ORIGINAL ARTICLE

CONTENTS

Brain morphometry and short-term stroke outcome

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ABSTRACT

Aim: The aim of the research was to investigate associations between brain morphometric changes and short-term stroke outcome.

Materials and Methods: In this study, 294 patients with acute stroke were enrolled. All participants underwent magnetic resonance imaging (MRI) and computed tomography (CT) assessment as well as clinical-neurological and cognitive testing.

Results: In the multivariable regression analysis, bicaudate index (OR = 1.3; 95 % CI 1.1 - 1.7, p=0.018) and ventricular index (OR = 0.7; CI 0.5 - 0.9, p=0.005) were associated with an unfavourable short-term stroke outcome. The univariable regression analysis revealed significant associations between mini-mental state examination scale score (MMSE) and width of the longitudinal cerebral fissure in the anterior part of the frontal lobes (FI) (b -0.8, 95% CI -1.6 – -0.1, p=0.037) as well as width of the cerebral fissure in the area of the skull vault (SW) (b -0.9, 95% CI -1.8 – -0.1, p=0.023). In the multivariable regression model bicaudate index was associated with MMSE score (b coefficient (b) = -1.2; 95 % CI -2.1 – -0.3, p = 0.011).

Conclusions: our results show that altered brain morphometric indices are associated with unfavourable short-term stroke outcome and cognitive decline.

KEY WORDS: stroke, MMSE, mRS, brain morphometry, bicaudate index

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INTRODUCTION

Stroke is the leading cause of long-term disability and the second most common cause of death on the globe. The estimated global cost of stroke is over US $ 891 billion (1.12% of the global GDP) [1]. The clinical outcome of stroke patients depends on multiple factors [2], however the data on the brain morphometric changes beyond stroke lesion and their relationship to stroke outcome are sparse.

Vascular dementia is the second most common cause of dementia affecting the elderly. [3]. Hence, understanding the relationship between brain morphometrics, stroke outcome and cognitive decline can be useful for early diagnostics and prognostic purposes.

Brain atrophy reflects a final common pathway for pathological processes in both cerebrovascular and neurodegenerative disorders [4, 5]. Therefore, more precise, and thorough measurements of the brain morphology can help formulating better prognosis and prevention strategies after stroke.

We tested a hypothesis that altered brain ventricular indices and cortical sulci span are predictors of unfavourable short-term stroke outcome at discharge.

AIM

The aim of the research was to investigate associations between brain morphometric changes and short-term stroke outcome.

MATERIALS AND METHODS

SUBJECTS

This research is a part of a prospective cohort study "Diagnosis and predictive value of cerebral small vessel disease in the acute phase of cerebral stroke", which was conducted from December 2016 to December 2021 and was based at specialised stroke department (Stroke Unit) № 22 of the Vinnytsia Regional Psychoneurological Hospital named after acad. O.I. Yushchenko. Between December 2016 and December 2019 294 consecutive patients with acute stroke were recruited. We collected clinical, neurological and neuroimaging data during the period of hospitalization of the patients. In face-to-face interviews with patients or their caregivers we collected a variety of data, which is described below. This information was cross-referenced with primary care records

and medical records during follow-up. The average age of the participants was 61.9 ± 10.1 years, of which 179 were men and 115 women. The follow-up period was 9.4 ± 4.2 days. The study was approved by the local ethics committee (Protocol № 9 of November 14, 2016, and Protocol №4 of May 18, 2023). All patients signed informed consent before the enrolment procedure.

The main criteria for the selection of patients were confirmed diagnosis of stroke, proper quality of neuroimaging scans and obtained informed consent to participate in the study. The exclusion criteria were: age under 18 years old, insufficient quality of neuroimaging data or presence of neuroimaging artifacts, neuroimaging evidence of brain lesions of non-vascular origin.

IMAGE ACQUISITION

120 patients underwent MRI, 174 - CT. Some of the subjects 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 collected MRI and CT data of each patient and visually assessed such brain morphometrics as Evans index, third ventricle index, fourth ventricle index, ventricular index, Shlatenbrandt-Nurenberger index, bicaudate index, cella media index (also known as Schiersmann's index), Huckman number using computer software "The Horos Project". All ventricular indices were multiplied by 100 for better representation. We also measured cortical areas: FI, the width of the right and left insular cisterns and their sum (ICR, ICL, ICRL), SW and the maximum width of the cerebellar fissure (CFW) [6].

CLINICAL ASSESSMENT

The demographics and the risk factors were collected: age, sex, body mass index (BMI), Charlson comorbidity index [7], previous stroke, smoking, hypercholesterolemia. NIHSS score [8], modified Rankin scale (mRS) score [9], Barthel index score (BI) [10], Glasgow coma scale (GCS) [11], MMSE score [12] were assessed on admission and at discharge as part of the clinical workup. Stroke subtypes were determined based on the TOAST criteria [13]. The short-term functional outcome was assessed with the mRS and BI at discharge. Also, the functional outcome was measured with the mRS at discharge as favourable outcome (mRS ≤ 2) or unfavourable outcome (mRS > 2) [14]. We defined short-term period as a time from initial presentation to discharge; mean time of hospitalisation was 9.4 ± 4.2 days.

STATISTICAL ANALYSIS

Both univariable and multivariable regression models were used to determine the associations between morphometric data and stroke outcome. The results are shown as odds ratio (OR) and 95% confidence intervals (CI) or as a b-coefficient and 95% CI in case of linear regression. Continuous variables were presented as mean ± standard deviations (SD) or median and interquartile range (ICR). A p value < 0.05 was considered statistically significant. A two groups comparison of brain morphometrics between patients with favourable and unfavourable stroke outcome (functional dependence, mRS >2) was performed by Student's *t*-test in normal distribution or Mann–Whitney *U* test if the variables were not normally distributed. Categorical variables were presented as percentages and were compared with Pearson's chi square test or Fisher's exact test (if number of observations was <5). Statistical analysis was performed by The jamovi project (2022). Jamovi (Version 2.3) [Computer Software]. Sydney, Australia.

RESULTS

In the table 1 clinical and demographical data of the total population is shown. To reveal their associations with stroke outcome along with the indices we build a multifactorial regression model, where most of these predictors as well as brain indices (step by step) were included.

According to the univariable regression analysis, the third ventricle index, Shlatenbrandt-Nurenberger index, bicaudate index, FI, SW significantly associated with poorer BI at discharge (b: -2.5; (95 % CI -4.6 - -0.3, p = 0.024), 0.5; (95 % CI 0.1 - 0.9, p = 0.022), -1.7; (95 % CI -2.8 - -0.6, p = 0.002), -3.1; (95 % CI -5.6 - -0.6, p = 0.014), -2.9; (95 % CI -5.5 - -0.4, p = 0.026) respectively).

After adjusting for age and sex, in the multivariable regression analysis significant associations were found between bicaudate index and BI at discharge (b = -1.3; 95% CI -2.4 – -0.1, p=0.035).

In the next multivariable regression 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 ventricular index and BI at discharge (b = 1.4; 95 % CI

Table 1. Clinical and demographic characteristics of the participants, N=294

Characteristics	
Age	61,9 ± 10,1
Sex male female	 179 (61%) 115 (39%)
TOAST classification, n (%) large artery atherosclerosis cardioembolism small vessel occlusion other determined stroke undetermined stroke	134 (48 %) 71 (25 %) 42 (15 %) 3 (1 %) 29 (11 %)
Period of hospitalisation, days	9,4 ± 4,2
Smoking	66 (29%)
History of previous stroke	71 (24%)
Hypertension	267 (92%)
Ischemic heart disease	34 (12 %)
Atrial fibrillation	96 (33 %)
Diabetes Mellitus	47 (16%)
Charlson comorbidity index	Median 2 (IQR 1 – 3)
Complications	84 (29 %)
BMI	29,7 ± 4,8
Hypercholesterolemia	167 (61 %)
Stroke size, ml	38,0 ± 69,6
NIHSS on admission	11 (8 – 16)
NIHSS at discharge	5 (2 – 11)
mRS on admission	4 (4 – 5)
mRS at discharge	3 (1 – 4)
GCS on admission	14 (13 – 15)
GCS at discharge	15 (14 – 15)
BI at discharge	75 (40 – 100)
MMSE	18,7 ± 10,5

0.2 - 2.6, p = 0.024). Also, significant associations were found between index stroke severity by NIHSS and BI at discharge (b = 1.4; 95 % CI 0.2 - 2.6, p = 0.024), comorbidities and BI at discharge (b = -4.0; 95 % CI –7.3 - -0.7, p = 0.019), presence of complications and BI at discharge (b = -19.3; 95 % CI –27.2 - -11.4, p < 0.001). In this model, third ventricle index, bicaudate index and Evans index showed near-marginal significance (p < 0.1).

The univariable regression analysis revealed a significant association between MMSE and FI (b = -0.8; 95% CI -1.6 – -0.1, p=0.037) as well as SW (b = -0.9; 95% CI -1.8 – -0.1, p=0,023), ICRL was nearly significant (b = -0.2; 95% CI -0.5 – 0.03, p=0.084).

In the multivariable linear regression model, adjusted for age, sex, NIHSS on admission and the brain indices, only bicaudate index was associated with MMSE score (b = -1.2; 95 % CI -2.1 – -0.3, p = 0.011) along with NIHSS on admission (b = -1.2; 95 % CI -1.4 – -1.0, p < 0.001).

In table 2 and fig. 1, bicaudate index, ventricular index, FI and SW significantly differ in case of favourable (mRS 0 – 2, functional independence) vs unfavourable (mRS 3 – 6, functional dependence) stroke outcome.

Further, multifactorial regression analysis was performed, adjusted for age, sex and NIHSS on admission along with all morphometric indices to evaluate their impact on the unfavourable stroke outcome. Both crude and adjusted odds ratio are shown in table 3.

The next multifactorial regression model was made using only ventricular indices, adjusted for each other's, age and sex, as shown in fig. 2.

DISCUSSION

In this study we investigated brain morphological alterations and their associations with short-term stroke outcome. Our findings confirm that brain morphomet-

Table 2. Comparisons of brain morphometrics between patients with favourable and unfavourable stroke outcome (functional dependence, mRS >2)

Brain measurement	favourable outcome Mean ± SD	unfavourable outcome Mean ± SD
Evans index	26.8 ± 3.9	27.5 ± 3.9
The third ventricle index	4.9 ± 1.7	5.2 ± 1.8
Shlatenbrandt- Nurenberger index	23.6 ± 9.3	21.7 ± 8.7
The fourth ventricle index	12.5 ± 1.6	12.5 ± 2.0
Bicaudate index	14.8 ± 3.3	16.0 ± 3.6**
Ventricular index	16.8 ± 2.6	16.2 ± 2.5*
Cella media index (Schiersmann's index)	5.3 ± 1.2	5.1 ± 1.2
Huckman number	55.9 ± 8.7	57.9 ± 9.8
FI	5.3 ± 1.5	5.7 ± 1.6*
ICR	7.0 ± 2.4	7.4 ± 2.8
ICL	7.7 ± 2.7	7.8 ± 2.5
ICRL	14.7 ± 4.5	15.2 ± 4.9
SW	4.1 ± 1.4	4.5 ± 1.6*
CFW	2.5 ± 1.1	2.6 ± 1.2

* p<0,05, **p<0,01.

Table 3. Brain morphometric indices, reflecting its impact on the unfavourable stroke outcome (functional dependence, mRS >2) at discharge.

Brain measurement	Crude OR (95% CI, p)	Adjusted OR (95% CI, p)
Evans index	1.1 (1.0-1.2, p=0.118)	0.8 (0.6-1.0, p=0.099)
The third ventricle index	1.1 (1.00-1.3, p=0.061)	1.4 (0.9-2.4, p=0.166)
Shlatenbrandt- Nurenberger index	0.98 (0.95-1.00, p=0.072)	1.1 (0.99-1.2, p=0.080)
The fourth ventricle index	0.99 (0.9-1.1, p=0.922)	0.9 (0.8-1.1, p=0.295)
Bicaudate index	1.1 (1.0-1.2, p=0.003)	1.3 (1.1-1.7, p=0.018)
Ventricular index	0.9 (0.8-1.0, p=0.073)	0.7 (0.5-0.9, p=0.005)
Cella media index (Schiersmann's index)	0.9 (0.7-1.1, p=0.298)	1.0 (0.7-1.6, p=0.858)
Huckman number	1.0 (1.00-1.1, p=0.066)	0.9 (0.8-1.1, p=0.332)
FI, 1 mm	1.2 (1.0-1.4, p=0.024)	0.97 (0.7-1.3, p=0.840)
ICR, 1 mm	1.1 (1.0-1.2, p=0.219)	0.7 (0.1-3.4, p=0.765)
ICL, 1 mm	1.0 (0.9-1.1, p=0.605)	0.6 (0.1-3.0, p=0.705)
ICRL, 1 mm	1.0 (1.0-1.1, p=0.288)	1.6 (0.3-16.2, p=0.760)
SW, 1 mm	1.2 (1.0-1.5, p=0.018)	1.2 (0.9-1.7, p=0.155)
CFW, 1 mm	1.1 (0.9-1.3, p=0.418)	1.3 (0.9-1.8, p=0.161)
Age, 10 years	1.4 (1.1-1.8, p=0.006)	1.1 (0.8-1.6, p=0.536)
Sex, female	1.0 (0.7-1.7, p=0.888)	1.1 (0.6-2.3, p=0.734)
NIHSS at admission, 10 points	1.3 (1.2-1.4, p<0.001)	1.4 (1.3-1.5, p<0.001)

rics are significantly correlated with short-term stroke consequences.

The results revealed that some morphometric indices deteriorate stroke severity during the time of hospitalisation. According to the univariable regression analysis, the third ventricle index, Shlatenbrandt-Nurenberger index, bicaudate index, FI, SW were significantly associated with poorer BI at discharge (b: -2.5; 0.5; -1.7; -3.1; -2.9; respectively). In multivariable regression analysis, bicaudate index (b = -1.3; 95% CI -2.4 – -0.1, p=0.035) and ventricular index (b = 1.4; 95 % CI 0.2 - 2.6, p = 0.024) were also significantly associated with poorer BI at discharge.

When we dichotomized stroke outcome as a favourable (mRS at discharge 0 – 2) and an unfavourable (mRS at discharge 3 – 6, – functional dependence), in the univariable regression analysis bicaudate index (OR = 1.1; 95 % CI 1.0 - 1.2, p=0.003), FI (OR = 1.2; 95 % CI 1.0 - 1.4,

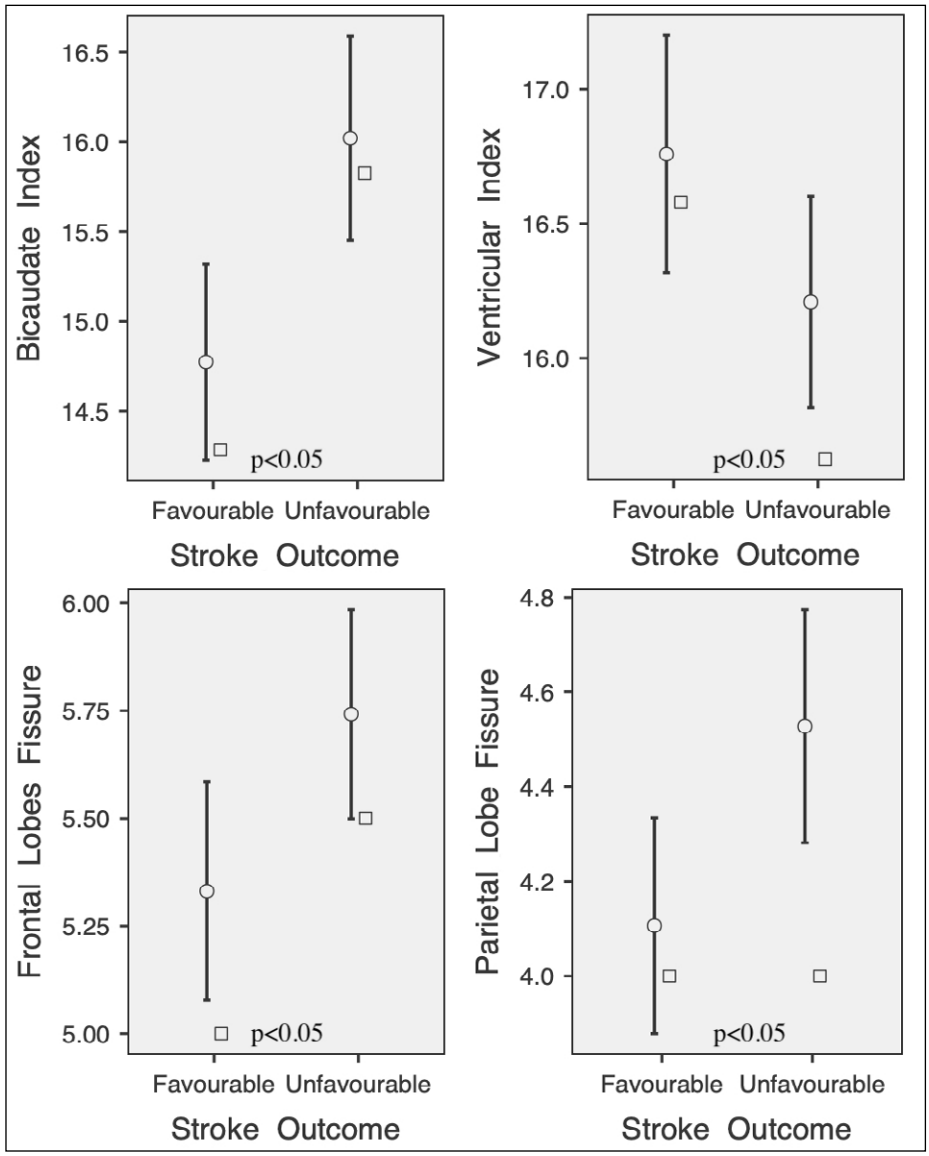

Fig.1. Significant differences in brain morphometrics depending on stroke outcome, o - mean (95 % CI), ▢ - median.

p=0.024), SW (OR = 1.2; 95 % CI 1.0 - 1.5, p=0.018) were associated with an unfavourable stroke outcome. In the multivariable regression model, adjusted for age, sex, NIHSS on admission, bicaudate index (OR = 1.3; 95 % CI 1.1 - 1.7, p=0.018) and ventricular index (OR = 0.7; CI 0.5 - 0.9, p=0.005) were associated with an unfavourable short-term stroke outcome.

There are several possible explanations for this: larger ventricular sizes reflect decreasing white matter volume, which may lead to a loss of functional connectivity. It can disrupt the white matter tracts or U-fibers that mediate cortical–cortical or cortical–subcortical connections. Besides, some research revealed that local white matter lesions may influence the grey matter in remote areas [15]. Hence, altered brain morphometric indices can be linked with unfavourable stroke outcome by impaired recovery of lost functions.

The indices enlargement reflects end-term lesions of the brain parenchyma and imply a variety of pathophysiological aspects, which unfavourably affect clinical consequences of stroke. Acute phase of stroke require comprehensive vascular and neural mechanisms to cope with ischemia, but presence of atrophy can deteriorate that through neuronal disintegration. Promotion of new brain cortical maps and networks is probably worsened due to disintegration of neuronal connections, which are seen at the macroanatomical level as altered cortical and ventricular morphometric parameters.

Over time, particular cortical areas can not only atrophy, but get thicker. Possible causality might occur due to the neuroplasticity mechanisms triggered by the stroke and occurring at a distance from the lesion [16]. Further investigation of the relationship between cerebral morphometric parameters and long-term motor and cognitive recovery after stroke can be of interest to test these hypotheses.

Lower MMSE score was significantly associated with

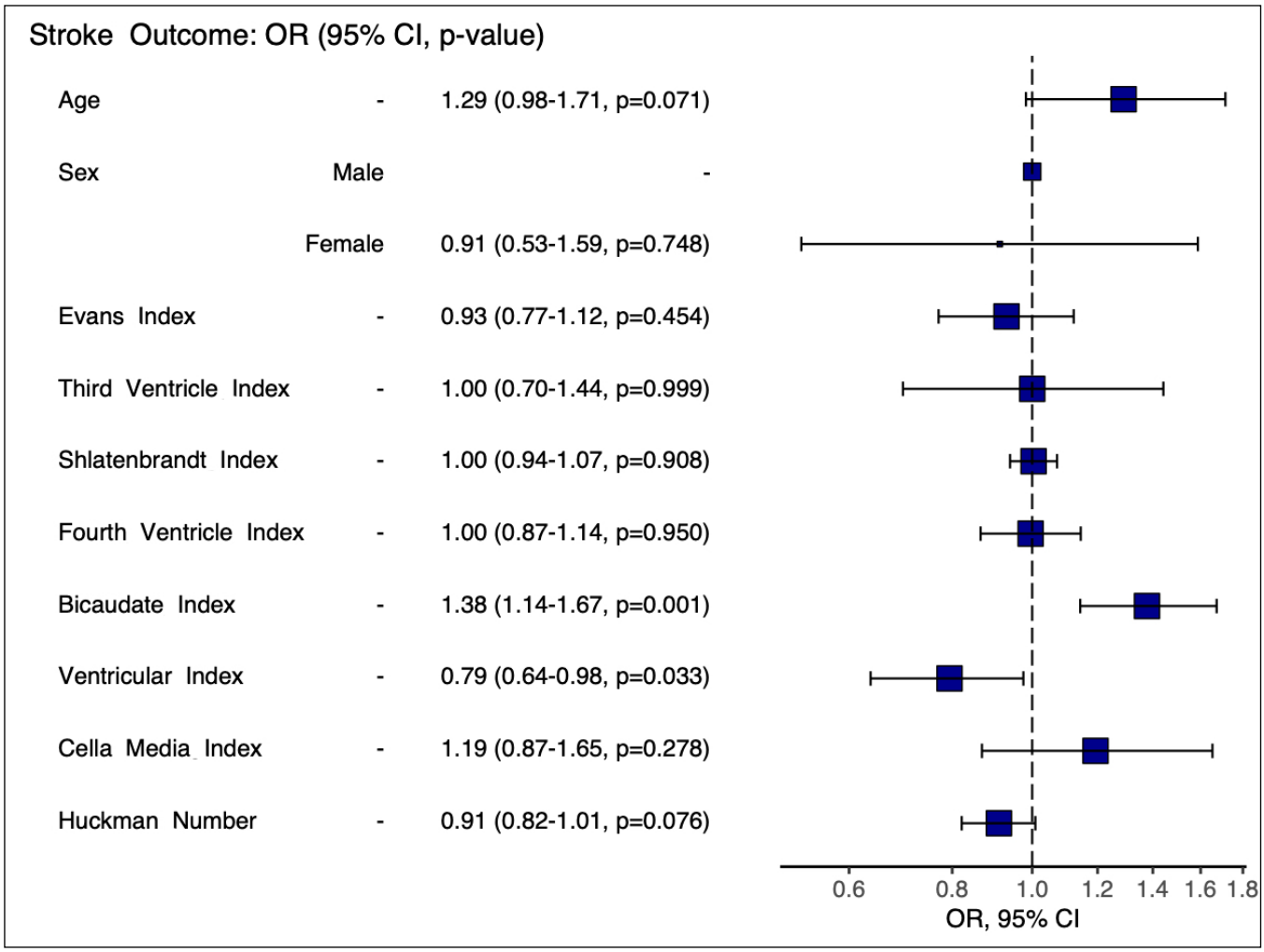

Fig.2. Forest-plot of ventricular indices associations with unfavourable stroke outcome at discharge.

altered cortical indices (cortical thinning) in the univariable regression analysis: FI (b -0.8, 95% CI -1.6 – -0.1, p=0.037) as well as SW (b -0.9, 95% CI -1.8 – -0.1, p=0.023), ICRL was nearly significant (b -0.2, 95% CI -0.5 - 0.03, p=0.084). In the multivariable regression model only bicaudate index was associated with MMSE score (b = -1.2; 95 % CI -2.1 – -0.3, p = 0.011) along with NIHSS on admission (b = -1.2; 95 % CI -1.4 – -1.0, p < 0.001). Other indices lost significance, suggesting that in an acute phase of stroke the lesion size and NIHSS severity on admission are key contributors to an acute cognitive deterioration. Some findings suggest that white matter damage that occurred due to cerebral small vessel disease promote atrophy (ventricular and sulci span enlargement), which, in turn, drives cognitive decline [17].

Neurobehavioral features of vascular dementia are slowed processing speed and executive dysfunction and emerged as the most prominent clinical features of white matter damage. With respect to cognitive slowing, the normal physiological function of myelin to increase axonal conduction velocity would be deteriorated [19]. Slowed processing speed can result from white matter degradation, which associated with ventricular system enlargement.

Many cognitive processes are realised by spatially distributed neural networks in the brain. The prefrontal and temporal cortex are a set of functionally connected regions that plays crucial roles in internal cognitive processing like working memory, attention and language, processing speed, autobiographical memory etc. [19, 20]. The parietal lobe is a heteromodal convergence zone of various brain networks that is central to realizing key cognitive operations across different levels of the neural processing hierarchy. These mental operations include lower level processes, such as spatial attention, as well as higher level processes that are distinctly elaborate in the human species, like semantic memory and modes of social exchange [21]. So, its damage can cause cognitive deterioration. Early injury of temporal lobes might be the reason of more serious cognitive decline [15], that is why measurement of the width of the insular cisterns and other cortical and subcortical regions might be useful for patients selection for early cognitive decline prevention, like acetylcholinesterase inhibitors etc., whether it is neurodegeneration or vascular origin. Hence, atrophy of cortical

areas, that are seen as altered aforementioned indices, can dramatically impair various cognitive functions, which is important to diagnose at the early stages.

For further investigations, measurements of ventricles sizes and cortical sulci span may be of interest, particularly for understanding how they impact long-term stroke outcome; as well as whether some brain morphometrics alterations associated with specific cognitive, functional, or behavioural changes. It is also necessarily to elicit how rehabilitation and other therapy can affect morphometric changes' progression in long-term perspective in stroke-survivors.

CONCLUSIONS

1. Brain morphometric alterations were associated with short-term stroke outcome in hospitalization period: in the multivariable regression analysis, bicaudate index (OR = 1.3; 95 % CI 1.1 - 1.7, p=0.018) and ventricular index (OR = 0.7; CI 0.5 - 0.9, p=0.005) were associated with an unfavourable short-term stroke outcome (functional dependence) and lower level of activities of daily living according to BI at discharge: bicaudate index (b = -1.3; 95% CI -2.4 – -0.1, p=0.035), ventricular index (b = 1.4; 95 % CI 0.2 - 2.6, p = 0.024).
2. Morphometric indices were associated with cognitive decline in acute phase of stroke: in the multivariable regression model bicaudate index was negatively associated with MMSE score (b = -1.2; 95 % CI -2.1 – -0.3, p = 0.011). In the univariable regression analysis, wider frontal, temporal and parietal sulci span were associated with lower cognitive functions according to MMSE scale.
3. Measurements of both ventricular and cortical brain morphometrics' parameters can be a useful tool for patients' selection for early treatment and preventive strategies.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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