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SURVIVAL ANALYSIS IN STROKE PATIENTS WITH CEREBRAL SMALL VESSEL DISEASE

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Key words: *cerebral small vessel disease, stroke, survival analysis, lacunes, white matter hyperintensity, magnetic resonance imaging, computed tomography, vascular pathology*
Ключові слова: *захворювання дрібних судин мозку, інсульт, аналіз виживаності, лакуни, гіперінтенсивність білої речовини, магнітно-резонансна томографія, комп'ютерна томографія, судинна патологія*

Abstract. Survival analysis in stroke patients with cerebral small vessel disease. Bartiuk R.S., Smolko D.G., Marunkevych Ya.Yu., Smotrytska T.V., Moskovko S.P. *Cerebral small vessel disease has been considered to worsen short-term stroke outcome in upcoming 90 days, whereas few research have evaluated the role of cerebral small vessel disease in long-term prognosis (for instance, beyond a year). The aim of the research is to investigate the association between cerebral small vessel disease burden and long-term post-stroke survival in patients with acute stroke. It was a*

prospective single-center cohort study. 294 consecutive patients with acute stroke were recruited. All participants underwent magnetic resonance imaging and computed tomography assessment for cerebral small vessel disease markers as well as clinical-neurological testing.. To determine the associations of small vessel disease with mortality in patients after stroke, we used multivariate survival analysis using Cox regression with Kaplan-Meier survival curves for 5 years of follow-up after discharge. In multivariable Cox regression proportional hazards model, cerebral small vessel disease presence was associated with long-term all-cause post-stroke mortality (hazard ratio =3.8; 95% confidence interval 1.9-7.9, p<0.001). In the same model, cerebral small vessel disease severity grade 1 (hazard ratio =2.4; 95% confidence interval 1.1-5.4, p=0.033), cerebral small vessel disease severity grade 2 (hazard ratio =6.9; 95% confidence interval 3.2-15.0, p<0.001) were associated with poor survival. We also found significant association between presence of lacunes and mortality: (adjusted hazard ratio =6.2; 95% confidence interval 3.3-11.5, p<0.001); as well as severe white matter hyperintensity and mortality: (adjusted hazard ratio =2.1; 95% confidence interval 1.1-4.1, p=0.019). Cerebral vessel disease is significantly associated with mortality in patients after stroke during 5 years of follow-up. It may be useful in determining patient prognosis and future patient selection for preventive strategies.

Реферат. Аналіз виживаності хворих з інсультом за наявності захворювання дрібних судин головного мозку. Бартюк Р.С., Смолко Д.Г., Марункевич Я.Ю., Смотрицька Т.В., Московко С.П. *Захворювання дрібних судин мозку може погіршувати короткострокові наслідки інсульту в перспективі 90 днів. Проте даних щодо довгострокового прогнозування інсульту, наприклад понад рік за наявності захворювання дрібних судин мозку, на сьогодні не достатньо. Мета дослідження: встановити зв'язок між захворюванням дрібних судин мозку та довготривалою постінсультною виживаністю хворих з гострим мозковим інсультом. У дослідженні взяли участь 294 хворих з гострим мозковим інсультом. Усім пацієнтам була виконана магнітно-резонансна та комп'ютерна томографія головного мозку для виявлення ознак захворювання дрібних судин мозку, також проводилась динамічне клініко-неврологічне оцінювання стану пацієнтів у госпітальному періоді. Для визначення асоціацій захворювання дрібних судин мозку зі смертністю хворих після інсульту ми застосовували багатофакторний аналіз виживаності методом регресії Кокса з кривими виживаності Каплан-Мейєра протягом 5 років спостереження після виписки. У багатофакторному аналізі виживаності наявність захворювання дрібних судин мозку асоціювалась з постінсультною смертністю від усіх причин (відношення ризиків =3,8; 95% довірчий інтервал 1,9-7,9, p<0,001). У цій же моделі захворювання дрібних судин мозку 1 ступеня тяжкості (відношення ризиків =2,4; 95% довірчий інтервал 1,1-5,4, p=0,033), захворювання дрібних судин мозку 2 ступеня тяжкості (відношення ризиків = 6,9; 95% довірчий інтервал 3,2-15,0, p<0,001) також негативно асоціювались з виживаністю хворих. До того ж ми виявили достовірний зв'язок між наявністю лакун (скоректоване відношення ризиків =6,2; 95% довірчий інтервал 3,3-11,5, p<0,001); а також тяжким лейкоареозом та смертністю (скоректоване відношення ризиків =2,1; 95% довірчий інтервал 1,1-4,1, p=0,019). Захворювання дрібних судин мозку достовірно асоціюється зі смертністю хворих після інсульту протягом 5-ти років спостереження. Це може бути корисним для визначення прогнозу та відбору пацієнтів для профілактичних цілей.*

Stroke is the leading cause of long-term disability and the second most common cause of death on the planet [1, 2]. The estimated global cost of stroke is over US $ 891 billion (1.12% of the global GDP). From 1990 to 2019, the burden (in terms of the absolute number of cases) increased substantially (70.0% increase in incident strokes, 43.0% deaths from stroke, 102.0% prevalent strokes, and 143.0% disability-adjusted life-years lost), with the bulk of the global stroke burden (86.0% of deaths and 89.0% of disability-adjusted life-years lost) residing in lower-income and lower-middle-income countries [3].

Cerebral small vessel disease (CSVD) refers to any pathologic process that damages small terminal arteries, arterioles, capillaries, and brain venules. It is the most common pathology underlying vascular cognitive impairment, lacunar stroke and intracerebral hemorrhage. Other clinical features include motor and balance impairment, falls, vascular parkinsonism and psychiatric and behavioral symptoms, such as depression, apathy, and personality change. Characteristic on magnetic resonance imaging (MRI) or computed tomography (CT) features are used to define CSVD, including lacunes, white matter hyperintensities (WMH), cerebral microbleeds, enlarged perivascular spaces and brain atrophy. These CSVD-related brain abnormalities usually co-occur in different etiologies, and their clinical courses are variable [4].

Some studies have investigated the prediction of mortality and functional outcome following stroke over the period to day 90 [5], whereas few have evaluated the role of CSVD in long-term prognosis (for instance, beyond a year). Understanding the longitudinal association between CSVD burden and long-term stroke prognosis could lead to development of better predictive and preventive strategies as well as new therapeutic approaches.

We aimed to investigate the association between cerebral small vessel disease burden and long-term post-stroke survival in patients with acute stroke.

MATERIALS AND METHODS OF RESEARCH

The study was approved by the medical ethics committee of Vinnytsia National Pirogov Memorial Medical University according to the guidelines of the

Declaration of Helsinki of 1975 (Protocol No. 9 of November 14, 2016). Written informed consent was obtained from all patients participating in the study.

It was a prospective single-center cohort study based at specialized stroke department (Stroke Unit) No. 22 of the Vinnytsia Regional Clinical Psychoneurological Hospital named after acad. O.I. Yushchenko VRC. Between December 2016 and December 2021, a total of 294 consecutive patients with acute stroke were recruited (age: 61.9±10.1, 179 males). Until the end of 2021 the patients were followed-up via telephone interviews in the time period of 3 months, 1 year, 3 years and 4-5-years post-stroke. Patients hospitalized in 2016-2019 were followed for 5-2 years, respectively. A death was confirmed by asking patients family members. All patients were under surveillance from enrollment, until the occurrence of death, the last telephone contact, or the end of the follow-up (December 2021). Since the cause of mortality cannot be reliably validated without medical papers being available, we did not analyze the different causes of mortality in this study. Period of follow-up: median 829 (IQR 180-1030) days, maximum 1755 days (up to 5 years). 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. 311 patients were examined for eligibility, among them 15 were excluded due to transient ischemic attack diagnosis, 1 patient – cancer diagnosis, 1 patient – presence of demyelinating lesions on MRI. 294 consecutive patients confirmed eligible and included in the study.

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 with a magnetic field strength of 1.5 T. The standard brain scanning protocol included the following whole brain scans: T1-weighted, T2-weighted, fluid-attenuated inversion recovery (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.

Stroke was defined according to World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal or global disturbance of cerebral function lasting ≥24 hours or leading to death with no apparent cause other than of vascular origin [6]. Stroke diagnoses were verified by an experienced vascular neurologist and classified as ischemic or hemorrhagic based on neuroimaging reports (CT and/or MRI) of experienced radiologists.

The severity of WMH was assessed using the Fazekas scale (from 0 to 3). Periventricular: Fazekas=0: absent; Fazekas =1: caps or pencil-like thin layer; Fazekas= 2: smooth halo; Fazekas =3: extension into deep white matter. Deep white matter: Fazekas =0: absent; Fazekas =1: punctate lesions; Fazekas =2: lesions beginning to confluence; Fazekas =3: lesions confluent and united in sheets [7]. A lacune of presumed vascular origin was defined as a lesion of 3-20 mm in diameter and CSF-like intensity with hyperintensities on T2-weighted and hypointensities on T1-weighted images, with a perilesional halo on FLAIR images sometimes. On CT a "lacuna of presumed vascular origin" was defined to be a round or ovoid, subcortical cavity of diameter 3-20 mm that was filled with a fluid similar in appearance to cerebrospinal fluid [8]. If territorial infarct lesion was too large, we analyzed contralateral side only.

Total CSVD score was calculated using an ordinal scale ranging from 0 to 2 by combining the two individual CSVD markers with one point allocated to each of the following: the presence of even one lacune, deep WMH, Fazekas score reached 2 or periventricular WMH, Fazekas score reached 3 [9]. We did not include enlarged perivascular spaces and microbleeds as majority of patients underwent CT. We also excluded brain atrophy as it can represent neurodegenerative disorders. We combined CT and MRI data to include more patients. Intrarater reliability testing showed near perfect reliability with kappa values for the lacunes presence of 0.964 and for the total Fazekas score of 0.910.

Demographics and risk factors were collected: age, sex, body mass index, history of hypertension, diabetes, atrial fibrillation, smoking, alcohol consumption, hypercholesterolemia, a previous history of stroke, Charlson comorbidity index [10]. Various concomitant diseases, such as hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation etc. were confirmed by an experienced physician. National Institutes of Health Stroke Scale (NIHSS) score [11], mRS score [12], Glasgow coma scale (GCS) [13], Mini-mental state examination scale (MMSE) [14] were assessed by trained neurologists at the time of initial presentation and at the discharge as part of the clinical workup. Stroke subtypes were determined based on the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria: large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined, or undetermined stroke [15]. The functional outcome was assessed with the mRS and BI at 90 days, 1, 3, 4-5 years by telephone interviews.

We used the Cox proportional hazard analysis to calculate the unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the

occurrence of all-cause mortality in CSVD group compared to the non-CSVD group. A Kaplan–Meier survival curve was plotted, and the log-rank test was applied to test the difference in survival between the groups [16]. 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). Continuous variables were presented as mean ± standard deviations (SD) or median and interquartile range (ICR). A p value <0.05 was considered statistically significant. Comparison of two groups was performed by Student's t-test in normal distribution or Mann-Whitney U test if the variables were not normally distributed [17]. Statistical analysis was performed by The jamovi project (2022). Jamovi (Version 2.3) [Computer Software]. Sydney, Australia. Retrieved from https://www.jamovi.org (free computer software).

RESULTS AND DISCUSSION

The demographic and clinical characteristics of the non-CSVD and CSVD patients are summarized in Table 1. In the total population the most frequent stroke risk factor was arterial hypertension, 267/290 (92%), followed by family history of stroke, 86/208 (41%), atrial fibrillation, 96/293 (33%), smoking, 66/225 (29%), previous stroke, 71/292 (24%), diabetes, 47/291 (16%), severe ischemic heart disease or myocardial infarction, 34/285 (12%), alcohol abuse, 23/223 (10%), and peripheral arterial disease, 10/290 (3%). Thrombolytic therapy was performed in 185/294 (63%) patients within the first 4.5 hours.

Table 1

Clinical and demographic data based on CSVD presence, n (%), M±SD, Me (Q1-Q3)

Variable	Non-CSVD, 165	CSVD, 129
Age, years	**58.9±10.4**	**65.8±8.3*****
Sex, n (%)		
male	**69 (42%)**	**83 (64%)**
female	**96 (58%)**	**46 (36%)**
Stroke classification, n (%)		
large artery atherosclerosis	**75 (46%)**	**59 (50%)**
cardioembolism	**43 (27%)**	**28 (24%)**
small vessel occlusion	**20 (12%)**	**22 (19%)**
other determined stroke	**3 (2%)**	**0 (0%)**
undetermined stroke	**21 (13%)**	**8 (7%)**
cryptogenic		
Period of hospitalization, days	**8.9±3.7**	**10.1±4.6*****
Smoking, n (%)	**36 (27%)**	**30 (32%)**
Alcohol abuse, n (%)	**13 (10%)**	**10 (11%)**
History of previous stroke, n (%)	**26 (16%)**	**45 (35%)****
Hypertension, n (%)	**139 (86%)**	**128 (99%)*****
Ischemic heart disease, n (%)	**14 (9%)**	**20 (16%)**
Atrial fibrillation, n (%)	**53 (32%)**	**43 (33%)**
Diabetes mellitus, n (%)	**22 (13%)**	**25 (20%)**
Traumatic brain injury, n (%)	**9 (5%)**	**5 (4%)**
Vein varicosis, n (%)	**17 (10%)**	**19 (15%)**

continuation of Table 1

Variable	Non-CSVD, 165	CSVD, 129
Peripheral arterial disease, n (%)	**2 (1%)**	**8 (6%)***
Chronic kidney diseases, n (%)	**7 (4%)**	**7 (6%)**
Chronic lung diseases, n (%)	**19 (12%)**	**28 (22%)***
Chronic gastrointestinal diseases, n (%)	**24 (15%)**	**18 (14%)**
Charlson comorbidity index, median (IQR)	**1 (1-2)**	**1 (1-3)*****
BMI, kg/m^2	**29.8±5.0**	**29.5±4.6**
Hyperlipidemia, n (%)	**92 (59%)**	**75 (63%)**
Stroke volume, ml	**28.8±52.1**	**49.8±85.8***
NIHSS upon admission, median (IQR)	**11 (7-15)**	**13 (9-17)***
mRS upon admission, median (IQR)	**4 (4-4)**	**4 (4-5)**
MMSE at discharge, median (IQR)	**25 (16-28)**	**20 (4-26)*****

Notes: values are number (%), mean±SD or median (interquartile range); *p value <0.05, **p value <0.01, ***p value <0.001; CSVD: cerebral small-vessel disease; BMI: body mass index; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin scale; MMSE: mini-mental state examination scale; M: mean, SD: standard deviation; Me: median; Q1: first quartile; Q3: third quartile.

Patients with CSVD were of advanced age, had significantly longer hospitalization time and more often had history of cardiac risk factors (hypertension, history of previous stroke, peripheral arterial disease, chronic lung diseases), had higher Charlson comorbidity index, more complications, larger stroke volume and more severe stroke index based on NIHSS scale (Table 1). Thrombolytic therapy was performed in 111 (67%) non-CSVD patients and in 74 (57%) CSVD patients, the difference was not significant. 51 (40%) CSVD patients had complications during hospitalization versus 33 (20%) non-CSVD patients (p<0.001).

In the total population, CSVD presence was diagnosed in 129 (44%) patients, severe CSVD (grade 2: presence at least 1 lacune along with severe WMH) had 43 (15%) patients, moderate CSVD (presence either at least 1 lacune or severe WMH) – in 86 (29 %) patients. Presence of lacunes was noted in 68 (23 %) patients, among them 25 (37%) had multiple (>1) lacunes. WMH had 97% participants, among them 106 (36%) had severe WMH (Fazekas score 3), 122 (42%) – moderate WMH (Fazekas score 2), 56 (19%) – mild WMH (Fazekas score 1).

Median survival for CSVD group was 785 days, (IQR 108-894 days), maximum 1720 days and 855 days (IQR 690-1247 days), maximum 1755 days for non-CSVD group (p=0.006).

In the Cox regression proportional hazards model we used 2 models: in model 1, we adjusted for age, sex, stroke severity by NIHSS and Charlson comorbidity index (which reflects mortality risk); in model 2, we in addition adjusted separately for varied vascular risk factors and predictors (incorporating history of hypertension, coronary heart disease, atrial fibrillation, diabetes mellitus, peripheral artery disease, history of previous stroke, alcohol abuse, and smoking status besides stroke severity by NIHSS, age and sex).

The effect of CSVD on overall post-stroke survival (endpoint: all-cause death) was determined by Kaplan-Meier log rank analysis (Fig. 1, 2). We added to the pictures unadjusted HR at multiple time points.

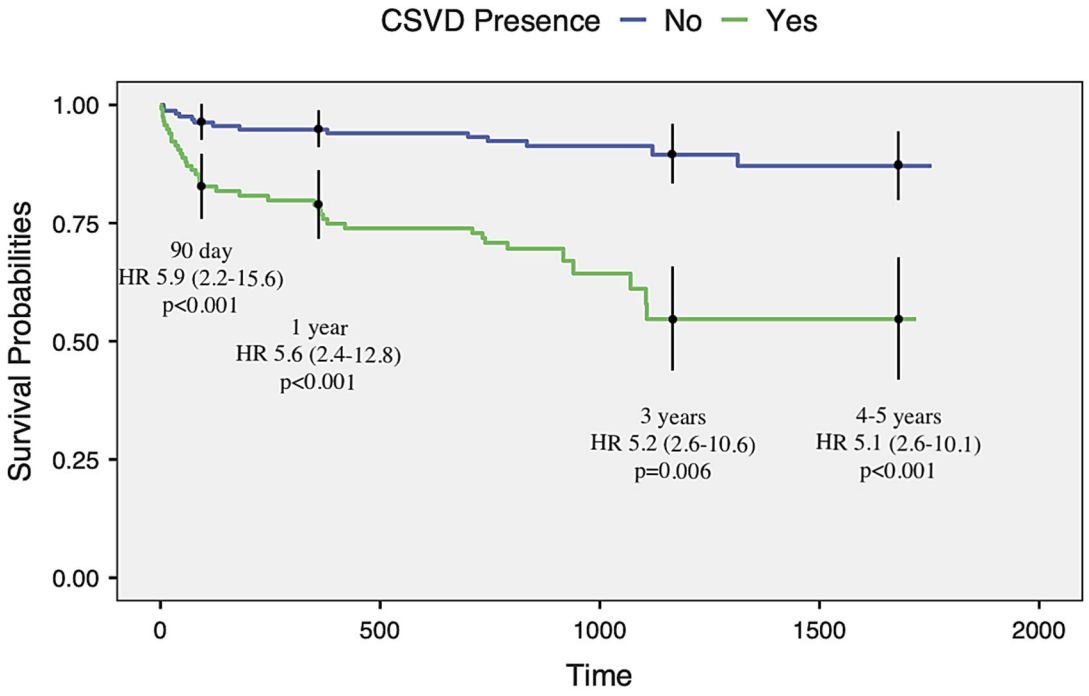

Fig. 1. Kaplan-Meier survival curve with crude HR of how post-stroke survival was effected by CSVD presence. Log rank test: $X^2 = 27.2$, df 1, p<0.001

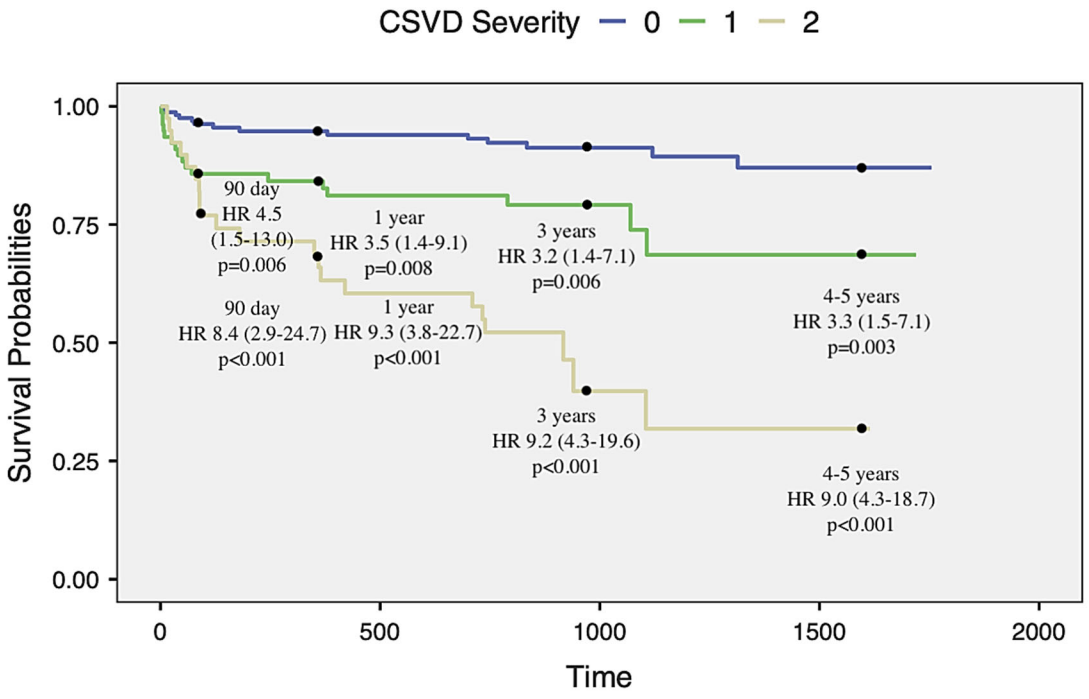

Fig. 2. Kaplan-Meier survival curve with crude HR of how post-stroke survival was effected by (CSVD severity. Log rank test: $X^2 = 45.2$, df 2, p<0.001

In the first Cox regression proportional hazards model, CSVD presence (HR=3.8; 95% CI 1.9-7.9, p<0.001) and stroke severity by NIHSS (per 10 scores) (HR=3.2; 95% CI 1.9-5.3, p<0.001) were associated with poor survival (Table 2, Fig. 3).

In the model 1, we found significant association between lacunes presence and mortality, (crude HR=6.4; 95% CI 3.6-11.4, p<0.001), (adjusted HR=6.2; 95% CI 3.3-11.5, p<0.001); as well as between severe WMH and mortality (crude HR=3.5; 95% CI 2.0-6.4, p<0.001), (adjusted HR=2.1; 95% CI 1.1-4.1, p=0.019).

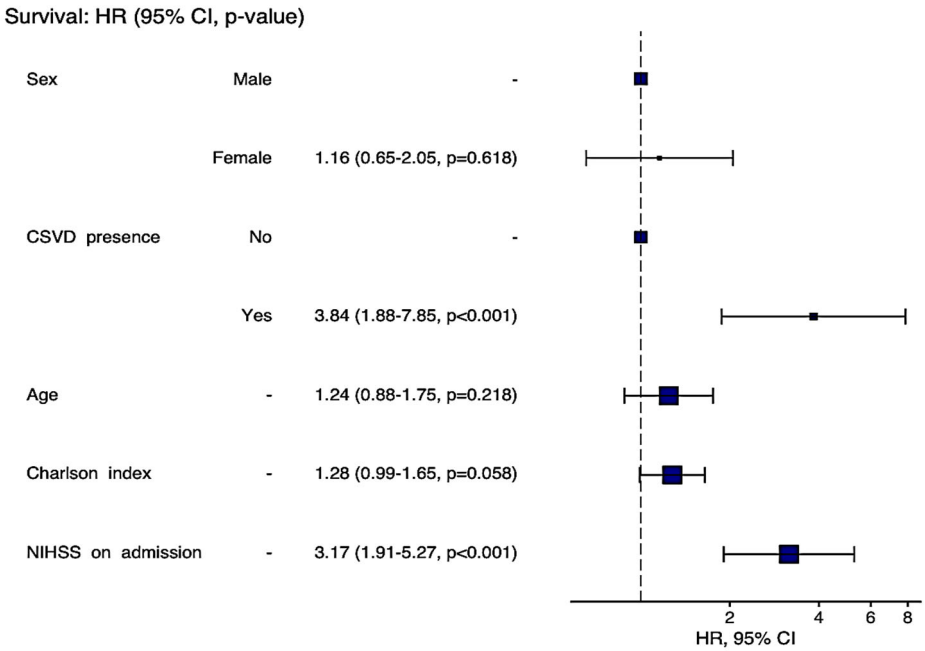

Fig. 3. Effect of CSVD presence on post-stroke survival considering sex, age (per 10 years), Charlson comorbidity index and National Institutes of Health Stroke Scale (NIHSS) score on admission (per 10 scores)

In the same first Cox regression proportional hazards model, CSVD severity grade1 (HR=2.4; 95% CI 1.1-5.4, p=0.033), CSVD severity grade 2 (HR=6.9; 95% CI 3.2-15.0, p<0.001) and stroke severity by NIHSS (per 10 scores) (HR=3.3; 95% CI 2.0-5.6, p<0.001) were associated with poor survival (Fig. 4).

In the univariable analysis, the differences in survival were noted from the day 90 and confirmed in 1 year, 3 years and 4-5 years of follow-up for all CSVD characteristics (CSVD presence, CSVD severity, lacunes presence and severe WMH in comparison to mild-moderate WMH).

Table 2

Results of Cox regression analysis of survival, model one

	day 90	1 year	3 years	4-5 years
CSVD presence	**HR=3.3; (1.2-9.1), p=0.024**	**HR=3.6; (1.5-8.5), p=0.004**	**HR=3.5; (1.7-7.4), p=0.001**	**HR=3.8; (1.9-7.9), p<0.001**
CSVD grade 1	**HR=2.3; (0.8-6.9) p=0.138**	**HR=2.2; (0.8-5.8) p=0.109**	**HR=2.1; (0.9-4.9) p=0.086**	**HR=2.4; (1.1-5.4), p=0.033**
CSVD grade 2	**HR=6.8; (2.1-22.1), p=0.002**	**HR=7.2; (2.7 - 19.2), p < 0.001**	**HR=6.4; (2.9-14.3), p<0.001**	**HR=6.9; (3.2-15.0), p<0.001**
Lacunes presence	**HR=6.1; (2.6–14.4), p<0.001**	**HR=5.6; (2.7–11.7), p<0.001**	**HR=6.2; (3.3-11.8), p<0.001**	**HR=6.2; (3.3-11.5), p<0.001**
Severe WMH	**HR=1.5; (0.6–3.7), p=0.349**	**HR=2.1; (1.0–4.5), p=0.059**	**HR=1.9; (1.0-3.7), p=0.051**	**HR=2.1; (1.1–4.1), p=0.019**

Notes: CSVD: cerebral small-vessel disease; HR: hazard ratio; WMH: white matter hyperintensity.

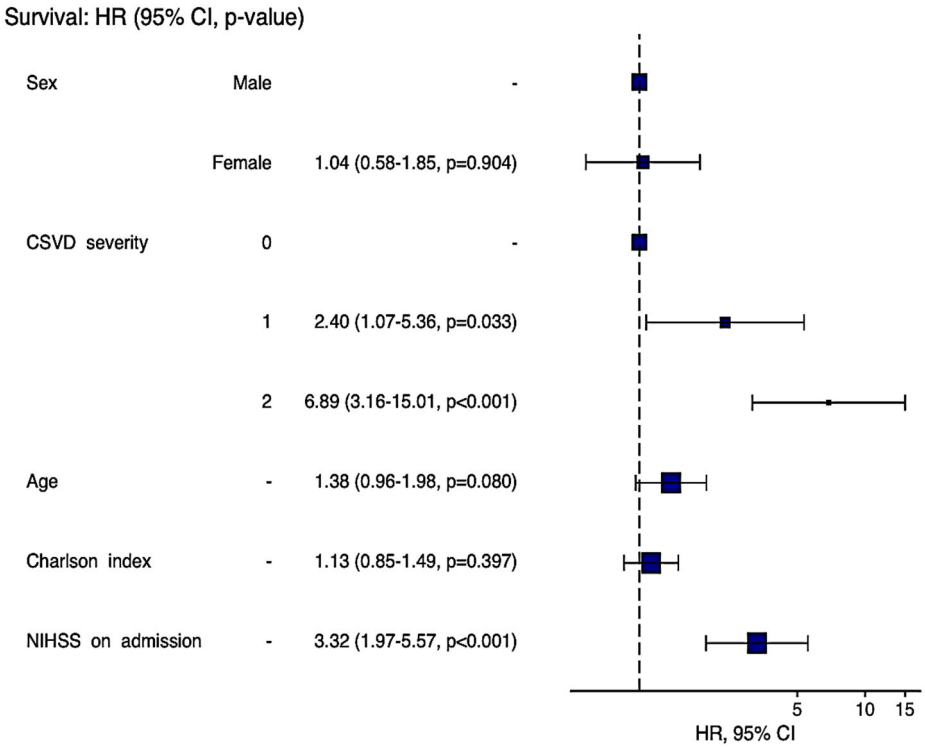

Fig. 4. Effect of CSVD severity on post-stroke survival considering sex, age (per 10 years), Charlson comorbidity index and NIHSS scale score on admission (per 10 scores)

In the second Cox regression proportional hazards model, CSVD presence (crude HR=7.6; 95% CI 2.6-22.7, p<0.001), (adjusted HR=7.5; 95% CI 2.2-25.4, p=0.001), as well as CSVD severity grade 1 (crude HR=3.6; 95% CI 1.0-12.8, p=0.048), grade 2 (crude HR=17.3; 95% CI 5.6-52.0, p<0.001), (adjusted HR=23.9; 95% CI 6.2-92.2, p<0.001) were associated with poor survival. CSVD severity grade 1 was nearly significant (adjusted HR=3.3; 95% CI 0.8-13.1, p=0.098).

In the model 2, also we found significant association between lacunes presence and mortality, (crude HR=10,0; 95% CI 4.1-24.2, p<0.001), (adjusted HR=16.9; 95% CI 6.0-48.0, p<0.001). As well as severe WMH and mortality, (crude HR=5.3; 95% CI 2.1-13.5, p=0.001), (adjusted HR=4.7; 95% CI 1.6-14.0, p=0.005).

The key findings of this study are that CSVD was an independent predictor of poor long-term stroke survival and was associated with increased risk for all-cause death in up to 5-year follow-up, which is in line with the other studies. Yi F. et al. found that baseline white matter hyperintensity volume, presence of lacunes and total brain volume were associated with all-cause mortality after adjusting for age, sex, and vascular risk factors during 16-years' follow-up of non-stroke patients [18]. Lee W.J. et al., determined the association of CSVD with 5-year all-cause mortality in middle-to-old aged stroke-free and non-demented participants [19]. Kitagawa K. et al. showed that the total CSVD score was independently associated with stroke and all-cause death during a median follow-up period of 4.6 years in stroke-free cohort. Patients with higher total CSVD scores were significantly more likely to have a stroke [20]. Hakim A. et al. found out that both the continuous number of microbleeds and the presence of lacunes were independent significant predictors of stroke outcome in patients with a first-ever anterior circulation ischemic stroke. [21]. In the research of Melkas S. et al., ischemic stroke cohort of patients aged 55-85 years with a 12-year follow-up, acute index stroke attributable to CSVD was associated with poorer long-term survival [22]. Kissela B. et al. confirmed that WMH associated with poor functional outcome after stroke at 3 month and 4 years [23]. Leonards C.O. with colleagues revealed that moderate to severe WMH associated with poor stroke outcome at 1 year [24]. In the study of Xu M. et al., cumulative CSVD score ≥2 was associated with a decreased survival rate after intracerebral hemorrhage during follow-up of 5 years [25].

These relationships were independent of stroke severity by NIHSS, demographics, comorbidities and cardiovascular risk factors at baseline. Moreover, grade 2 CSVD severity (combined CSVD markers) was

associated with an almost 3-fold increased risk of death. An explanation may be that simultaneous presence of both severe WMH and lacunes reflect more severe brain parenchyma damage and associated with higher prevalence of vascular risk factors.

Presence of one CSVD marker (severe WMH or at least 1 lacune) in univariable analysis is also significantly associated with post-stroke death, as well as in the first multivariable Cox regression model up to 5 years. In the future research we are going to analyze associations between WMH characteristics as well as lacunes features and post-stroke survival in more details.

The differences in survival were noted from the day 90 and confirmed in 1 year, 3 years and 4-5 years of follow-up.

We found that the risk of mortality was predominantly determined by stroke severity and age, and CSVD as well. Comorbidities by Charlson index at baseline were nearly significant.

Previous studies showed that pathologic changes in the small cerebral vessels can induce secondary ischemia [26]. CSVD is a result of cummulation of cardiovascular risk factors, such as hypertension, smoking, aging, diabetes, which are themselves associated with worse stroke outcome as well as genetic factors, which are not well understood yet [27]. Severe CSVD could be a marker of an impaired neurovascular network, which could inhibit plasticity and adversely affect the recovery after stroke [19].

It is interesting that the micro-environment of adult neurogenesis is called the "vascular niche". There is a highly developed microvascular network of small brain vessels, which may control the function of neuronal stem cells residing in the two major neurogenic niches of the adult brain, namely the sub-ventricular zone and the hippocampus [28]. According to our data, a significant difference was observed in the prevalence of mediotemporal hippocampal atrophy between CSVD vs non-CSVD group: the 3rd grade of hippocampal atrophy in the CSVD group was noted in 17.9% vs 3.4% in the comparison group ($p<0.001$). Therefore, CSVD can reduce neurogenesis in stroke patients and impair post-stroke survival.

According to obtained data, many patients with stroke had lacunes without previous stroke history, i.e. asymptomatic lacunar infarcts. It implies that silent lacunar infarcts, which are generally not diagnosed and not treated, may impair post-stroke survival and actually are important for the prognosis [18].

When we separately analyzed WMH and lacunes associations with post-stroke survival, lacunes had much higher risks of contributing to patients' death. Our suggestion and possible explanation for this may be that lacunes represent more severe deterioration of anti-ischemic protective mechanisms, which already led to "small" stroke. In addition, up to date understanding of the pathogenesis of lacunes implies the underlying numerous systemic causes of their formation [29], which will negatively impact the survival.

The strengths of our study are the relatively long-term follow-up, adjustment of confounders, separate and cumulative analysis of CSVD markers.

The limitations of the study are the following: we did not stratify causes of death, we excluded some CSVD markers, like enlarged perivascular spaces, microbleeds as majority of the patients underwent CT, and we combined CR and MRI data.

CONCLUSIONS

1. Cerebral small vessel disease is significantly associated with long-term post-stroke mortality up to 5 years of surveillance (hazard ratio, adjusted for age, sex, comorbidity index, National Institutes of Health Stroke Scale, stroke severity at admission (3.84, 95% confidence interval 1.88-7.85, $p<0.001$).
2. Presence of lacunes and severe white matter hyperintensity have added value to predict prognosis and in combination possess much higher risks than two factors separately (adjusted hazard ratio =6.9, 95% confidence interval 3.2-15.0, $p<0.001$).
3. The results may be useful for determining prognosis and selecting patients for additional preventive interventions.

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