DOI: 10.31393/morphology-journal-2025-31(1)-04

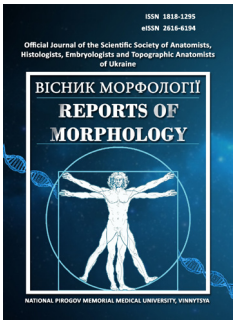
Reports of Morphology, Vol. 31, №1, Pages 30-36

ISSN 1818-1295 eISSN 2616-6194

REPORTS OF MORPHOLOGY

Official Journal of the Scientific Society of Anatomists, Histologists, Embryologists and Topographic Anatomists of Ukraine

journal homepage: https://morphology-journal.com



Characteristics of cerebral morphometric parameters in acute stroke patients and its associations with 90 days stroke outcome

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ARTICLE INFO

Received: 3 April 2024

Accepted: 26 November 2024

UDC: 616.45-091.8:616.5-001.17-06]-085.36

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

Not applicable.

DATA SHARING

Data are available upon reasonable request to corresponding author.

Brain morphometry is widely used to diagnose and predict mainly neurodegenerative diseases, but cerebrovascular diseases have received much less attention, especially for predicting long-term consequences of stroke. The aim of the research was to investigate the associations between changes in brain morphometric parameters and stroke outcome at 90 days. 294 consecutive patients with acute stroke were recruited. All participants underwent brain magnetic resonance imaging and/or computed tomography assessment as well as clinical-neurological evaluation. Statistical analysis was performed in the program The Jamovi project (2022), Jamovi (Version 2.3) [Computer Software], Sydney, Australia using parametric and nonparametric statistical methods. We found that enlarged ventricular and cortical morphometric parameters are associated with unfavorable stroke outcome at 90 days. In the univariable analysis, enlarged third ventricle index (the regression coefficient b=-2.6, p=0.014), Shlatenbrandt-Nurenberger index (the regression coefficient b=0.6, p=0.007), bicaudate index (the regression coefficient b=-1.5, p=0.006), higher width of the longitudinal cerebral fissure in the anterior part of the frontal lobes (the regression coefficient b=-3.5, p=0.005), higher width of the cerebral fissure in the area of the skull vault (the regression coefficient b=-3.5, p=0.006) significantly associated with lower Barthel index at 90 days. In the multivariable analysis, significant association was found between enlarged third ventricle index and Barthel index at 90 days (the regression coefficient b=-2.6, p=0.045). In the other model of multivariable analysis, enlarged bicaudate index significantly associated with higher level of functional dependence at 90 days (odds ratio=1.1, p=0.031). Our findings confirmed that enlarged cerebral morphometric indices are associated with unfavorable short-term stroke outcome at 90 days.

Key words: *nervous system disorders, stroke, brain morphometry, bicaudate index, ventricular index.*

Introduction

Measurements of brain morphometry, like cortical thickness and subcortical brain volumes are widely used in clinical and scientific practice. Individual differences in morphometric parameters have been linked to aging, brain diseases and behavior [17, 35]. Moreover, morphometric distinct “signature” patterns of brain anatomical changes are useful for prognosis and long-term outcome surveillance [8, 23], including cerebrovascular disease [40]. However, most of the studies were devoted to neurodegenerative disorders, like Alzheimer disease, fronto-temporal dementia, etc. [7, 15, 33]. Still, the association between stroke outcome and morphological brain changes has not been studied exhaustively. Some research showed changes of brain anatomical parameters in response to external manipulations [3, 22]. Therefore, it can be highly informative to study stroke outcome and structural plasticity based on basic morphological brain “profile” for diagnostic and predictive purposes.

Cerebrovascular diseases are major contributors to death, long-term disability, cognitive decline and dementia [1, 2, 19]. There are well-known stroke outcome predictors, such as stroke severity at admission, admission systolic and diastolic blood pressure, baseline comorbidities, etc. [1, 41], but less attention was given to underlying structural

non-stroke lesion changes and its associations with stroke outcome. Brain morphological changes reflect global underlying pathological changes and brain fragility for both cerebrovascular and neurodegenerative disorders [13]. Hence, assessment of deep and cortical morphometrics can be clinically valuable predictors for a long-term stroke outcome.

We tested a hypothesis that altered brain morphometric indices predict unfavorable stroke outcome at 90 days.

The aim of the research was to investigate associations between brain morphometric changes and 90 days stroke outcome.

Materials and methods

Subjects. 294 consecutive patients between December 2016 and December 2019 were enrolled (115 females and 179 males). The study was based at specialized stroke department (Stroke Unit) № 22 of the Vinnytsia Regional Psychoneurological Hospital named after acad. O. I. Yushchenko. The mean age of the patients was 61.94±10.11 years, mRS on admission – 4 (4-5) scores. The study was approved by the local ethics committee (Protocol № 9 of November 14, 2016). All patients signed informed consent before the participation. It was a prospective single-center cohort study. We thoroughly assessed neuroimaging data as well as clinical-neurological status.

The criteria for the selection of the patients were confirmed diagnosis of stroke, good quality of neuroimaging scans and absence of neuroimaging artifacts, as well as obtained informed consent to participate in the study.

Neuroimaging. Among 294 participants, 120 underwent MRI, 174 – CT. Some of them were imaged with either MRI or CT, some of them – with MRI and CT both. MRI was performed on a Philips Achieva 1.5T. The brain scanning protocol included the following whole brain scans: T1-weighted, T2-weighted, FRAIR and DWI sequences, slice thickness was 3.5-5 mm. CT was performed on a General Electric CT/e (Italy) with a tomographic slices of 3-7 mm.

Measurements of the brain morphometry. We visually measured deep ventricular indices, that are Evans index, third ventricle index, fourth ventricle index, ventricular index, Shlatenbrandt-Nurenberger index, bicaudate index, cella media index (also known as Schiersmann's index), and Huckman number. We also assessed cortical morphometrics: longitudinal cerebral fissure in the anterior part of the frontal lobes (FI), the width of the right (ICR) and left insular cisterns (ICL), and their sum (ICRL), width of the cerebral fissure in the area of the skull vault (SW), and the maximum width of the cerebellar fissure (CFW) [11] (Fig. 1). For the assessment we used computer software "The Horos Project".

Clinical assessment. We gathered demographics and stoke risk factors: age, gender, comorbidities with Charlson comorbidity index [21], smoking, alcohol overuse, body mass index (BMI), history of previous stroke. We performed comprehensive neurological examination for stroke patients on patients admission and at discharge: NIHSS score [42],

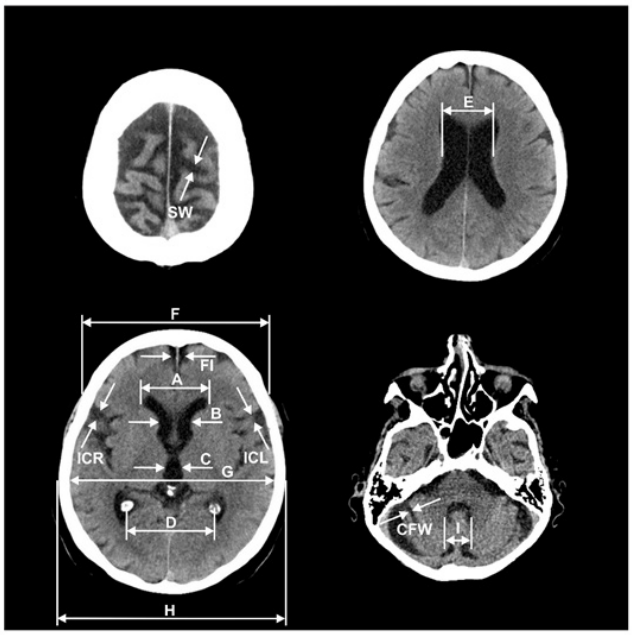

Fig. 1. Brain morphometry measurements. A – the frontal horns greatest width; B – intercaudate distance; C – the third ventricle distance; D – the choroid plexuses distance; E – the lateral ventricles greatest width at the level of cella media; I – the fourth ventricle distance; ICL – the left insular cistern width; ICR – the right insular cistern width; FI – the longitudinal cerebral fissure width in anterior part; SW – the cerebral sulci greatest width at the skull vault; CFW – the cerebellar fissures greatest width; G – the temporal bones greatest internal distance; H – the temporal bones greatest external distance; F – the frontal bone greatest external distance.

modified Rankin scale (mRS) score [30], Barthel index score (BI) [26], Glasgow coma scale (GCS) [10], MMSE score [20]. The stroke subtypes were determined based on the TOAST criteria [12]. The 90-day functional outcome was assessed with the mRS and BI by telephone interviews. Also, the functional outcome was measured with the mRS at 90 days as favorable (mRS≤2) or unfavorable (mRS>2) [5].

Statistical analysis. Statistical analysis was performed by The Jamovi project (2022), Jamovi (Version 2.3) [Computer Software]. Sydney, Australia. Linear variables were presented as mean (M) ± standard deviation (SD). A two groups comparison was performed by nonparametric Mann-Whitney U-test. To calculate the associations between brain morphometric parameters and 90 days stroke outcome we employed univariable and multivariable regression analysis. The results are shown as odds ratio (OR) and 95 % confidence intervals (CI) or as the regression coefficient b (b) and 95 % CI in case of linear regression.

Results

The baseline cerebral morphometric parameters in men and women are shown in Table 1.

In Table 1 and Figure 2, Evans index, bicaudal index, ventricular index, Shlatenbrandt index, third ventricle index, Huckman number and FI are significantly different in favorable

Table 1. Comparison of brain morphometric parameters between patients with favorable (mRS 0-2) and unfavorable (mRS>2, functional dependence) stroke outcome at 90 days, distributed by gender.

Morphometric indices	Men, (M±SD)		Women, (M±SD)	
	favorable outcome, (n= 114)	unfavorable outcome, (n=55)	favorable outcome, (n=74)	unfavorable outcome, (n=34)
Evans index	27.26±3.26	28.28±2.88*	26.45±4.68	26.85±4.98
3rd ventricle index	4.947±1.730	5.627±1.687*	4.710±1.790	5.314±1.987
Shlatenbrandt-Nurenberger index	23.23±9.51	19.45±6.10*	24.49±9.56	21.42±8.30
4th ventricle index	12.42±1.62	12.48±1.97	12.51±1.90	12.44±2.29
Bicaudate index	15.51±2.98	16.99±3.34*	14.29±3.75	15.60±4.30
Ventricular index	16.45±2.07	15.76±1.73*	16.89±3.32	16.67±3.30
Schiersmann index	5.017±1.014	5.015±1.293	5.449±1.238	5.425±1.451
Huckman number	58.05±7.89	61.14±7.93*	53.55±10.33	54.87±11.79
FI	5.505±1.497	6.038±1.627*	5.143±1.355	5.806±1.620t
ICR	7.167±2.600	7.191±2.579	7.078±2.693	7.179±2.605
ICL	7.746±2.729	7.991±2.458	7.481±2.685	7.909±2.321
ICRL	14.91±4.835	15.182±4.559	14.56±4.81	15.18±4.77
SW	4.252±1.337	4.596±1.421	4.041±1.359	4.732±1.960t
CFW	2.552±1.161	2.505±1.367	2.586±1.016	2.500±1.174

Note: * – significant differences between brain morphometric parameters in favorable (mRS 0-2) and unfavorable (mRS 3-6) 90 days stroke outcome (p<0.05); t – trend towards significance (p<0.1).

(mRS 0-2, functional independence) vs. unfavorable (mRS 3-6, functional dependence) stroke outcome in men. In women, trends towards statistical significance were found for FI (5.143±1.355 vs. 5.806±1.620, p=0.091) and SW (4.041±1.359 vs. 4.732±1.960, p=0.071).

According to the univariable analysis, the third ventricle index (b=-2.6; 95 % CI -4.7 – -0.5, p=0.014), Shlatenbrandt-Nurenberger index (b=0.6; 95 % CI 0.2 – 1.0, p=0.007), bicaudate index (b=-1.5; 95 % CI -2.5 – -0.4, p=0.006), FI (b=-3.5; 95 % CI -5.9 – -1.1, p=0.005), SW (b=-3.5; 95 % CI -6.1 – -1.0, p=0.006) significantly associated with poorer BI at 90 days.

After adjusting for age and sex, nearly significant association was found between FI and BI at 90 days (b=-2.1; 95 % CI -4.6 – 0.4, p=0.095).

In the next model, adjusted for age, sex, history of smoking, comorbidity index, body mass index, history of stroke, hyperlipidemia, presence of complications, index stroke severity by NIHSS, significant association was found between the third ventricle index and BI at 90 days (b=-2.6; 95 % CI -3.4 – -0.1, p=0.045). In this model, Shlatenbrandt-Nurenberger index, the fourth ventricle index, bicaudate index, FI and SW showed near-marginal significance (p<0.1).

Further, multifactorial analysis was performed, adjusted for age and sex along with all morphometric indices to evaluate their associations with the unfavorable stroke outcome. Both crude and adjusted odds ratio are shown in Table 2.

Table 2. Brain morphometric indices and their associations with the unfavorable stroke outcome (functional dependence, mRS>2) at discharge.

Brain measurement	Crude OR (95 % CI, p)	Adjusted OR (95 % CI, p)
Evans index	1.0 (1.0-1.11, p=0.143)	1.0 (1.0-1.1, p=0.412)
The third ventricle index	1.1 (1.00-1.3, p=0.096)	1.1 (0.9-1.2, p=0.484)
Shlatenbrandt-Nurenberger index	1.0 (0.9-1.0, p=0.096)	1.0 (0.99-1.1, p=0.579)
The fourth ventricle index	1.0 (0.9-1.1, p=0.901)	1.0 (0.9-1.2, p=0.945)
Bicaudate index	1.1 (1.0-1.2, p=0.004)	1.1 (1.0-1.2, p=0.031)
Ventricular index	0.9 (0.8-1.0, p=0.090)	0.9 (0.8-1.0, p=0.192)
Cella media index (Schiersmann's index)	0.9 (0.8-1.1, p=0.382)	1.0 (0.8-1.2, p=0.889)
Huckman number	1.0 (1.0-1.1, p=0.090)	1.0 (0.9-1.0, p=0.306)
FI	1.2 (1.0-1.4, p=0.034)	1.0 (1.1-1.3, p=0.161)
ICR	1.1 (1.0-1.2, p=0.311)	1.0 (0.9-1.1, p=0.687)
ICL	1.0 (0.9-1.1, p=0.678)	1.0 (0.9-1.0, p=0.994)
ICRL	1.0 (0.9-1.1, p=0.374)	1.0 (0.9-1.1, p=0.994)
SW	1.2 (1.0-1.4, p=0.027)	1.1 (0.9-1.3, p=0.171)
CFW	1.1 (0.9-1.3, p=0.475)	1.0 (0.9-1.3, p=0.702)

As seen in Table 2, bicaudate index, FI and SW were significantly associated with unfavorable stroke outcome at 90 days. After adjusting for age and sex, only bicaudate

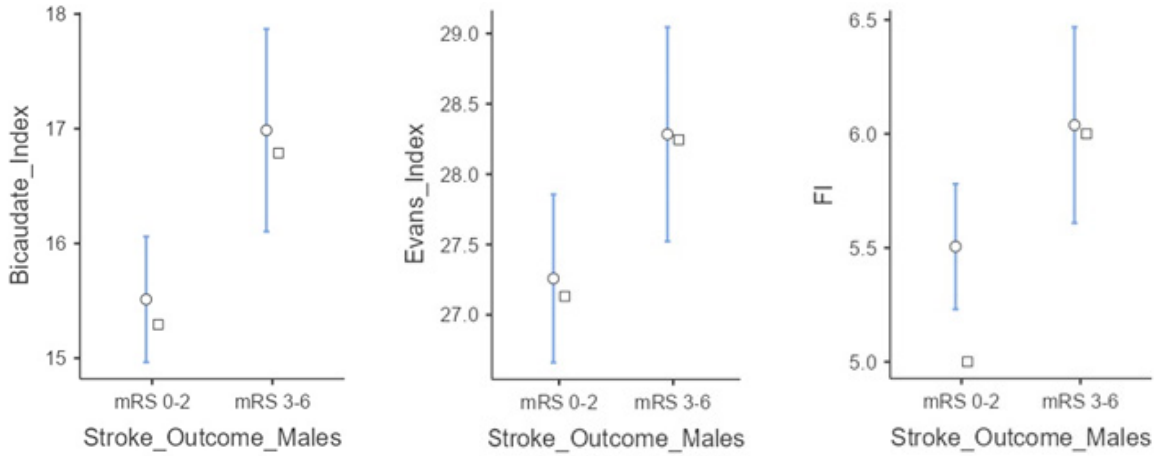

Fig. 2. Significant differences in morphometric parameters depending on the stroke outcome in men. ○ – mean, □ – median.

index was significantly associated with unfavorable stroke outcome at 90 days, as shown in Fig. 3.

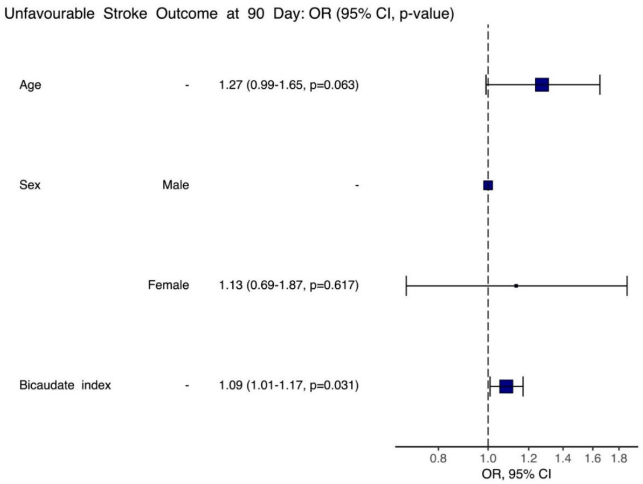

Fig. 3. Forest-plot adjusted for age and sex of bicaudate index association with unfavorable stroke outcome at 90 days.

Discussion

Previously we found that altered cerebral morphometric parameters significantly associated with short-term stroke outcome at discharge. In the current paper we investigated associations between brain morphometrics and 90 days stroke outcome.

In the two-groups comparison analysis, in men almost all ventricular indices and FI were significantly higher in the group of unfavorable stroke outcome at day 90, while in women, FI and SW were close to significance. These results can be explained by different sample sizes (169 men, 108 women), but vascular risk factors, which are more common in men, may be of greater importance. Hence, more severe baseline subcortical and cortical atrophic brain changes can worsen 90 days stroke outcome.

Increased ventricular indices represent enlarged deep cerebrospinal fluid spaces, and on the other hand – atrophy of frontal, parietal lobes and shrinking of basal ganglia, including caudate nuclei. Enlarged FI represents frontal lobes cortical atrophy, SW – parietal lobes cortical atrophy. Therefore, frontal and parietal lobes atrophy is one the most important predictors for post-stroke rehabilitation and restoration of lost brain functions. As it is known, there are complicated neural circuits, which connect basal ganglia (extrapyramidal system) and frontal cortex, which is crucial for motor, cognitive and emotional functioning [27]. Altered morphometric indices reflect reduced brain reserve for neuroplasticity and neurogenesis and are direct predictors of impaired abilities for post-stroke recovery.

In the univariable analysis our results showed that enlarged subcortical indices - the third ventricle index, Shlatenbrandt-Nurenberger index, bicaudate index, as well as cortical parameters - FI, SW were significantly associated with poorer BI at 90 days.

In the multivariable analysis, adjusted for age and sex, nearly significant association was found between FI and BI at 90 days (b=-2.1, p=0.095).

In the next multivariable model, adjusted for age, sex, history of smoking, comorbidity index, body mass index, history of stroke, hyperlipidemia, presence of complications, index stroke severity by NIHSS, significant association was found between the third ventricle index and BI at 90 days (b=-2.6, p=0.045). In this model, Shlatenbrandt-Nurenberger index, the fourth ventricle index, bicaudate index, FI and SW showed near-marginal significance (p<0.1).

We also found that bicaudate index – (OR=1.1, p=0.004), FI – (OR=1.2, p=0.034) and SW – (OR=1.2, p=0.027) were significantly associated with unfavorable stroke outcome (mRS 3-6) at 90 days. After adjusting for age and sex, only enlargement of bicaudate index was significantly associated with unfavorable stroke outcome at 90 days – (OR=1.1, p=0.031).

Our results are consistent with the others findings, such as J. Y. Zhou et al. [42], who demonstrated that brain atrophy is an independent predictor of unfavorable stroke outcome at 90 days. However, in the study by S. H. Lee et al. [25], increased intercaudate distance was associated with a protective effect on the outcomes of large cerebral infarct with a trend of saving patients from a malignant clinical outcome. A. K. Tam et al. [37] demonstrated that the severity of brain atrophy was associated with worse outcome of subarachnoid hemorrhage at 6 weeks. In the study by J. P. Appleton et al. [2], brain atrophy as a component of the “brain frailty” was associated with unfavorable outcomes of both territorial and lacunar stroke at 90 days.

A series of studies have shown the associations of cerebral atrophy and stroke outcome after reperfusion therapy, which were quite heterogeneous: in the study by F. Arba et al. [6], the presence of severe cerebral atrophy more than doubled the odds of unfavorable functional outcome at 90 days. In another study by F. Arba et al. [4], no significant association with brain atrophy was found. In the study by C. Delcourt et al. [14], the presence of any degree of atrophy was significantly associated with a decreased likelihood of a good functional outcome according to mRS at 90 days. In the study by W. K. Diprose et al. [16], increasing cerebrospinal fluid volume associated with a reduced likelihood of good functional outcome (mRS 0-2) at 90 days. In the work of I. Lauksio et al. [24] cerebral atrophy was a significant predictor of mortality at 90 days. S. Mönch et al. [29] found no association between atrophic changes of the brain and stroke outcomes and mortality at 90 days. M. I. Pedraza et al. [31] found cortical atrophy to be significantly associated with unfavorable stroke outcome after recanalization. O. Tschirret et al. [38] found no association between brain atrophy and stroke outcomes at 3 months.

The mechanisms by which brain atrophy and enlarged cerebral morphometrics may affect functional recovery after stroke are still not well understood. It is possible that the association may be mediated by a decrease of the brain’s reserve capacity for functional recovery [32, 34]. Brain

atrophy, manifested by dilation of the ventricles and cortical sulci span, is often associated with leukoaraiosis, lacunes, and enlarged perivascular spaces, which are hallmarks of cerebral small vessel disease [39]. These features have been shown to be associated with endothelial dysfunction, impaired cerebral blood flow, and loss neuronal connectivity, which may hinder functional recovery and lead to worse outcomes after stroke. In addition, brain atrophy is also associated with cognitive impairment and dementia, which are known to be predictors of poor functional outcome after stroke [9].

As we previously speculated, altered cerebral morphometric parameters could possibly lead to loss of functional brain connectivity, which, in turn, deteriorates post-stroke recovery [18].

Besides, increased deep morphometric indices, which represent white matter shrinking, can diminish processing speed and cause executive dysfunction, and cortical indices deterioration can lead to loss of higher brain functions, as consequence – impaired motor and cognitive post-stroke recovery [28, 36].

For future research, it can be of interest to investigate the associations between brain morphometrics and ultra long-term stroke outcome – beyond 90 days, for instance, in a year or more.

Conclusions

1. Enlarged cerebral morphometric indices significantly associated with unfavorable 90 days stroke outcome.

2. The most important brain morphometric predictors of unfavorable stroke outcome at 90 days are Bicaudate index, Ventricular index, frontal and parietal lobes fissure width.

3. Measurement of cerebral morphometrics can be of interest to predict stroke outcome and select patients for treatment and preventive strategies.

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ХАРАКТЕРИСТИКА ЦЕРЕБРАЛЬНИХ МОРФОМЕТРИЧНИХ ПАРАМЕТРІВ У ПАЦІЄНТІВ З ГОСТРИМ МОЗКОВИМ ІНСУЛЬТОМ ТА ЇХ ЗВ'ЯЗКИ ІЗ НАСЛІДКОМ ІНСУЛЬТУ НА 90-ТУ ДОБУ

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Морфометрію головного мозку широко використовують для діагностики та прогнозування переважно нейродегенеративних захворювань. У той же час, цереброваскулярним захворюванням приділялось значно менше уваги, особливо для прогнозування довготривалих наслідків інсульту. Метою нашого дослідження було дослідити залежності між змінами морфометричних показників головного мозку та наслідком інсульту на 90-ту добу. До дослідження були послідовно набрані 294 пацієнта з гострим інсультом. Усім хворим була проведена комп'ютерна томографія та/або магнітно-резонансна томографія головного мозку, а також клініко-неврологічна оцінка стану хворих. Статистичний аналіз проводили у програмі The Jamovi project (2022), Jamovi (Version 2.3) [Computer Software], Sydney, Australia з використанням параметричних і непараметричних методів оцінки отриманих результатів. Нами встановлено, що збільшені шлуночкові та кіркові морфометричні параметри асоціюються із неблагоприємним наслідком інсульту на 90-ту добу. В однофакторному аналізі підвищені індекс третього шлуночка (коефіцієнт регресії b=-2,6, p=0,014), Шлатенбрандт-Нюренбергера (коефіцієнт регресії b=0,6, p=0,007), бікаудальний індекс (коефіцієнт регресії b=-1,5, p=0,006), збільшені ширина поздовжньої церебральної щілини у передній частині лобних часток (коефіцієнт регресії b=-3,5, p=0,005), ширина мозкової щілини в ділянці склепіння черепа (коефіцієнт регресії b=-3,5, p=0,006) достовірно асоціювалися з нижчим індексом Бартел на 90-ту добу. У багатофакторному аналізі достовірні асоціації були знайдені між збільшеним індексом третього шлуночка та індексом Бартел на 90-ту добу (коефіцієнт регресії b=-2,6, p=0,045). В іншій багатофакторній моделі, збільшений бікаудальний індекс достовірно асоціювався із вищим ступенем функціональної залежності на 90-ту добу (відношення шансів=1,1, p=0,031). Отже, наші дані підтвердили, що збільшені церебральні морфометричні індекси асоціюються з несприятливим наслідком інсульту на 90-ту добу.

Ключові слова: *захворювання нервової системи, інсульт, церебральна морфометрія, бікаудальний індекс, шлуночковий індекс.*

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