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# The Relationship between Integral Assessment of Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease and Clinical and Functional Status in the Acute Period of Ischemic Stroke

***The Relationship between Integral Assessment of Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease and Clinical and Functional Status in the Acute Period of Ischemic Stroke***

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*Cerebral small vessel disease (CSVD) is the most common neurological pathological process and contributes to the process of aging and to the development of dementia and stroke. At the same time, the role of CSVD as a factor influencing the course of acute ischemic stroke (IS) has been little studied. There is no generally accepted magnetic resonance imaging (MRI) scale for the integrated assessment of CSVD markers.*
***Objective:*** *to carry out an integrated assessment of the MRI manifestations of CSVD in acute ischemic stroke and to analyze a correlation of both individual markers and the final indicator with the clinical and functional status of patients.*
***Patients and methods.*** *100 patients with acute IS were examined. All patients underwent standard clinical, laboratory and instrumental examinations, as well as brain MRI estimating the number of lacunae, visible perivascular spaces (PVSs) and leukoaraiosis. The number of cerebral microbleeds (CMBs) was additionally calculated in 57 patients. Integral scale scores were calculated by gradation and summation of four MRI markers of CSVD.*
***Results.*** *The patients with acute IS showed the high representativeness of individual markers for CSVD. The values of MRI markers for CSVD correlated with age, education level, and cardiovascular parameters in patients. An integrated CSVD severity assessment scale was developed. The overall manifestations of CSVD, which were assessed using this scale, were associated with the severity of a stenotic process in the brachycephalic arteries, with BP levels at admission, ejection fraction, hyperglycemia, and atherogenic index of blood lipids. The high CSVD score was also correlated with low mobility and more severe disability in patients being discharged from hospital. The high severity of CSVD was associated with lower neurological deficit regression during inpatient treatment. Subgroup analysis showed the greatest negative impact of CSVD on the severity of stroke in female patients, young and middle-aged ones, diabetics, as well as in patients with noncardioembolic stroke, a small-sized focus, and intima-media thickening.*
***Conclusion.*** *The overall manifestations of CSVD calculated using the original scale based on the analysis of the degree of lacunae, PVSs, leukoaraiosis, and CMBs are associated with premorbid cardiovascular parameters in a patient and are important indicators for the neurological, cognitive, and functional outcomes of acute IS.*

***Keywords:*** *stroke; cerebral small vessel disease; cerebral microbleeds; outcome.*
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The term «cerebral small vessel disease» (CSVD) characterizes a number of pathological conditions and mechanisms resulting in damage to small vessels (arteries, arterioles, capillaries and venules) of the white and grey brain matter. This term is used for the description of clinical, neuropsychiatric and neuroimaging syndromes. CSVD is the most frequent neurological pathology, which contributes to the processes of aging and development of stroke and dementia [1]. The major markers of CSVD according to the results of magnetic resonance imaging (MRI) include acute lacunar infarcts, lacunes, white matter hyperintensities (WMHs), visible perivascular spaces (PVSs), cerebral microinfarctions and microbleeds (CMBs) [2].

According to L. Pantoni, the most common pathogenetic variant of CSVD is type 1 (hypertensive CSVD) [1], which is age-associated and develops under the impact of atherosclerosis, arterial hypertension, diabetes mellitus (DM) and other cardiovascu-

lar risk factors. Clinical significance of CSVD arises from the fact that it is the main cause of vascular cognitive impairment, posture and pelvic disorders and depression; furthermore, it leads to age-related loss of independence [1, 3]. CSVD is a direct cause of every fifth stroke, it doubles the risk of cerebral catastrophe and contributes to hemorrhagic complications of antithrombotic therapy and systemic thrombolysis [2]. We have not found any unified validated scale for neuroimaging assessment of CSVD in the available literature, although there have been several approaches to its development [4]. The role of CSVD as a factor influencing the course of the acute period of ischemic stroke (IS) has not been studied enough so far.

**The objective** of the study was to conduct an integrated assessment of MRI signs of CSVD in the acute period of ischemic stroke and to analyze the relationships between individual CSVD markers and their sum total and clinical and functional status of patients.

**Patients and methods.** One hundred patients having ischemic stroke (IS) were examined (the study group). The control group consisted of 10 patients without stroke and cognitive deficiency, comparable with the study group in the main characteristics. The age of patients with IS ranged from 32 to 91 years (average – 66.6±11.0 years); there were 57 men and 43 women.

*Inclusion criteria* were as follows: the acute period of DWI[1]-verified IS, an opportunity to conduct a standard brain MRI scan and the availability of the image of a good quality.

Exclusion criteria: data of the patients who died were not included in the study.

All patients underwent clinical, laboratory and instrumental examination according to the current procedure and standard for providing medical aid to patients with acute impairment of cerebral blood flow.

Severity of stroke was measured using NIHSS score (National Institutes of Health Stroke Scale), functional status on discharge was assessed using the Rivermead Mobility Index (RMI) and the Modified Rankin Scale (MRS), cognitive status was evaluated with the help of Mini-Mental State Examination scale (MMSE).

After 5–10 days of treatment MRI scans were conducted for all patients on MRI-scanner GE Healthcare Brivo MR 355 (1.5 T). The scanning algorithm included pulse patterns T1, T2, FLAIR and Diffusion weighted images (DWI). Vascular lacunes appeared as round or oval subcortical zones 3-15 mm in diameter, identical in their signal characteristics to the cerebrospinal fluid (CSF). Leukoaraiosis was identified as an area of hyperintensive signal from the brain white matter (WMH) on T2 weighted images without cavities. PVSs were defined as spaces following typical routes of the vessels through the grey or white matter identical to the CSF in their signal characteristics, not more than 3mm in diameter. CMBs were identified as small (2-3, maximally 10 mm in diameter) areas of lost signal with «blooming effect» on T2*-weighted images with the use of pattern T2 Star Weighted ANgiography (SWAN) [5].

A concept used by J. Staals et al. [4] was taken as a basis for gradation of neuroimaging signs of CSVD. These authors suggested using a 4-point scale, according to which 1 point is assigned for the presence of each of the following 4 markers: ⩾1 lacune; ⩾1 CMBs; WMH of degrees 2 and 3; moderate and markedly expressed PVSs in basal ganglia. The same concept was used for further ranging of individual MRI markers.

The quantity of lacunes was assessed in absolute numbers and on the scale of lacunar infarcts [6]: 1 point – not more than 2 lacunes; 2 points – 3–5 lacunes; 3 points – >5 lacunes. To quantify the WMHs the visual Fazekas scale was used. For PVS gradation the MacLullich scale was chosen [7]: 0 points – absence of PVS; 1 point – <10 PVS; 2 points – 10–20 PVS; 3 points – 21–40 PVS; 4 points – >40 PVS. The quantity of CMBs was assessed in absolute numbers in 57 cases.

Analyzing the neuroimaging data of 57 patients in whom all four CSVD markers (lacunes, PVS, WMHs and CMBs) were assessed, we developed an integral CSVD scale. A calculation on this scale was carried out as follows: PVS count was equal to 0 or 1 point if MacLullich score was 0-1 or 2–4 points, respectively; 1 point was added if there were PVSs in radiate crown; WMH was assessed as 0 or 1 point if Fazekas score was equal to 0–1 or 2–3 points, respectively, regardless of their localization; for lacune count points were added using the scale by _. Hassan et al. [6]; the rating score for CMBs was calculated similarly: 0 points – absence of CMBs; 1 point – not more than 2 CMBs; 2 points _ 3_5 CMBs; 3 points _ >5 CMBs, regardless of their localization.

Therefore, total assessment of CSVD severity according to the developed scale ranged from 0 to 9 points. A degree of CSVD severity was provisionally interpreted as low if the total score was 0–3; moderate – if the total score was 4–5 and high – if the total score was 6–9 points.

Statistical analysis was conducted using the software package Statistica 8.0. A comparative quantitative analysis of two independent groups was performed using Mann–Whitney U-test, qualitative analysis – using «2 criterion. For correlation analysis Spearman`s criterion was used. The Tables present the median and interquartile ranges.

**Results.** Clinical characteristics of the patients are presented in Table 1.

As it is shown in Table 1, repeated stroke was observed in almost every third patient. Mild neurological symptoms (according to NIHSS) prevailed. Frequency of intravenous thrombolysis in the analyzed cohort was rather high (18%). Atherothrombotic mechanism of stroke was seen in the majority of patients (41%), though a significant proportion of patients (29%) had cardioembolic stroke. 40% of patients completed the first stage of treatment and rehabilitation with «excellent» functional outcome according to the MRS.

Characteristics of CSVD MRI markers are presented in Table 2

In comparison with the control group, the patients with IS had a greater number of PVSs in the basal ganglia of both hemispheres, a greater number of lacunes, especially in the ipsilateral hemisphere and marked anterior and posterior leukoaraiosis (WMHs). There were no differences in the number of CMBs between the patients in the acute period of IS and the control group. There was no significant difference between the MRI markers of CSVD in ipsi – and contralateral hemispheres either.

Twelve patients (12%) had more than 5 lacunes. The maximum number of lacunes was 14, at the same time, 39 (39%) patients had no lacunes. There were no WMHs in 1 (1%) case, 27 patients (27%) had the first stage of WMH on Fazekas scale, 43 patients (43%) – the second stage, and 29 patients (29%) – the third stage. Figure 1 demonstrates the distribution of CMBs.

[1]DWI – diffusion-weighted imaging

Table 1. *Clinical characteristics of patients (n=100)*

| Characteristic | Number |
|---|---|
| **Premorbid status** | |
| Family history of stroke | 35 (35) |
| Smoking | 32 (32) |
| AH | 86 (86) |
| CHD | 27 (27) |
| Atrial fibrillation | 29 (29) |
| DM | 28 (28) |
| Obesity | 32 (32) |
| Intake (before the admission): | |
| Antihypertensive medicines | 59 (59) |
| Antiplatelet medicines | 26 (26) |
| Oral anticoagulants | 5 (5) |
| Statins | 9 (9) |
| **Characteristics of stroke and therapy** | |
| Repeated stroke | 33 (33) |
| NIHSS on admission, points | 5 (3–8) |
| Systolic AP on admission, mmHg | 150 (140–170) |
| Intravenous thrombolysis | 18 (18) |
| Atherothrombotic stroke | 41 (41) |
| Cardioembolic stroke | 29 (29) |
| Lacunar stroke | 13 (13) |
| Unknown etiology of stroke | 17 (17) |
| **Characteristics of an outcome of the acute period of stroke** | |
| MRS 0–1 points | 40 (40) |
| NIHSS score | 2 (1–5) |
| RMI score | 13 (7–14) |

**Note.** Unless stated otherwise, the values are given as n (%). AH – arterial hypertension; CHD – coronary heart disease, DM – Diabetes mellitus; BP – blood pressure.

Figure 1 shows that most patients (56%) had no CMBs, meanwhile in 11% of cases more than 10 CMBs were found.

The resulting CSVD scale score varied from 0 to 9 points (the average result was 4 points; Table 3). In 21 (37%) patients the CSVD scale score was 0–3 points (degree 1), in 23 cases (40%) – 4–6 points (degree 2) and in 13 patients (23%) – 7–9 points (degree 3).

The results of correlations between MRI markers of CSVD and laboratory and instrumental findings are presented in Table 4.

As it is shown in Table 4, patients' age is associated with a higher intensity of anterior periventricular WMH. Higher educational level of patients is connected with fewer CMBs on the side of IS focus. Increased blood pressure (BP) is related to a higher degree of posterior WMHs in the ipsilateral hemisphere and with a high score on the CSVD scale. IMT correlates with the quantity of basal PVSs and WMHs on the side of the IS focus. Intensity of stenotic process in the carotid arteries is directly associated with the CSVD scale score. A decrease in the left ventricular ejection fraction was accompanied by a greater number of basal and cortical PVSs and an increased CSVD scale score. Hyperglycemia is associated with an increase in the number of CMBs in both hemispheres and a high CSVD scale score. High atherogenic index correlates with an increase in PVSs and a higher CSVD scale score. There were no significant differences in MRI markers with regard to gender, smoking status, presence of ciliary arrhythmia, diabetes mellitus and overweight.

Analyzing correlations between CSVD scale scores and clinical and functional status of patients we found that a high score was associated with a low RMI value (r=0.54; p=0.024) and an increase in the degree of neurological disability on the MRS (r=0.54; p=0.024).

We also analyzed correlations between the total of MRI markers, CSVD scale score, and clinical and functional data in the subgroups of patients. Thus, among women an association of RMI with a degree of WMH (r=-0.37; p=0.017) and total CSVD score (r= -0.48; p=0.029) was found. There was also a correlation between MMSE result and the quantity of CMBs (r=-0.50; p=0.021) in the female group. For males MRI markers were not associated with the results of the clinical scales. Among patients younger than 65 years old associations between CSVD score and NIHSS score on discharge (r=0.44; p=0.040), MMSE score (r=-0.48; p=0.044) and MRS (r=0.52; p=0.013) were observed. In patients older than 65 years the CSVD scale score was connected only with NIHSS dynamics (r=-0.36; p=0.044), there was also a correlation between neurological deficit dynamics and the quantity of CMBs (r=-0.36; p=0.038).

In patients without cardiac fibrillation the result of the CSVD scale is associated with RMI (r=-0.33; p=0.043) and MRS score (r=0.32; p=0.047). In the subgroup of patients having cardiac fibrillation there was no association between MRI markers and clinical data. In the subgroup of patients suffering from DM there was a correlation between the MRS score, the amount of PVSs (r=0.38; p=0.048) and CSVD score (r=0.54; p=0.024), while in patients without DM there was only a correlation between the NIHSS score dynamics and quantity of CMBs (r=-0.32; p=0.044). Correlation between MRS and CSVD scale score remained significant only in patients having IS focus < 20 mm in size (r=0.39; p=0.027). In patients having a bigger size of the focus associations between RMI and WMH (r=-0.30; p=0.034), and between NIHSS dynamics and the number of CMBs (r=-0.42; p=0.048) were observed.

In the group of patients with IMT less than 1mm there was an association between the number of CMBs and MMSE parameters (r=-0.48; p=0.039), and in patients having IMT>1mm the number of CMBs was connected with NIHSS score dynamics (r=-0.35; p=0.037). In this group we also observed a correlation between CSVD score and NIHSS score dynamics (r=-0.40; p=0.023), mobility (r=-0.39; p=0.029) and the level of dependence in daily activities (r=0.47; p=0.007).

The association between CSVD scale score and MRS was evident only among patents with the level of blood low-density lipoproteins <3 mmol/l (r=0.53; p=0.006) and the level of total cholesterol <5.2 mmol/l (r=0.49; p=0.028). Associations between CSVD markers and clinical data were lost also in patients with blood glucose level <5.6 mmol/l. It is remarkable, that in the group of patients with fasting glucose level ⩾5.6

Table 2. *Characteristics of CSVD MRI markers*

| Study group | | | Control group*** | p |
|---|---|---|---|---|
| **PVS, points** | | | | |
| | **IH*** | **CH**** | | |
| Basal ganglia | 2 (1–2) | 2 (1–2) | 0 (0–1) | <0,001*-***<br><0,001**-** |
| Radiate crown | 0 (0–1) | 0 (0–1) | 0 (0–1) | NS |
| **Lacunes, abs.** | | | | |
| | **IH** | **CH** | | |
| | 1 (0–2) | 0 (0–2) | 0 (0–0) | 0,006*-***<br>0,022**-*** |
| **WMH, points** | | | | |
| | **IH** | **CH** | | |
| Anterior horns | 2 (1–2) | 2 (1–2) | 0 (0–0,5) | <0,001*-***<br><0,001**-*** |
| Posterior horns | 2 (1–2) | 1 (1–2,5) | 0 (0–0) | <0,001*-***<br><0,001**-*** |
| **CMBs, abs.** | | | | |
| | **IH** | **CH** | | |
| | 0 (0–1) | 0 (0–1) | 0 (0–0,5) | Н/д |

**Note.** Here and in Table 4: IH – ipsilateral hemisphere; CH – contralateral hemisphere; NS – no significant difference.

mmol/l the quantity of CMBs is connected with MMSE result (r=-0.57; p=0.001).

The patients having the 3rd degree of CSVD according to the developed scale were characterized by less pronounced neurological deficit on admission in comparison with the patients having the 2nd degree of CSVD. Compared with the patients having the 1st and the 2nd degree of CSVD, the patients with the 3rd degree showed lower regress of neurological deficit during the inpatient treatment. The patients with the 1st degree of CSVD demonstrated a better mobility than the patients having the 2nd degree of the disease and a better functional outcome after the first stage of treatment, compared with the patients having the 2nd and the 3rd degree. (Table. 5, figure 2).

**Discussion.** Our study was devoted to the analysis of correlations between individual MRI markers of CSVD, the results of the developed integral scale, and laboratory, instrumental and clinical data of patients in the acute period of IS.

Patients with IS had a higher expression of 3 of the four main MRI markers of CSVD (lacunes, PVSs, WMH) than age-comparable controls. There were no significant differences only between the number of CMBs. It is important to note, that the main pathogenic factor of CSVD development is arterial hypertension, and the main manifestation of its ischemic phenotype is lacunar infarction [3]. But only 13% of patients in the investigated cohort had lacunar type of stroke, this fact points to a universal significance of CSVD in IS development. There were no differences between the expression of the investigated MRI markers depending on the lateralization of IS focus. These results demonstrate that due to the interference of the pathogenetic mechanisms of the main pathogenetic types of IS based on their common risk factors, CSVD serves as a negative cerebral predisposition for acute ischemic brain damage.

The most common marker of CSVD is leukoaraiosis (WMH) that reached the 2nd degree of intensity on Fazekas scale in 43% of patients. Moreover, confluent areas of hyperintensity were observed almost in one third of patients. CBMs were detected in 44% of patients, that corresponds to literature data, according to which this marker is observed in 35–71% of patients having IS [8]. This frequency of CMBs is much higher than in general population – 5% according to The Northern Manhattan Study (NOMAS) [9].

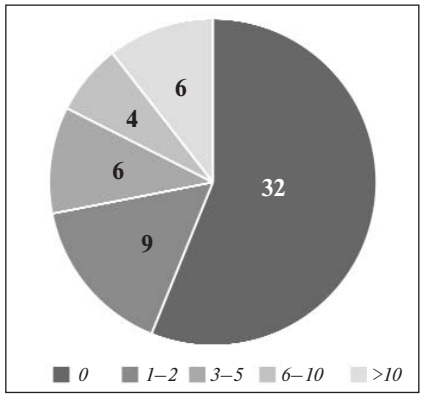


**Figure 1.** *Distribution of CMBs in patients with IS (n=57)*

One in ten patients in the acute period of IS had more than 10 CMBs. This fact is extremely important because patients with > 5 CMBs have a 2.7 times higher risk of IS and a 14 times higher risk of cerebral hemorrhage [10]. It should be mentioned that a significant number of patients in the acute period of IS get double antiaggregant therapy in spite of the fact that therapeutic indications for this regime of antithrombotic therapy are not clearly defined and depend on a physician's decision. Determining the number of CMBs can become one of the factors, contributing to pathogenetic approach to the choice of antiaggregant therapy regime.

In spite of the relevance of the problem, there is no unified validated scale for neurovascular assessment of CSVD in the available literature. Therefore, we attempted to develop this diagnostic instrument on the basis of the principle proposed by J. Staals at al. [4]. The resulting scale is a sum of 4 subscales, assessing expression of lacunes, PVSs, WMHs and CMBs. The result of this scale in the group of patients with IS was 8 times as high as in the control group. The majority of patients had the 2nd degree of CSVD on this scale.

Correlation analysis has shown that both final CSVD score and underlying MRI markers are connected with a wide range of factors characterizing the cardiovascular status of patients. Level of AP on admission, degree of carotid stenosis, pumping ability of the heart, glycemic status and atherogenity of the lipid spectrum turned out to be the most significant factors. Therefore, manifestations of CSVD in patients with IS are associated with arterial hypertension, atherosclerosis, dyslipidemia, hyperglycemia, which generally corresponds to the results obtained by J. Staals et al. [4]. At the same time, some detected associations (ejection fraction, degree of stenosis) point to an important role of hypoperfusion in CSVD pathogenesis. This result corresponds to the concept recently suggested by I. Masafumi and Y. Yamamoto [11], according to which a dysfunction of the blood-brain barrier, caused by hypoperfusion on the background of the major cerebral arteries atherosclerosis is an important element of CSVD pathogenesis. Nevertheless, according to an opposite point of view, aging and WMH are accompanied by loss of the brain tissue resulting in increased necessity for perfusion [12].

Table 3. *Elements of the integral CSVD score (points)*

| Study group (n=57) | Control group (n=10) | p |
|---|---|---|
| | **PVS** | |
| 1 (1–1) | 0 (0–1) | 0,019 |
| | **Lacunes** | |
| 1 (1–2) | 0 (0–0) | 0,002 |
| | **WMHs** | |
| 1 (0–1) | 0 (0–0) | <0,001 |
| | **CMBs** | |
| 1 (0–2) | 0 (0–0,5) | 0,19 |
| | **Final score** | |
| 4 (3–5) | 0,5 (0–1) | <0,001 |

Table 4. *Results of the analysis of correlations between CSVD MRI markers and laboratory/instrumental findings*

| Indicator | PVS | | | | Lacunes | | | | WMHs | | CMBs | | CSVD scale |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BG | | RC | | | | AH | | PH | | | | |
| | IH | KH | IH | KH | IH | KH | IH | KH | IH | KH | IH | KH | |
| Age | 0 | 0 | 0 | 0 | 0 | 0 | + | + | 0 | 0 | 0 | 0 | 0 |
| Education | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | – | 0 | 0 |
| AP on admission | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | + |
| Size of the focus | – | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IMT | + | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 |
| Carotid stenosis max. | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + |
| Ejection fraction | 0 | – | – | – | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | – |
| Glucose | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | + | + | + |
| Atherogenic index | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + |

**Note.** BG – basal ganglia; RC – radiate crown; AH – anterior horns; PR – posterior horns; IMT – intima-media thickness; Carotid stenosis max – maximum percentage of carotid arteries stenosis; 0 – the correlation is statistically insignificant; «+» _ significant direct correlation; «_» _ significant inverse correlation.

It is remarkable that a clear link between the level of glycaemia and the number of CMBs was detected. This connection indicates the role of hyperglycemia in the development of the hemorrhagic phenotype of CSVD. Literature data about the connection of CMBs with diabetes mellitus are contradictory [13]. The size of IS focus does not significantly influence CSVD manifestations, which allows to regard it as just an indicator of the resulting mechanism of brain catastrophe development.

Our study has not identified a higher expression of CMBs in patients with atrial fibrillation, which has been described by a number of authors [14]. This fact might be caused by a small size of the subgroup of patients having atrial fibrillation and by the fact that most of them did not take anticoagulants before hospitalization.

The study has shown that the higher the CSVD scale score, the lower the mobility of patients, and the higher their dependence in daily activities assessed by MRS. We have not found similar investigations performing an assessment of associations

Table 5. *Clinical and functional status of patients in accordance with CSVD scale score*

| Indicator | Expression of CSVD according to the scale | | | p |
|---|---|---|---|---|
| | 1st degree* | 2nd degree** | 3rd degree*** | |
| NIHSS on admission | 4 (2,5–8) | 6 (4–8) | 4 (3–6) | 0,036**-*** |
| NIHSS difference | 2 (1,5–5) | 2 (1–4) | 1 (0–2) | 0,042*-***<br>0,016**-*** |
| RMI | 14 (11–15) | 12,5 (7–14) | 11 (3–14) | 0,046*-** |
| MRS | 1 (0–3) | 3 (1–3) | 3 (2–4) | 0,032*-**<br>0,036*-*** |

**Note.** NIHSS difference – difference between NISS score on admission and on discharge

between the sum of the four MRI markers of CSVD and functional outcomes of the acute period of IS. Analyzing clinical parameters of patients having different degrees of CSVD we found that those having the 1st degree had a higher mobility than patients having the 2nd degree of the disease and a better functional status on MRS at the end of the first stage of treatment and rehabilitation in comparison with patients having the 2nd and the 3rd degrees. Generally, these data correspond to the results of the studies, demonstrating negative influence of individual CSVD markers (especially WMH) on functional outcomes of the recovery period of IS [15].

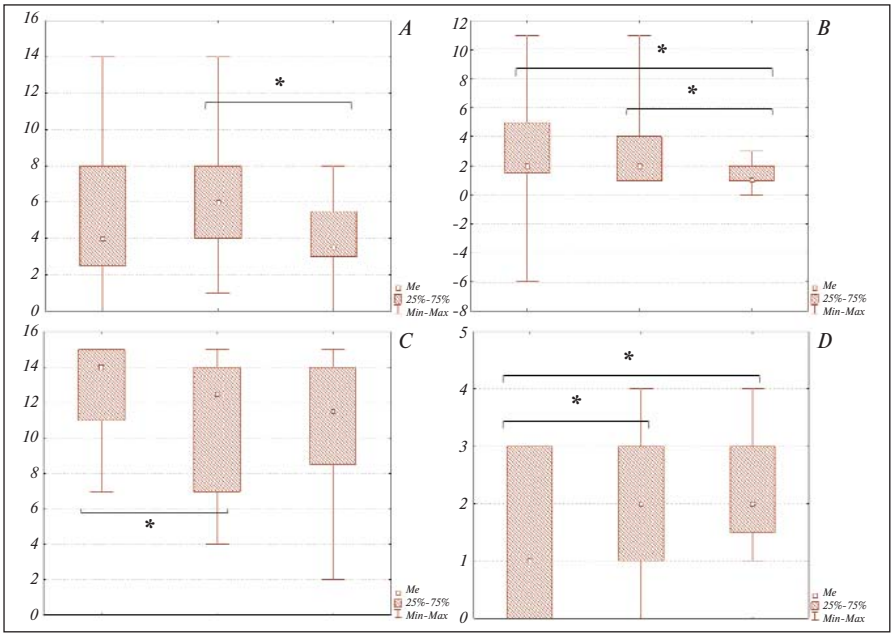


**Figure 2.** *Differences between NIHSS score on admission (A); between NIHSS score on admission and on discharge (B); between RMI (C) and MRS score (D) on discharge, depending on the degree of CSVD according to the developed scale*

The results of the subgroup analysis also seem to be interesting. Thus, the connection between the CSVD markers and clinical status was pronounced among women and insignificant among men. In the group of patients younger than 65 years significant associations of CSVD signs with neurological, cognitive and functional status were observed, and in older patients an important role of CMBs as a factor influencing neurological deficit dynamics was stated. The scores of the CSVD scale and its subscales did not differ in the described age groups of patients. This fact allows to assume that in elderly patients CSVD may be considered to be an aging-associated process and is of low clinical significance; on the contrary, in younger patients it becomes an indicator of a more severe clinical course of cerebrovascular disease, low cerebral reserve and aggravates the IS course.

The presence of diabetes mellitus caused a significant number of clinical and radiological associations. The number of CMBs was connected with cognitive functions in patients with hyperglycemia. Although it is known that in heterogenic populations the quantity of CMBs is associated with a slight decrease in cognitive functions, this question remains controversial. On the one hand, many patients with lobar CMBs suffer from cerebral amyloid angiopathy which is connected with the development of cognitive dysfunction; on the other hand, this association can result from the influence of vascular risk factors connected with this MRI marker. Moreover, the direct mechanism of the influence of CMBs on cognitive functions remains unclear as they do not cause any significant damage to the brain tissue and the conducting tracts [16].

A correlation between the developed scale score and clinical data was observed in the group of patients without atrial fibrillation, which is consistent with the results of the investigations demonstrating less frequent CMBs in cardioembolic stroke than in ischemic one [17]. The size of the studied group was not sufficient to assess these differences. Nevertheless, we can assume that because of vessel wall fragility CSVD is an important element of the pathogenesis of noncardioembolic IS [8].

The result of the integral scale is significant in patients with the IS focus size < 2 cm, whereas in patients with larger foci the important parameters are the presence of WMH and the quantity of CMBs. Thus, the bigger the focus is, the less CSVD influences the outcome. This fact may be connected with specific interactions of cerebral predisposition with IS focus and with the fact that this size of the focus is characteristic of lacunar stroke (if it is located in the zones of the perforating arteries supply).

An important clinical significance of MRI markers of CSVD was observed in patients with thickened intima-media

complex, whereas in patients having normal IMT, the quantity of CMBs was connected with their cognitive status. On the one hand, these data confirm the leading role of vascular risk factors in the pathogenesis of CSVD [11], on the other hand, they show that CSVD has clinical consequences in the presence of other adverse cardiovascular factors. These findings correspond to the results of other studies which identified correlations between arterial wall rigidity and CSVD [18].

It is noticeable that the associations between CSVD manifestations and clinical parameters were lost in patients having hypercholesterolemia, which corresponds to the scientific hypothesis of non-atherosclerotic nature of CSVD [3]. This point of view is implicitly confirmed by the results of the studies demonstrating ineffectiveness of statins for slowing CSVD progression [19], and the studies that showed an increase in hemorrhagic complications and the absence of additional benefit of double antiaggregant therapy in lacunar stroke [20].

Thus, patients in the acute period of IS have a higher expression of individual CSVD markers and their sum total in comparison with elderly people without stroke. Total expression of CSVD assessed by means of the original scale based on the analysis of the quantity of lacunes, PVSs, WMHs and CMBs is associated with a number of cardiovascular parameters, and is an important indicator of neurological, cognitive and functional status of patients on completion of the 1st stage of treatment. The greatest negative contribution of CSVD in IS severity was observed in women, young and middle-aged patients, patients with DM, non-cardioembolic stroke, small size of IS focus and thickened intima-media complex.

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