration in acute ischemic stroke depends on infarct topography and stroke subtype [71].

However, infarct progression is a grave condition that limits alternatives and leads medical staff to make urgent decisions, thus preventing standard protocols. Small sample size also causes restrictions. Further studies with larger patient populations are needed to resolve these problems.

## CONCLUSIONS

There is no statistically significant difference between diabetic vs. non-diabetic patients regarding the localization correlated with DM, the double location being statistically insignificant between the two batches. Age-related location is statistically significant due to the unique location difference or double, the double location having a higher frequency in elderly patients. In case of correlation of localization with NIHSS severity score, double location of a territory affected significantly increases the severity score, the difference being strongly statistical. Localization correlation with number of hospitalization days with poor prognosis for patients with double location compared to the single-location group with a more favorable prognosis. The survival rate in patients with double localization is low compared to patients with unique vascular territory.



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