Pre-Existing Cerebral Small Vessel Disease Limits Early Recovery in Patients with Acute Lacunar Infarct

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Background and Purpose: To assess whether neuroimaging markers of chronic cerebral small vessel disease (cSVDm) influence early recovery after acute ischemic stroke (AIS). *Methods:* Retrospective analysis of patients diagnosed with AIS and included in the Spanish Neurological Society Stroke Database. Inclusion criteria: (1) Brain MRI performed after acute stroke and (2) Premorbid modified Rankin scale (mRS) = 0. Exclusion criteria: (1) Uncommon stroke etiologies, (2) AIS not confirmed on neuroimaging, or (3) Old territorial infarcts on neuroimaging. Patients scored from 0 to 2 according to the amount of cSVDm. Patients were divided into lacunar ischemic stroke (LIS) and nonlacunar ischemic stroke (NLIS) groups according to TOAST classification. Primary outcome: Distribution of mRS at discharge. Secondary outcomes: NIHSS improvement more than or equal to 3 at 24 hours and at discharge, NIHSS worsening more than or equal to 3 points at 24 hours. *Results:* We studied 4424 patients (3457 NLIS, 967 LIS). The presence of cSVDm increased the risk of worsening 1 category on the mRS at discharge in the LIS group ([1] cSVDm: OR 1.89 CI 95% 1.29-2.75, $P = .001$. [2] cSVDm: OR 1.87, CI 95% 1.37-2.56 $P = .001$) and was an independent factor for not achieving an improvement more than or equal to 3 points on the NIHSS at discharge for all the patients and the LIS group (all stroke patients: [1] cSVDm: OR 0.81 CI 95% .68-.97 $P = .022$. [2] cSVD: OR 0.58 CI95% .45-.77, $P = .001$./LIS: [1] cSVDm: OR 0.64, CI 95% .41-.98, $P = .038$. [2] cSVDm: OR 0.43, CI 95% .24-.75 $P = .003$). *Conclusions:* Pre-existing SVD limits early functional and neurological recovery after AIS, especially in LIS patients.

Key Words: Small vessel disease—lacunar stroke—stroke recovery—white matter hyperintensity—lacune—microbleed

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Introduction

The term cerebral small vessel disease (SVD) comprises a set of clinical, neuroimaging, and pathological features caused by the damage of cerebral perforating arterioles, capillaries, and venules.[1] SVD can cause cognitive decline,[2] manifest as an acute lacunar infarct or be found as clinically silent chronic vascular lesions on neuroimaging.[3] Acute lacunar infarcts have been associated with a diffuse dysfunction of the blood-brain barrier[4] and some authors suggest that they might be part of a diffuse brain vasculopathy.[5] However, other pathogenic mechanisms such as cardiac or artery-to-artery emboli may underlie the acute lacunar infarct.[6,7]

On the other hand, dilated perivascular spaces, chronic lacunes, microbleeds and white matter hyperintensities, or leukoaraiosis are chronic SVD neuroimaging markers (cSVDm) that can be easily observed in conventional brain MRI. The presence of different cSVDm has been associated with an increased risk of mortality[8] and acute ischemic stroke (AIS),[9] but its role on stroke recovery is less clear. Part of stroke recovery depends on the integrity of different neural networks and white matter tracts[10] which could be disrupted by chronic brain lesions caused by SVD.

It has been described that the presence of white matter hyperintensities limits stroke recovery in patients with mild stroke,[11,12] striatocapsular stroke[13] and after intravenous thrombolysis,[14] although this association has not been confirmed in a small study of patients treated with thrombectomy.[15] A large study of patients treated with intravenous thrombolysis found an association between the presence of brain microbleeds and poor clinical outcome.[16] However, the majority of the aforementioned studies included a limited number of patients and were focused on a single cSVDm. Some authors have suggested that a score able to reflect the total burden of SVD should be used to study the role of SVD on stroke mortality, recurrence and prognosis.[1,14,17] For that reason, we aimed to: First: Study in a large cohort of patients the influence of pre-existing SVD on early stroke recovery using a single measure to reflect SVD burden. Second: Observe whether the role of cSVDm on early stroke recovery was different in patients with acute lacunar infarcts compared to other AIS etiologies.

Materials and Methods

We studied patients included in the RENISEN registry, a nationwide hospital-based stroke registry sponsored by the Spanish Neurological Society Stroke Study Group that was started in January 2011 and includes prospective demographic, clinical, and neuroimaging data. All the participating hospitals belong to the Stroke Project of the Spanish Cerebrovascular Disease Study Group. These centers follow the same guidelines[18-21] and also the project's recommendations to guarantee quality management.

We selected patients diagnosed with AIS until January 2018 that fulfilled the following criteria: (1) A brain MRI had been performed as part of stroke work-up. (2) Premorbid modified Rankin scale (mRS) equal to 0. Patients diagnosed with AIS but without an established acute ischemic lesion on the brain MRI and patients with infrequent stroke etiologies (nonatherosclerotic arteriopathies, genetic disorders, coagulation disorders, systemic diseases, neoplasms, and infections) were excluded.

In the neuroimaging section, the registry includes 2 fields where the local investigators can introduce the presence of 2 out of 3 cSVDm: that is, white matter hyperintensities, chronic lacunes, or microbleeds. Consequently, patients were classified into 3 groups according to the presence of 0, 1, or 2 cSVDm. Lacunes and microbleeds we considered to be present if they were found on any number. White matter hyperintensities were considered to be present if they were observed on any grade. To avoid the potential influence of chronic vascular lesions not associated with SVD we also excluded those patients with evidence of previous territorial infarcts on brain MRI. To assess whether the influence of cSVDm on stroke recovery was different in patients with acute lacunar infarcts from patients with different AIS etiologies we divided all AIS patients into a lacunar ischemic stroke (LIS) group and nonLIS (NLIS) group according to TOAST classification.

The primary outcome was defined as the functional status at discharge according to the distribution of the mRS at that time. Secondary outcomes were: neurological improvement at discharge and at 24 hours defined as a reduction more than or equal to 3 points on the NIHSS, and early neurological worsening at 24 hours defined as an increase more than or equal to 3 points on the NIHSS. We set up a cutoff value of 3 for the NIHSS to be able to compare LIS and NLIS groups, since most of the patients on the LIS group had NIHSS values at admission equal or inferior to 3.

Statistical analysis was performed with IBM SPSS 20.0 software. Student t test and ANOVA test were used to compare continuous variables and chi-square test for proportions. For the multivariate analysis we entered those variables that had achieved a level of significance less than .1 in the univariate analysis. We performed ordinal regression analysis or binary regression analysis as appropriate. Level of statistical significance was set up at a P value less than .05. Hospital Jose Trueta institutional review board acted as central ethics committee. Given the retrospective nature of the study informed consent was not required.

Results

We studied 4424 patients with AIS: 967 LIS and 3457 NLIS. Detailed characteristics of the patients are described in Table 1. In summary, LIS patients were younger, more

Table 1. *Demographic and clinical characteristics of the patients*

	All patients	NLIS (n = 3457)	LIS (n = 967)
Age mean (SD)*	66.9 (17.4)	67.47 (18.5)	64.85 (12.3)
Sex (male %)*	66.1	65	70.3
Hypertension (%)*	68.5	66.6	75.3
Hypercholesterolemia (%)*	52.2	50.7	57.8
Diabetes (%)*	27.2	25.8	32.1
Smoking (%)*	32.1	29.5	41.3
NIHSS, median (IQR)*	3 (2-8)	4 (2-9)	2 (1-4)
Thrombolysis (%)*	18.9	22.6	5.4
Thrombectomy (%)*	3.8	4.9	NA
mRS 0-2 at discharge (%)*	69.5	66.7	79.3
Days to discharge, mean (SD)*	8.2 (6.3)	8.7 (6.8)	6.4 (3.7)
NIHSS improvement ≧ 3 at 24 h*	23.9	27.5	11
NIHSS improvement ≧3 at discharge*	35.6	40.2	19.4
SVDm (%)*			
0	48.6	53.9	29.5
1	38.7	36.7	46
2	12.7	9.4	24.5
TOAST (%)			
Large-artery atherosclerosis		28.4	NA
Cardioembolic		35.8	NA
Lacunar		NA	100
Undetermined		35.8	NA

Abbreviations: cSVDm, chronic small vessel disease marker; LIS, lacunar ischemic stroke; mRS, modified Rankin scale; NA, not applicable; NLIS, nonlacunar ischemic stroke.

*$P \leqq .001$ for the comparison between NLIS and LIS groups.

frequently male, had a less severe stroke, more traditional vascular risk factors, and more cSVDm on neuroimaging. More patients on the NLIS group were treated with either thrombolysis or thrombectomy. Time to hospital discharge (mean [SD]) was 8.2 (6.3) days for all the patients, 8.7 (6.8) days for the NLIS group and 6.4 (3.7) days for the LIS group. Ninety percent of the patients were discharged from hospital within the first 14 days since admission (15 days for NLIS and 11 days for LIS).

Figure 1 shows the distribution of mRS at discharge according to the number of cSVDm and stroke subgroups. In the LIS group, the proportion of patients achieving a mRS 0-2 at discharge decreased as more cSVDm were present on neuroimaging. After adjustment for age, gender, baseline NIHSS, hypertension, diabetes, smoking and recanalization treatments, ordinal regression analysis showed that the risk of worsening 1 category on the mRS was independently associated with the presence of cSVDm only in the LIS group (Table 2).

In the same way, the proportion of patients that experienced an improvement on the NIHSS more than or equal to 3 at 24 hours and at discharge decreased as long as they accumulated more cSVDm (Fig 2). Binary logistic regression analysis after adjustment for age, gender, hypertension, diabetes, hypercholesterolemia, smoking and recanalization treatments showed that the presence of 1 or 2 cSVDm was an independent factor for not achieving an improvement on the NIHSS more than or equal to 3 at discharge but not at 24 hours (Table 3). This effect was observed in the whole cohort of patients and the LIS group but not in the NLIS group. On the other hand, the presence of either 1 or 2 cSVDm was not associated with a higher proportion of patients with early neurological worsening in patients with LIS or NLIS (data not shown).

Discussion/Conclusion

White matter hyperintensities and brain microbleeds have been associated with a poor clinical outcome after AIS.[11,14,16] The studies that have investigated the role of SVD on functional recovery after AIS have mainly focused on individual cSVDm, but clinical data addressing the global impact of SVD on stroke recovery are scarce.

The main finding of our study is that a simple measure of SVD burden in patients with AIS was associated with a reduced likelihood of early functional and neurological recovery as reflected by the mRS and NIHSS scales at discharge. Moreover, neurological improvement was less likely as patients accumulated more cSVDm, an association that reinforces the role of SVD on stroke recovery. Most of the patients in our study were discharged from hospital within 2 weeks after acute stroke, making us to witness the influence of SVD on the early stages of stroke recovery. We did not observe a significant effect on neurological improvement at 24 hours after adjustment for potential confounders. In the same line, we have not seen any effect for cSVDm on early neurological worsening during the first 24 hours. These results might reflect that pre-existing SVD limits brain capacity to rearrange some kind of subacute functional reorganization that precedes clinical recovery but has a limited impact on the very early phases of AIS.

Interestingly, the role of SVD on early recovery seemed to be limited to the LIS group. Lacunar infarcts are restricted to 1 single perforating artery and have consequently more homogenous infarct volumes than nonlacunar infarcts. For this reason, we hypothesize that chronic brain damage caused by SVD might play a more relevant role on the recovery of LIS whereas the weight of the acute ischemic lesion would be more important on the clinical recovery of the more heterogeneous nonlacunar infarcts.

We acknowledge that our study has several limitations. Due to the characteristics of the study (data taken from a multicenter registry) there has not been a central reading of brain neuroimaging and the criteria of

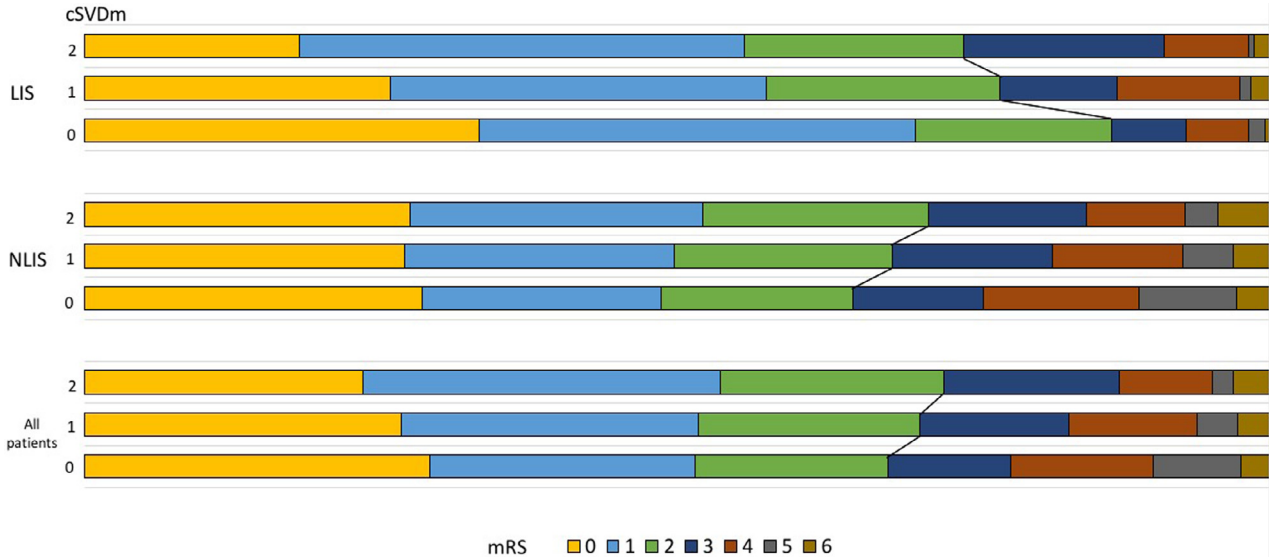

Figure 1. *Distribution of mRS at discharge by stroke subgroup and number of cSVDm. LIS: lacunar ischemic stroke. Abbreviations: cSVDm, chronic small vessel disease marker; NLIS, nonlacunar ischemic stroke.*

different investigators may likely cause some kind of bias. However, all the participating hospitals belong to the Stroke project of the Spanish Cerebrovascular Disease Study Group. These centers follow the same guidelines[18-21] and also the project's recommendations to guarantee quality management. Lacunar stroke is defined in the Spanish Cerebrovascular Disease Study Group guidelines as a small subcortical infarct in the territory of perforating arteries less than 1.5 cm in diameter[22] but given the aforementioned potential different criteria of several investigators we cannot completely rule out that some large subcortical infarcts had been included into the LIS group. However, the recent definition of recent small subcortical infarct that sets an upper diameter of 2 cm for AIS associated with SVD[3] makes lees likely that subcortical infarcts much larger than a lacunar stroke had been included in the LIS group.

Table 2. *Ordinal logistic regression. Distribution of mRS at discharge*

	OR	CI 95%	*P* value
All patients			
2 cSVDm	1.21	.99-1.48	.056
1 cSVDm	1.11	.97-1.27	.133
NLIS			
2 cSVDm	1.07	.83-1.37	.609
1 cSVDm	.97	.83-1.13	.660
LIS			
2 cSVDm	1.89	1.29-2.75	.001
1 cSVDm	1.87	1.37-2.56	.001

Abbreviations: CI, confidence interval; cSVDm, chronic small vessel disease marker; LIS, lacunar ischemic stroke; NLIS, nonlacunar ischemic stroke; OR, odds ratio.

RENISEN registry offers only 2 entries for the assessment of chronic SVD lesions, which limits our analysis to the presence of a maximum of 2 cSVDm and precludes us to offer reliable individual data of the different cSVDm. We acknowledge that it would had been of great interest to have an individual field for each cSVDm, including dilated perivascular spaces, but this is a limitation of the registry that we cannot overcome. On the other hand, we can only analyze the presence or absence of certain cSVDm but neither its number nor its severity. For that reason, we decided to study SVD as a whole with a measure that reflects at least partially SVD burden.

Moreover, in view of the low NIHSS scores, patients with severe stroke are probably underrepresented in our study. We believe that this selection bias is caused by many patients with severe stroke not undergoing a brain MRI due to a poor clinical condition.

Despite the aforementioned limitations, we consider that our study offers reasonable evidence supporting a role for SVD in early neurological and functional recovery in patients with LIS. Pre-existing SVD might reduce brain reserve to recover from acute injury such as ischemic stroke. The main strength of our study is the analysis of a large number of patients admitted to hospitals with dedicated stroke units and standardized stroke protocols, in contrast to the majority of studies conducted in this regard. It will be probably very difficult to find studies in the literature that analyze SVD in such a large number of patients. However, we acknowledge that we cannot draw definitive conclusions and more studies that evaluate the individual role and potential interactions of all cSVDm with standardized neuroimaging protocols are warranted.

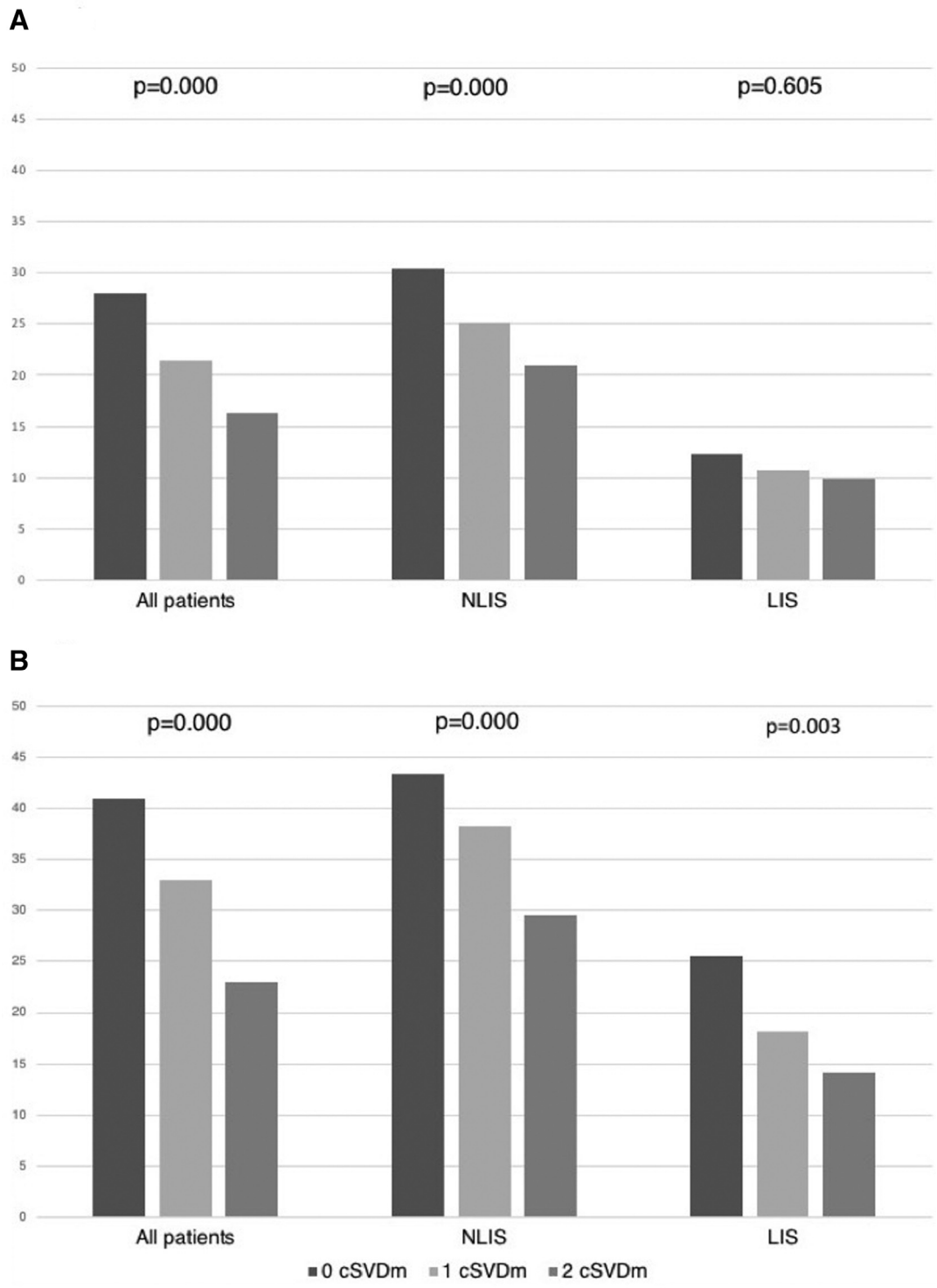

Figure 2. *(A) Proportion of patients achieving a neurological improvement on NIHSS ≧ 3 points at 24 hours (A) and discharge (B) by stroke subgroup and number of cSVDm.* P *values for comparison of proportions with chi-square test. Abbreviations: cSVDm, chronic small vessel disease marker; LIS, lacunar ischemic stroke; NLIS, nonlacunar ischemic stroke.*

Table 3. *Binary logistic regression. Improvement on the NIHSS ≥ 3 points at 24 hours and at discharge*

	OR	CI 95%	*P* value
All patients			
24 h			
2 cSVDm	.98	.72-1.34	.887
1 cSVDm	.91	.74-1.12	.379
Discharge			
2 cSVDm	.58	.45-.77	.001
1 cSVDm	.81	.68-.97	.022
NLIS			
24 h			
2 cSVDm	.73	.74-1.55	.727
1 cSVDm	.68	.76-1,19	.678
Discharge			
2 cSVDm	.72	.52-1.01	.053
1 cSVDm	.91	.75-1.11	.360
LIS			
24 h			
2 cSVDm	.99	.49-1.97	.977
1 cSVDm	.92	.52-1.63	.766
Discharge			
2 cSVDm	.43	.24-0.75	.003
1 cSVDm	.64	.41-0.98	.038

Abbreviations: CI, confidence interval; cSVDm, chronic small vessel disease marker; LIS, lacunar ischemic stroke; NLIS, nonlacunar ischemic stroke; OR, odds ratio.

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Statement of Ethics

Hospital Jose Trueta institutional review board acted as central ethics committee. Given the retrospective nature of the study informed consent was not required.

Conflict of Interest

The authors have no conflicts of interest to declare.

Authors Contributions

M. Gómez-Choco: Design and conceptualization of the study. Analysis and interpretation of the data. Drafting and revising the manuscript for intellectual content.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104312.

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