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TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Neurologia

NIHSS underestimates right hemisphere stroke injury: raising an old issue with a new cognitive approach

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Maio'2021

Abstract

Background: The National Institutes of Health Stroke Scale (NIHSS) is a widely used tool for quantification of stroke severity. However, prior studies suggest that this scale does not equitably assess the 2 hemispheres, reporting that the volume of right hemisphere (RH) lesions is underestimated. This is probably due to the fact that NIHSS attributes 2 points for neglect and 7 for language. While empirical assessment could suggest better functional outcomes for patients with neglect than for those with aphasia, some authors have reported that neglect is associated with worse functional outcomes.

Objectives: The aims were: a) to compare the correlations between the lesion volume of RH stroke and the NIHSS score from patients with neglect and without neglect and b) to study if a modification of the neglect scoring rules would increase the predictive capacity of the lesion volume.

Methods: Patients with right middle cerebral artery ischemic stroke were divided in two groups: patients with neglect and patients without neglect at admission. We correlated NIHSS scores and lesion volume in both groups and calculated the partial correlation between lesion volume, NIHSS and the variable group. Finally, we applied different modifications in the neglect scoring rules and repeated the statistical analysis.

Results: The correlation between lesion volume and NIHSS was lower in patients with neglect and neglect was a statistically significant covariate in the partial correlation analysis between NIHSS and lesion volume. With the neglect score tripled and with the sum of all neglect modalities doubled and tripled, the correlation between lesion volume and NIHSS was significantly higher than the correlation with the standard NIHSS and the partial correlation between lesion volume and the variable group, controlling for NIHSS, became no longer a statistically significant factor.

Conclusion: These results may foster the improvement of neglect scoring in the NIHSS scale.

Key words: Stroke, NIHSS, neglect

Resumo

Introdução: A escala de acidente vascular cerebral (AVC) do National Institute of Health (NIHSS) é uma ferramenta de quantificação da gravidade de um AVC. Apesar de amplamente utilizada, estudos sugerem que não avalia igualmente os 2 hemisférios cerebrais. Pensa-se que o NIHSS subestima o volume das lesões do hemisfério direito possivelmente devido ao facto de 2 pontos serem atribuídos ao *neglect* e 7 às alterações de linguagem. Embora o NIHSS de doentes com *neglect* possa sugerir melhor *outcome* funcional comparativamente com doentes com afasia, estudos demonstram que o *neglect* está associado a piores *outcomes*.

Objetivos: Comparar as correlações entre o volume da lesão e o NIHSS de doentes com *neglect* e sem *neglect* e estudar se uma modificação das regras de pontuação de *neglect* no NIHSS aumentaria a sua capacidade de predição do volume de lesão.

Métodos: A amostra de doentes com AVC na artéria cerebral média direita foi dividida 2 grupos: doentes com *neglect* e sem *neglect*. Comparámos as correlações entre o volume de lesão e o NIHSS dos grupos e calculámos a correlação parcial entre o volume da lesão, NIHSS e a variável ter ou não *neglect*. Estudamos ainda diferentes modificações das regras de pontuação de *neglect* e repetimos a análise.

Resultados: A correlação entre volume de lesão e NIHSS foi menor em doentes com *neglect* e a correlação parcial entre volume de lesão e a variável grupo, controlando o NIHSS, foi estatisticamente significativa. Com a pontuação de *neglect* triplicada e com a soma de todas as modalidades de *neglect* duplicada e triplicada, a correlação entre o volume da lesão e o NIHSS foi significativamente maior do que com o NIHSS original e a correlação parcial deixou de ser estatisticamente significativa.

Conclusão: Estas modificações na pontuação do *neglect* poderão melhorar a capacidade de predição de volume da lesão do NIHSS.

Palavras-chave: Acidente vascular cerebral, NIHSS, *neglect*

Table of Contents

Introduction

The National Institutes of Health Stroke Scale (NIHSS) is a widely used tool for quantification of stroke severity, based on evaluation of neurological impairment (Brott et al., 1989; Josephson et al., 2006). It has an important role to determine the appropriate stroke treatment, namely to select patients who are eligible for intravenous thrombolysis (Demaerschalk et al., 2016) and mechanical thrombectomy (Powers et al., 2018), and to predict patients' outcome (Adams et al., 1999; Frankel et al., 2000; Fonarow et al., 2012). Despite its relevance and broad validation, prior studies suggest that this scale does not equitably assess the two hemispheres, reporting that the volume of right hemisphere (RH) lesions is underestimated by NIHSS, compared to the left hemisphere (LH) lesions (Woo et al., 1999; Fink et al., 2002). This is probably due to the fact that NIHSS attributes a maximum of 2 points for neglect (Woo et al., 1999), typically a function of the RH (Corballis, 2014), while 7 points might be attributed for language deficits (Woo et al., 1999), most commonly associated with LH lesions (Corballis, 2014).

Indeed, some studies found that LH strokes are more frequently admitted to acute stroke treatments (Legge et al., 2005; Desai et al., 2018) and have better outcomes (Legge et al., 2006). There is also the possibility that RH stroke patients with low NIHSS but poor outcome may be excluded and, therefore, underrepresented in treatment trials (Almekhlafi et al., 2019). In addition, an empirical assessment could suggest that neglect would be associated with better functional outcomes than aphasia, however evidence has shown than this is not true (Hofgren et al., 2007). Neglect has been associated with a longer length of stay in a rehabilitation unit (Gillen et al., 2005; Wee & Hopman, 2008; Spaccavento et al., 2017), poorer rehabilitation improvements (Gillen et al., 2005; Wee & Hopman, 2008; Chen et al., 2015; Spaccavento et al., 2017; Bosma et al., 2020), and slower functional progress during rehabilitation (Gillen et al., 2005), when compared to patients without neglect.

The volume of stroke lesions is an independent predictor of stroke outcome (Thijs et al., 2000) and can be useful to predict long-term functional status after ischemic stroke (Löuvbld et al., 1997; Saver et al., 1999). In this way, a higher correlation between lesion volume and NIHSS would increase the predictive capacity of this score.

Here, we analysed a group of patients with right middle cerebral artery ischemic stroke, aiming to: a) compare the correlations between the lesion volume of RH stroke and the NIHSS score from patients with neglect and without neglect and b) study if a modification of the neglect scoring rules would increase the predictive capacity of the lesion volume.

Methods

Study sample

We performed a post-hoc analysis of the RePS (Reduplicative Paramnesia after Stroke) study. RePS was a prospective study that screened 400 patients with either ischemic or hemorrhagic strokes admitted to the Stroke Unit of Hospital of Santa Maria, from December 2016 to February 2020, for the presence of delusional misidentifications of space (Alves et al., 2021). Exclusion criteria were: decreased level of consciousness, no lesion or lesion poorly defined in brain imaging, acute confusional state, severe dysarthria, aphasia precluding assessment, brain images not available and epileptic seizures. From the RePS sample, we selected the patients with first-ever ischemic strokes restricted to the territory of the right middle cerebral artery. Patients that presented previous lesions (on computed tomography (CT) or on magnetic resonance imaging (MRI)) or that had lesions in other vascular territories were excluded.

The study was approved by the Ethics Committee of the Lisbon Academic Medical Center.

Clinical data

We recorded data about patients' demographics, aetiology of the stroke (cardioembolic, cerebral small vessel disease, large vessel atherosclerotic disease, other determined etiology, undetermined etiology), total NIHSS score and the individual NIHSS items at admission, acute phase treatment (intravenous thrombolysis, mechanical thrombectomy, both or neither) and the imaging modality of reference (CT or MRI).

Then, we collected the types of neglect presented by the patients, namely visual extinction, tactile extinction, auditory extinction, motor neglect, visuo-spatial neglect, anosognosia and anosodiaphoria.

The study sample (162 patients) was divided into 2 groups: patients without neglect at admission (No neglect group, n=54) and patients with neglect at admission (Neglect group, n=108 patients) (Figure1).

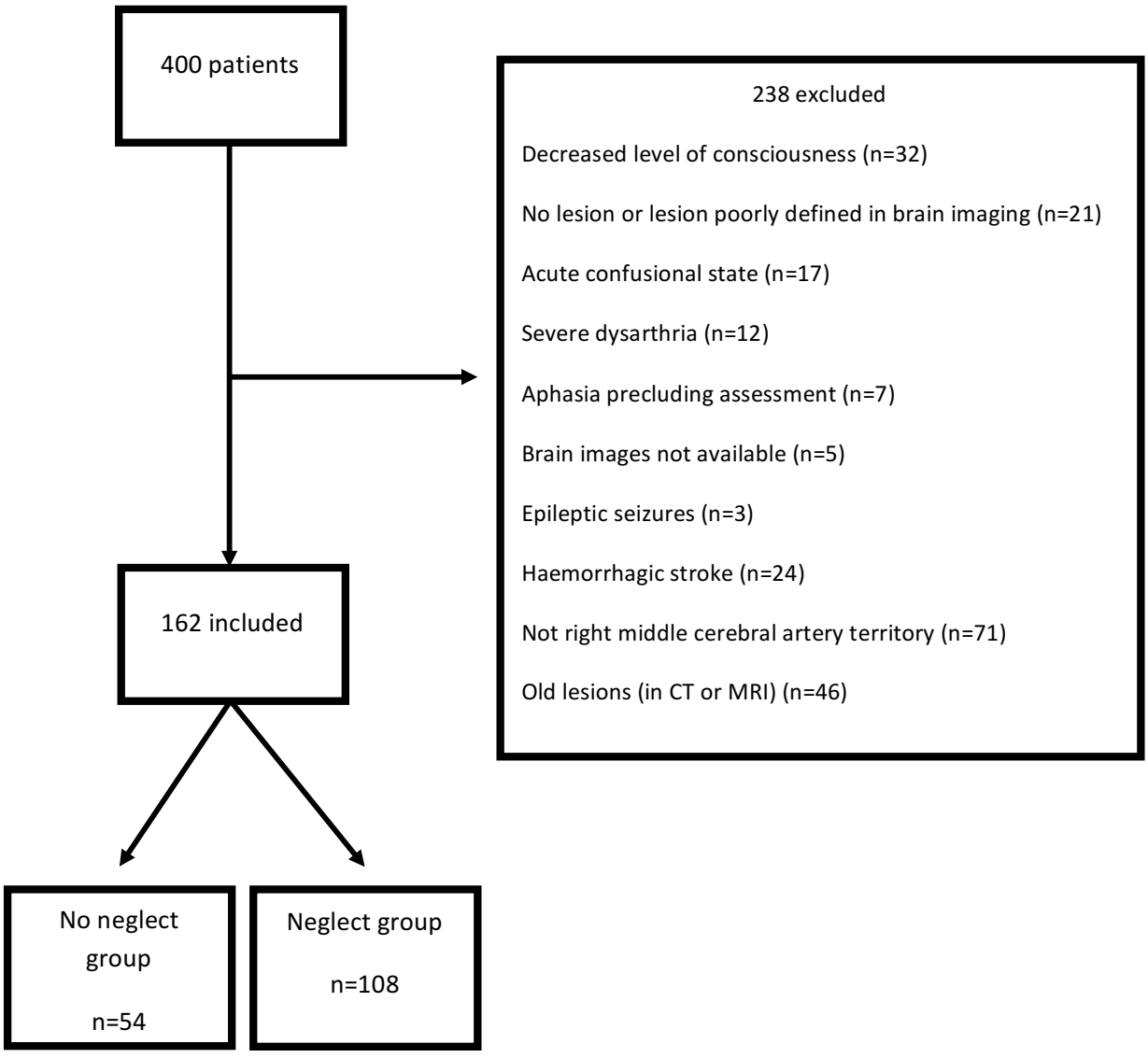

Figure 1. Flowchart of patient selection.

The division in 'Neglect group' and 'No neglect group' was made according to the NIHSS stroke scale at admission. When the patients presented a deterioration of neurological status before acute phase treatment, the NIHSS after the deterioration was considered (n=14). Because sometimes not all the neglect modalities are assessed

in an emergency context, we completed the information about the neglect modalities with data from the admission report at the Department of Neurology in 13 patients and from discharge report in 6 patients.

Correlation between Neglect and Lesion volume

First, we correlated NIHSS scores and lesion volume in the Neglect and in the No neglect groups. Second, we analysed: a) if there was a statistically significant difference between the correlations of the two groups; b) if the variable group (i.e. neglect) was a statistically significant covariate in the partial correlation analysis between NIHSS and lesion volume. Third, we performed modifications of the neglect scoring in the NIHSS scale to analyse if they significantly increase the correlation between NIHSS and lesion volume in the Neglect group. The modifications that were performed in the neglect scoring rules were:

a) we add all neglect modalities documented, each one having a score of one (all neglect modalities NIHSS);

b) we doubled the original neglect score (neglect x2 NIHSS);

c) we tripled the original neglect score (neglect x3 NIHSS);

d) we raised the original neglect score to the 2nd power (neglect x^2 NIHSS);

e) we raised the original neglect score to the 3rd power (neglect x^3 NIHSS);

f) we doubled the sum of all neglect modalities documented (all neglect modalities x2 NIHSS);

g) we tripled the sum of all neglect modalities documented (all neglect modalities x3 NIHSS).

For each modification, we subtracted the original neglect score from NIHSS score and added the modified neglect score. Then, we calculated the correlation between each modified NIHSS with lesion volume and the partial correlation between lesion volume, NIHSS and the variable group (i.e. presence of neglect) and we analysed if there was a statistically significant difference between the original correlation and the correlation obtained with the NIHSS score modification.

Imaging Analysis

The infarcted areas were manually delimited in the native space using FSLeyes version 0.32.0. For patients with MRI images available, the diffusion-weighted imaging (DWI) sequence was the sequence of reference. For the remaining, the lesion was delimited in the CT performed 24-72h after stroke onset. The observers were blinded to clinical information. Lesions were normalized to the MNI152 using T1 as the sequence of reference using linear and non-linear registration for MRI images, and linear registration for CT images (FSL's FLIRT and FNIRT tools). The registration warps were applied to lesion masks.

The infarct volume (cm3) was calculated using fslstats.

Statistical Analysis

Baseline features of the patients were compared in both groups. Continuous variables were compared with unpaired Student's t-test or Mann-Whitney test, according to their distribution. Categorical variables were compared using Chi2 or Fisher test, as appropriate.

Spearman correlation was used to determine the strength of association between the NIHSS and lesion volumes. The statistical difference between correlations was calculated using the R package 'cocor' (http://comparingcorrelations.org).

All statistical analyses were performed using *SPSS Version 26* and $p<0.05$ was considered level of significance.

Results

Baseline features of the patients are summarized in Table 1. There was a significant difference in baseline characteristics between the two groups in lesion volume, NIHSS, stroke aetiology and treatment. No statistical differences were found in age and imaging modality of reference.

	No Neglect group (54 patients)	Neglect group (108 patients)	p-value
Age (years; mean ± SD)	66.11 ± 13.330	70.05± 13.368	0.079
NIHSS at admission (mean ± SD)	9.52± 5.894	14.06 ± 4.812	**<0.001**
Volume (median [IQR])	6942.5 [1820.75; 31787.25)	37209.5 [10381.25; 96357.50)	**<0.001**
Aetiology (n (%))			**0.025**
Large artery atherosclerosis	10 (18.5%)	10 (9.3%)	
Cardioembolism	19 (35.2%)	58 (53.7%)	
Small-vessel occlusion	2 (3.7%)	0 (0%)	
Other determined	1 (1.9%)	6 (5.6%)	
Undetermined	22 (40.7%)	34 (31.5%)	
Imaging (n (%))			0.081
CT	30 (55.6%)	75 (69.4%)	
MRI	24 (44.4%)	33 (30.6%)	
Treatment (n (%))			**<0.001**
None	15 (27.8%)	5 (4.6 %)	
rtPA	16 (29.6 %)	31(28.7 %)	
EVT	14 (25.9 %)	27 (25.0 %)	
rtPA+EVT	9 (16.7 %)	45 (41.7 %)	

Table 1. Patients baseline features.

NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; IQR, interquartile range; CT, computed tomography; MRI, magnetic resonance imaging; rtPA, recombinant tissue plasminogen activator; EVT, endovascular thrombectomy.

The Spearman correlation between lesion volume and original NIHSS was r=0.429 ($p<0.01$) (Table 2, Figure 2).

Original NIHSS	All neglect modalities NIHSS	Neglect x2 NIHSS	Neglect x3 NIHSS	Neglect x^2 NIHSS	Neglect x^3 NIHSS	All neglect modalities x2 NIHSS	All neglect modalities x3 NIHSS
Spearman correlation between lesion volume and NIHSS							
0.429 (p<0.01)	0.446 (p<0.01)	0.446 (p<0.01)	0.464 (p<0.01)	0.443 (p<0.01)	0.456 (p<0.01)	0.475 (p<0.01)	0.498 (p<0.01)
Partial correlation between lesion volume and the variable group controlling for NIHSS							
0. 188 (p=0.017)	0. 178 (p=0.024)	0.154 **(p=0.051)**	0.124 **(p=0.119)**	0.170 (p=0.031)	0.152 **(p=0.054)**	0.133 (**p=0.092)**	0.095 **(p=0.233)**

Table 2. Spearman correlation between lesion volume and NIHSS and Partial correlation between lesion volume, NIHSS and the variable group (i.e. presence of neglect).

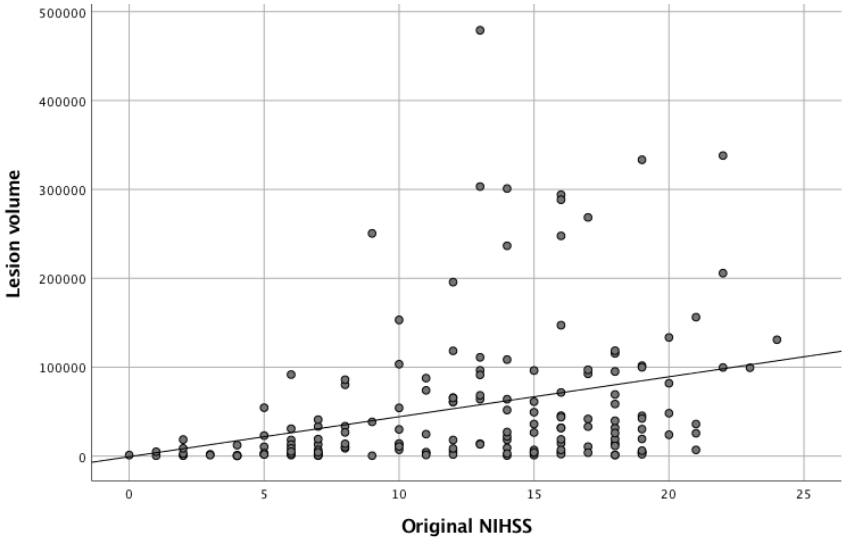

Figure 2. Lesion volume and original NIHSS.

There was a statistically significant difference between the correlation of lesion volume and NIHSS score in the No Neglect group and Neglect group (r= 0.540 and r=0.249, respectively; p=0.04).

The partial correlation between group and volume, after controlling for NIHSS, was statistically significant (r= 0.188, p = 0.017).

After adding all neglect modalities, the Spearman correlation between NIHSS and lesion volume was 0.446 (p <0.01) (Figure 3). It was significantly higher than the correlation obtained with the original NIHSS score (p<0.0079).

The partial correlation between group and volume, after controlling for NIHSS, was statistically significant (r= 0.178, p = 0.024).

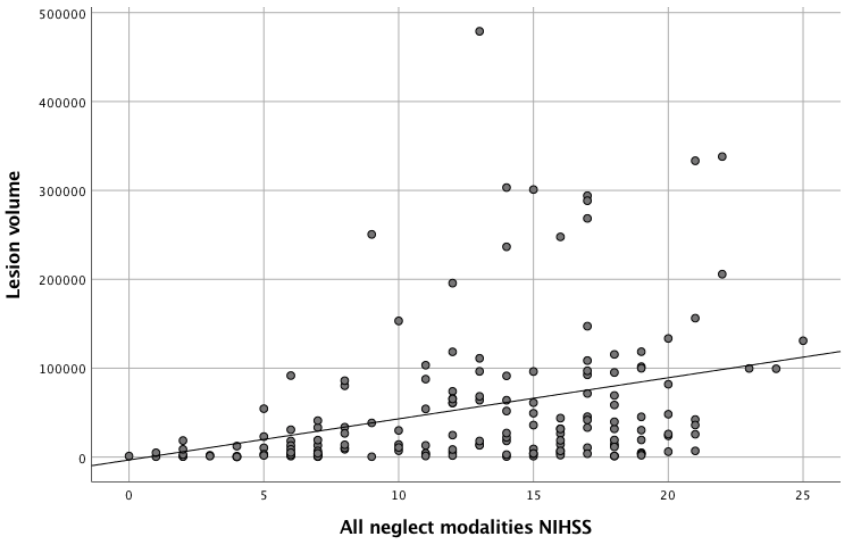

Figure 3. Lesion volume and sum of all neglect modalities NIHSS.

When the neglect score was doubled, the Spearman correlation between NIHSS and lesion volume was 0.446 (p <0.01). There was no statistically difference in the strength of this correlation and the original NIHSS correlation.

The partial correlation between group and volume, after controlling for NIHSS, was not statistically significant (r= 0.154, p = 0.051).

When the neglect score was tripled, the Spearman correlation between NIHSS and lesion volume was 0.464 (p <0.01) (Figure 4). It was significantly higher than the correlation obtained with the original NIHSS score (p <0.0432).
The partial correlation between group and volume, after controlling for NIHSS, was not statistically significant (r= 0.124, p = 0.119).

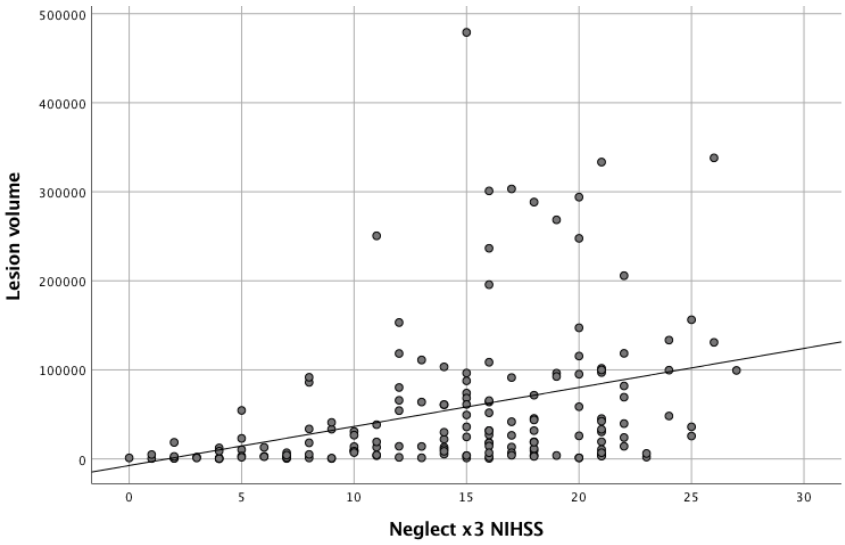

Figure 4. Lesion volume and neglect score tripled NIHSS.

When the original neglect score was raised to the 2nd power, the Spearman correlation between NIHSS and lesion volume was 0.443 (p <0.01). There was no statistically difference in the strength of this correlation and the original NIHSS correlation.
There was a partial correlation between group and volume, after controlling for NIHSS, which was statistically significant (r= 0.17, p = 0.031).

When the original neglect score was raised to the 3rd power, the Spearman correlation between NIHSS and lesion volume was 0.456 (p <0.01). There was no statistically difference in the strength of this correlation and the original NIHSS correlation.

The partial correlation between group and volume, after controlling for NIHSS, was not statistically significant (r= 0.152, p = 0.054).

After doubling the sum of all neglect modalities, the Spearman correlation between NIHSS and lesion volume was 0.475 (p <0.01) (Figure 5). It was significantly higher than the correlation obtained with the original NIHSS score (p<0.005).

The partial correlation between group and volume, after controlling for NIHSS, was not statistically significant (r=0.133, p=0.092).

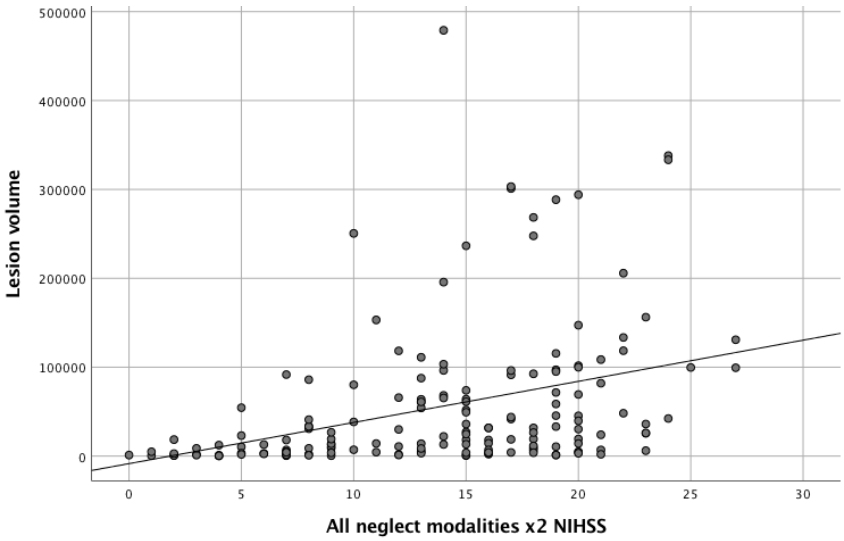

Figure 5. Lesion volume and sum of all neglect modalities doubled NIHSS.

After tripling the sum of all neglect modalities, the Spearman correlation between NIHSS and lesion volume was 0.498 (p <0.01) (Figure 6). It was significantly higher than the correlation obtained with the original NIHSS score (p <0.006).

The partial correlation between group and volume, after controlling for NIHSS, was not statistically significant (r=0. 095, p=0.233).

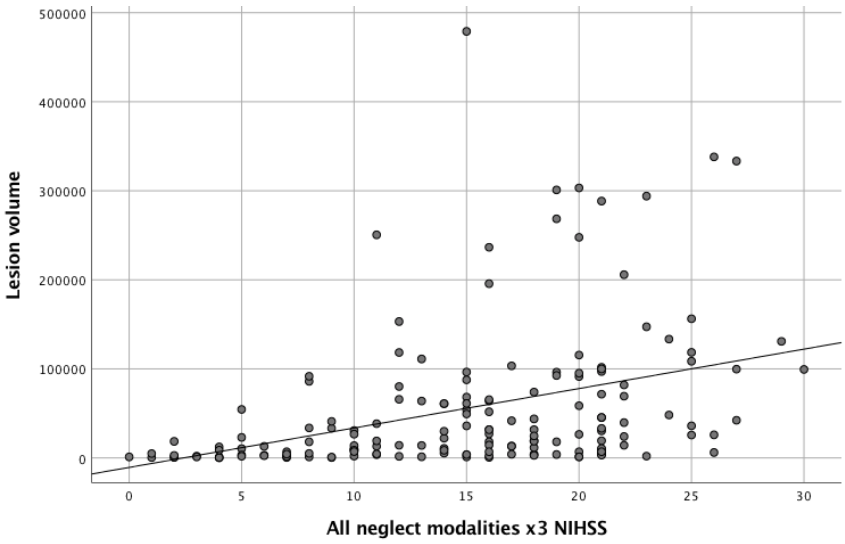

Figure 6. Lesion volume and sum of all neglect modalities tripled NIHSS.

Discussion

In this study we investigated the relationship between lesion volume and NIHSS in patients with ischemic stroke of the right middle cerebral artery with and without neglect. First, we found that the correlation between lesion volume and NIHSS was lower in patients with neglect, and that neglect was a statistically significant factor for this correlation. Second, we disclosed that modifications of neglect scoring in the NIHSS significantly improved the correlation between lesions volume and NIHSS. This effect was obtained by tripling the original NIHSS neglect score, by doubling the sum of all neglect modalities or by tripling the sum of all neglect modalities.

The Neglect group had higher lesion volumes. Consequently, it was expected that this group have higher NIHSS scores. Also expected were the differences found in the acute phase treatment and in aetiology, because neglect is more common in cardioembolic strokes ((Ringman et al., 2004).

There was a significant correlation between lesion volume and NIHSS score as reported in previous studies (Woo et al., 1999; Fink et al., 2002). The correlation in the Neglect group was significantly smaller. The partial correlation between the variable group and lesion volume, after controlling for NIHSS, was statistically significant. This data

shows that the presence of neglect is an independent factor in the prediction of lesion volume.

All the modifications in neglect scoring rules showed a tendency to increase the correlation between NIHSS and lesion volume. However, only the correlations between lesion volume and NIHSS with the sum of all neglect modalities, with the neglect score tripled, with the sum of all neglect modalities doubled and with the sum of all neglect modalities tripled were statistically higher. In this way, our analysis suggests that these 4 modifications may improve the prediction of lesion volume. In these 4 modifications, only the partial correlation between lesion volume and the variable group, controlling for all neglect modalities NIHSS, remained statically significant. This may be due to the fact that not all neglect modalities are evaluated in the admission time. In contrast, with the other 3 modifications in neglect scoring rules, the partial correlation between lesion volume and the variable group, controlling for NIHSS, became not statistically significant. These data indicate that neglect became no longer an independent factor for volume prediction.

It has been reported that for the same lesion volume the mean NIHSS is higher in the LH stroke than in the RH and, consequently, NIHSS underestimates the severity of right hemisphere stroke (Woo et al., 1999; Fink et al., 2002). Neglect can be one of the most disabling consequences of a stroke (Gillen et al., 2005; Wee & Hopman, 2008; Spaccavento et al., 2017), and negatively affects the activities of daily living (Bosma et al., 2020). Increasing the number of points attributed to neglect and becoming neglect no longer an independent factor for lesion volume prediction, our findings may have implications for clinical practice as they may minimize the lateralization bias between right and left hemisphere. Nonetheless, future research should involve left middle cerebral artery ischemic stroke patients and a prospective study should be made to validate these findings.

As limitations of our study, it is post-hoc analysis of a study not primarily design to assess neglect. Some neglect modalities may have not been assessed or registered. In addition, although some studies have found a correlation between lesion volume and

stroke severity (Löuvbld et al., 1997; Saver et al., 1999), the severity and function outcomes also depend on lesion location (Wu et al., 2015). Finally, a relationship with functional outcomes, besides lesion volume, needs to be assessed in further studies.

Conclusion

Increasing the number of points attributed to neglect, particularly tripling neglect score, doubling the sum of all neglect modalities and tripling the sum of all neglect modalities, may improve the correlation between lesion volume and NIHSS. These results may foster the improvement of neglect scoring in the NIHSS scale.

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