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MESTRADO INTEGRADO EM MEDICINA

Stroke laterality: impact on the time to admission and acute treatment

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR, UNIVERSIDADE DO PORTO

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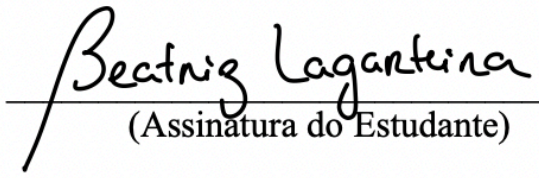

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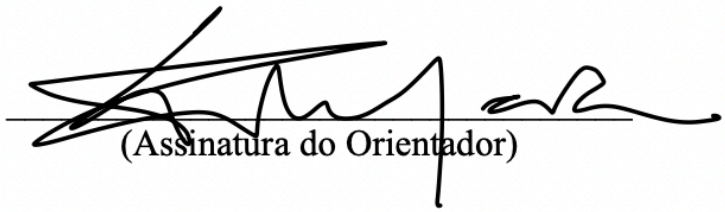

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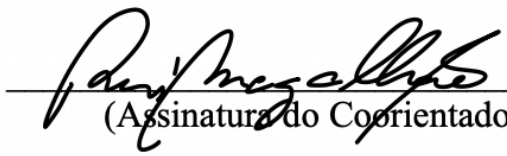

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RESUMO

Introdução: Os acidentes vasculares cerebrais isquémicos têm apresentações distintas, dependendo do hemisfério cerebral afetado. Eventos isquémicos esquerdos têm tendência a serem detetados mais facilmente dada a eloquência de sintomas como afasia, enquanto os direitos são mais dificilmente reconhecidos por apresentarem défices no autorreconhecimento, como anosognosia. Assim, este estudo pretende avaliar a influência da lateralização hemisférica no tempo para admissão hospitalar, tempo para primeiro tratamento e tipo de tratamento de fase aguda (trombólise vs trombectomia).

Métodos: Utilizamos o registo do BioStroke, um estudo prospetivo dos doentes admitidos no Centro Hospitalar Universitário do Porto como ativações da Via Verde AVC entre janeiro de 2019 e março 2020. Foram selecionados doentes com acidentes vasculares cerebrais isquémicos, não lacunares, da circulação anterior e classificados de acordo com o hemisfério afetado (esquerdo vs direito). Os dados demográficos, fatores de risco vasculares, pontuações da National Institute of Health Stroke Scale e Modified Ranking Scale, etiologia do evento isquémico, tempo para admissão, primeira imagem e primeiro tratamento foram obtidos do registo do estudo BioStroke. A escolaridade e se o doente vive ou não sozinho foram recolhidos retrospetivamente através de processos clínicos. Avaliamos o efeito da lateralização hemisférica nos tempos relacionados com a avaliação aguda destes doentes, decisão de tratamento e *outcome.*

Resultados: Nesta coorte prospetiva de 278 doentes com acidente vascular cerebral isquémico da circulação anterior, 145 (52%) afetaram o hemisfério esquerdo e 133 (48%) o direito. Não houve diferenças entre hemisférios em relação aos dados demográficos, fatores de risco e etiologia. Lesões esquerdas tiveram maior pontuação na National Institute of Health Stroke Scale à admissão. Não houve diferença no tempo entre instalação dos sintomas e admissão hospitalar (p=0.240), mesmo após exclusão de *wake-up strokes* (*p*=0.496), e entre admissão e primeira neuroimagem (*p*=0.493). A lateralização hemisférica não influenciou a decisão de tratamento (*p*=0.220), nem o tipo de tratamento (*p*=0.321). No entanto, lesões direitas apresentaram um atraso significativo no tempo entre admissão e primeiro tratamento (*p*=0.015), nomeadamente no subgrupo de doentes transferidos de outros hospitais e que realizaram trombectomia (p=0.042). Esta diferença não existiu em doentes submetidos a trombólise, nem em doentes admitidos primariamente no nosso centro, cujo primeiro tratamento foi trombectomia. A lateralidade também não teve impacto na National Institute of Health Stroke Scale e Modified Ranking Scale à data de alta.

Conclusões: Existe um atraso nos doentes com lesões direitas, no subgrupo de doentes provenientes de outros hospitais, no tempo até à trombectomia. Por outro lado, a lateralização hemisférica não parece influenciar o tempo entre a perceção dos sintomas e a admissão hospitalar,

a decisão para tratar, nem o tipo de tratamento selecionado. Estes dados ganham maior relevância uma vez que a incapacidade associada ao episódio isquémico foi semelhante entre hemisférios.

ABSTRACT

Introduction: Depending on the affected brain hemisphere, cerebrovascular events have distinct presentations. Left sided strokes are more readily detected due to eloquent symptoms like aphasia, whereas right-sided may be more difficult to recognize due to deficits of self-awareness like anosognosia. Having that in mind we will evaluate the influence of stroke laterality on time to admission, time to treatment, and on the type of acute treatment (thrombolysis and thrombectomy).

Methods: We used the registry from BioStroke, a prospective study of patients admitted to the Comprehensive Stroke Centre of Centro Hospitalar Universitário do Porto as stroke code activations, between January 2019 and March 2020. We selected patients with an ischemic, non-lacunar stroke of the anterior circulation and classified them according to the affected hemisphere (left vs right). Demographic data, vascular risk factors, National Institute of Health Stroke Scale (NIHSS) and Modified Ranking Scale scores, stroke etiology data and time of admission, neuroimaging and treatment were obtained from BioStroke patient registry. Scholarity level and living conditions were obtained retrospectively from patient e-records. We evaluated the effect of hemispheric location on the patient acute stroke care timeline, treatment decision and outcome.

Results: In this prospective cohort of 278 patients with ischemic stroke affecting the anterior circulation, 145 (52%) were left hemisphere strokes, and 133 (48%) were right. There were no differences regarding demographic, risk factors and etiology between hemispheres. Left lesions scored higher on National Institute of Health Stroke Scale at admission. There was no difference in time from symptom onset to hospital admission (p=0.240), even after excluding wake-up strokes (p=0.496), and from admission to first CT (p=0.493). Laterality did not influence the decision to treat (p=0.220), neither the type of acute treatment select (p=0.321). However, right sided strokes suffered from a significant delay from admission to first treatment (p=0.015), particularly the subgroup of patients that were transferred from other hospitals and were directly submitted to thrombectomy (p=0.042). This difference was not present in patients treated with thrombolysis, neither in patients that were directly admitted to our center and treated with thrombectomy. Laterality did not influence National Institute of Health Stroke Scale and Modified Ranking Scale at discharge.

Conclusions: We observed a delay on the time to thrombectomy in right strokes compared to left ones, in the subgroup of patients that were transferred from another hospital. On the other hand, stroke laterality did not seem to influence time from symptoms recognition to hospital admission, the decision the treat, neither the type of treatment selected. This observation gains further relevance since stroke associated disability in our series is similar between hemispheres.

Keywords: Stroke, laterality, time, acute treatment, impact

LIST OF ABBREVIATIONS

AIS: acute ischemic stroke
CHUPorto: Centro Hospitalar Universitário do Porto
CSC: comprehensive stroke center
CT: computed tomography
ER: emergency room
ICA: internal carotid artery
IV rt-PA: intravenous recombinant tissue plasminogen activator
LHS: left hemispheric stroke
MCA: middle cerebral artery
mRS: modified Ranking Scale
NIHSS: National Institutes of Health Stroke Scale
RHS: right hemispheric stroke

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INTRODUCTION

Stroke is the leading cause of death in Portugal[1] and the second leading cause of death worldwide[2]. According to the analysis of the Global Burden of Diseases, Injuries, and Risk Factors Studies (GBD) from 1990 to 2017, stroke incidence, prevalence, mortality and disability-adjusted life years (DALYs) rates have declined[3]. Still, the absolute number of people affected by it or remain disable from it almost doubled.[3]

The introduction of intravenous thrombolysis and endovascular stroke therapy as treatment of acute stroke have revolutionized the management and care of this entity. However, only a minority of the patients is eligible for treatment, and delayed presentation seems to be a major factor contributing for the eligibility for acute therapy [4,5], since only patients who present within 4.5 hours of onset of an acute stroke beneficiate from intravenous recombinant tissue plasminogen activator (IV rt-PA). [6] Furthermore, a study showed that a delay in time to recognizing symptoms to hospital admission is associated to a poor outcome, independently of patient ineligibility for acute stroke treatment [7], supporting the need to seek medical help as soon as possible.

Depending on the affected brain hemisphere, cerebrovascular events have distinct presentation. Left hemispheric strokes (LHS) are more readily detected due to eloquent symptoms like aphasia, whereas right hemispheric (RHS) may be more difficult to recognize due to deficits of self-awareness like anosognosia. As anosognosia impairs a person's ability to perceive a specific deficit, so that they can overestimate their abilities, or they can even deny they are unable to move a paretic limb [8]. This lack of self-awareness contributes to under-recognition of stroke symptoms by the patient and bystanders and might delay the decision to seek medical attention within the first few hours of symptom onset [9].

Doctors are also more likely to perceive right hemisphere symptoms as less severe, especially in patients presenting with mild weakness. This difference in medical attention could influence clinical decisions, which may reduce the frequency of IV rt-PA treatment in patients with RHS.[5] Furthermore, the majority of clinical score systems used in stroke evaluation tend to favor LHS recognition, [10] like the National Institute of Health Stroke Scale (NIHSS) which is the most widely used scale to quantify stroke clinical dysfunction.

In fact, NIHSS scores higher for left hemisphere function (aphasia), accounting for 7 possible points, when compared to the 2 possible points for right hemisphere function (extinction/inattention), which minimizes RHS disfunction. [11]

All these factors could contribute to a faster detection of neurological deficits in patients with left sided lesions, which lead to an early arrival to the emergency room, and potentially to a greater proportion of LHS patients being treated with acute therapy. In fact, there is some evidence that RHS take more time to be admitted to a hospital than LHS. [12] [13] Although in the study of *Foerch et al* more patients were admitted with left than right acute damage, the authors [13] have shown that this difference is more evident in individuals with mild-to-moderate strokes or in transient ischemic attacks and that these findings are not due to a reduced incidence of RHS in general population. This highlights the need to recognize RHS deficits. Also, *Portegies et all* [14] demonstrated a higher frequency of LHS, but there was no prevalence when comparing left and right strokes on MRI, further supporting that LHS are more easily recognized. However, there are also studies demonstrating that there was no association between stroke laterality and time to admission. [15] [16,17].

There's also conflicting data about the impact of laterality in the acute management of the patient. Some studies found no association between LHS and RHS in the rate of IV rt-PA patients[17], but this was not a consistent finding[12]. When it concerns to thrombectomy, few studies were addressed to evaluate the impact of laterality on this type of acute treatment. One found that RHS are less likely to be submitted to intra-arterial reperfusion[18], while another only found a difference in RHS with NIHSS score of 6-12[19].

Having that in mind, we hypothesized that patient with RHS present later to the hospital and consequently, may have lower chances of receiving IV rt-PA or thrombectomy, when compared with the LHS.

OBJECTIVES

This study aims to evaluate the influence of stroke hemispheric location (LHS vs RHS) on: 1) The timeline of acute stroke care (time since symptom onset to hospital admission; time since hospital admission to brain CT and to first treatment); 2) Acute treatment options; 3) Outcome at discharge.

METHODS

Biostroke Study

BioStroke is a prospective study of patients admitted to the Comprehensive Stroke Centre (CSC) of Centro Hospitalar Universitário do Porto (CHUPorto) as stroke code activations, between January 2019 and 13th March 2020. Patients included in the study had a complete neurological evaluation, brain neuroimaging and longitudinal blood sampling for biomarker assessment. Patients were referred to this CSC from Centro Hospitalar Universitário de São João (CSC partner) and from the following secondary hospitals: Centro Hospitalar Tâmega e Sousa, Hospital da Senhora da Oliveira, Centro Hospitalar De Trás-Os-Montes E Alto Douro, Unidade Local de Saúde Do Nordeste, Centro Hospitalar do Médio Ave, Unidade Local de Saúde de Matosinhos, Unidade Local de Saúde do Alto Minho, Centro Hospitalar de Vila Nova de Gaia/Espinho.

Stroke laterality inclusion and exclusion criteria

Patients were eligible for the study if they were referred to our CSC and met the following inclusion criteria: (1) Non-lacunar acute ischemic stroke of the anterior cerebral territory [middle cerebral artery (MCA) and internal carotid artery (ICA)]; (2) Baseline NIHSS total score obtained at hospital admission and registered on either the patient physical file or e-record; (3) Computed tomography angiography (CTA) performed after the clinical evaluation in the same hospital.

Exclusion criteria were: (1) Negative imaging study or other diagnosis than acute ischemic stroke; (2) Posterior circulation stroke; (3) Anterior cerebral artery stroke; (5) Bilateral stroke; (6) In-hospital stroke; (7) Lacunar stroke.

Clinical and neuroimaging assessment

Study participants were characterized according to demographic data, including, age, gender, previous functional status [using the modified Rankin Scale (mRS)], education level, living situation (alone or accompanied), comorbidities and risk factors such as tobacco use (current or past smokers), alcohol, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, chronic

kidney disease, chronic pulmonary disease, peripheral artery disease, congestive heart failure, myocardial infarction, acute ischemic stroke, migraine, dementia, and having a previous stroke. For that we considered previous diagnosis recorded in medical registries or, in the case of hypertension, diabetes or dyslipidemia, if under treatment.

Education level and living situation were obtained retrospectively from patient e-records.

We also evaluated the use of anticoagulants, antiplatelets, antihypertensive drugs, antidyslipidemic drugs, and antidiabetic drugs as chronic medication. In relation to stroke-related variables we collected time of symptom onset (defined by the time the patient was ''last known well''), if the episode was a wake-up stroke, mode of referral (medical emergency center vs another hospital vs walking), stroke etiology [according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria] [19], stroke laterality, affected artery (MCA or ICA), NIHSS score at admission, patients with RHS whose clinical presentation included extinction, anosognosia or asomatognosia, time of admission at first hospital and time of brain CT. Walking includes patients that came alone by their own car or were brought by someone else, excluding ambulance transportation. In the case of transferred patients, we recorded time of admission, time of brain CT at the referring hospital, and time of the first treatment, if that was the case, and time of admission at CHUPorto.

We also collected the following treatment-related variables: time and type of acute phase treatment (none vs thrombolysis vs thrombectomy vs both) post-treatment NIHSS, NIHSS and functional status (mRS) at discharge and date of hospital discharge. We defined 4 new parameters related to time: time of symptom onset to emergency room (ED) admission (symptom-to-admission), time from ED admission to CT scan (admission-to-CT), time from ED admission to first treatment (admission-to-treatment), either it was thrombolysis or thrombectomy, and number of days between admission to discharge (length of stay).

Statistical Analysis

Unless otherwise stated, continuous variables are reported as median (interquartile range) or mean (standard deviation) and categorical variables are reported as count or percentage. For comparison of means between two groups, Student's t-test was carried out. Regarding discrete variables/scores, the comparison of medians between 2 groups was performed using a Mann-Whitney U test. For the comparison categorical variables between groups we used a Chi-square test or a Fisher's exact when appropriate.

Statistical analyses were carried out using IBM® SPSS® Version 25.0. A p value <0.05 was considered statistically significant.

Ethical Approval

The study's protocol was approved by the Institutional Ethics Committee with the authorization Nº 2021.078(064-DEFI/067-CE).

RESULTS

AIS characteristics and etiology

During a follow-up of over 14 months, a total of 563 patients were admitted to the acute stroke pathway, out of which 366 were diagnosed with AIS. Of these, 278 had anterior circulation AIS, 145 (52%) LHS and 133 (48%) RHS (Figure 1). The remainder were excluded from the analysis as they had AIS in different territories (lacunar stroke= 39, posterior circulation stroke n=33, in-hospital event n=8, anterior cerebral artery stroke n=6, and bilateral stroke n=2). Baseline characteristics of these patients are described on Table I.

Regarding demographic characteristics, no significant differences were observed between patients with LHS and RHS, namely in age, sex, risk factors and comorbidities, chronic medication, education level and living situation (Table I). Baseline mRS score was also similar between patients with LHS and RHS (Table I and Figure 2).

In relation to stroke's etiology (TOAST), we observed that the proportion of each subtype was similar between LHS and RHS (Table II). However, a significant difference was detected regarding the affected artery, with LHS having an increased proportion of internal carotid artery origin (p = 0.027). Both groups (LHS and RHS) were homogenous regarding the number of wake-up strokes or mode of referral (Table I).

The median NIHSS score at admission was significantly lower in RHS (RHS=12 vs LHS=14; p = 0.035).

AIS treatment and outcome

Out of the 278 patients, a total of 196 (70%) underwent targeted acute stroke treatment, either pharmacological thrombolysis or thrombectomy. A similar proportion of patients with LHS and RHS were treated (Table II). In treated patients, 78 (40%) underwent initial treatment with rt-PA, while thrombectomy was performed in 118 (60%) patients. No differences were observed in the type of selected treatment between LHS and RHS (p = 0.220). (Table II). The median NIHSS after treatment was lower in RHS (RHS=8 vs LHS= 11; p = 0.015). However, NIHSS score at discharge was not statistically different between LHS and RHS (p = 0.847). Length of patient stay [3 (2-9) days] was similar between LHS [3 (2-8) days] and RHS [3 (2-12.75) days; p = 0.678]. Consistently, the same happened when analyzing mRS score at discharge in all patients (p=0.409), and in the subgroup of treated patients (p=0.590).

Acute Stroke Care Timeline

We started by evaluating the time from symptom onset or last known well to hospital admission (symptom-to-admission time) (304.4 ± 309.1 min) and found it to be higher in RHS (327.9 ± 311.3 min) than in LHS (282.3 ± 306.5 min), albeit non-significantly (p = 0.240). When we reassess this time interval excluding patients with wake-up strokes (to remove potential discrepancies of symptom assessment), the difference remained non-significant (198.7 ± 239.8 min) (210.7 ± 239.4 min for RHS; 188.4 ± 223.7 min for LHS; p = 0.496). No differences were observed for the time between patient admission and CT scan assessment (admission-to-CT time) (43.0 ± 42.2 min) (44.8 ± 46.3 for RHS; 41.3 ± 38.1 for LHS; p = 0.493) (Table III).

Remarkably, when we assessed the time from admission to the first treatment the patient received (admission-to-treatment time) (215.0 ± 264.3), we observed that patients with RHS took longer to be treated (261.6 ± 319.5 min) than those with LHS (169.1 ± 185.5 min; p = 0.015) (Table III). This difference was only significant in patients that underwent thrombectomy as first treatment (323.5 ± 294.3 min) (LHS: 259.1 ± 200.4 min; RHS: 386.4 ± 250.3; p = 0.018) and not in those whose first treatment was thrombolysis (LHS: 45.4 ± 22.5 min; RHS: 53.5 ± 42.7 min; p = 0.286). After further dissecting these differences (Figure 3), we found that RHS patients that had a significantly increased time from admission to first treatment belonged to the subgroup of patients that underwent thrombectomy and were transferred from a different hospital (392.9 ± 335.4 min) (RHS: 453.8 ± 379.7 min; LHS: 307.2 ± 241.1 min; p = 0.042). Importantly, in these patients we observed no difference between hemispheres in the time interval since admission at CHUP and thrombectomy (LHS: 127.2 ± 135.3 min; RHS: 123.64 ± 343.0; p= 0.956). Moreover, we did not observe any difference between RHS and LHS in patients directly admitted at CHUPorto for thrombectomy (189.1 ± 885.2) (RHS: 184.4 ± 74.8 min; LHS: 192.2 ± 92.9 min; p = 0.788).

RHS symptoms impact in acute stroke care timeline

Since RHS can present with specific cortical symptoms like extinction, anosognosia and/or asomatognosia, we assessed whether the presence of these symptoms had any influence on the timings of patient management (Table IV). We found no difference between symptom-to-admission time (p = 0.278), admission-to-CT time (p = 0.882) nor in admission-to-treatment time (p = 0.175). Furthermore, the choice of first treatment (thrombolysis or thrombectomy) was not different between RHS with and without cortical symptoms (p = 0.776). Also, we compared admission-to-treatment time in RHS between patients with and without cortical symptoms according to hospital of first admission (CHUPorto vs other hospital) and found no difference. This suggests that the presence of any cortical symptom did not significantly influenced the management of RHS patients.

DISCUSSION

Our major finding was that RHS had a greater delay in admission-to-treatment time, when compared to LHS. After dissecting this result, we found out that this occurred in the subset of patients that were transferred from another hospital and underwent thrombectomy at our CSC. We also found no difference between hemispheres in time of symptoms' recognition to hospital admission neither in the proportion of patients treated.

In the present study, laterality did not influence baseline characteristics, the proportion of wake-up strokes, the etiology of strokes, mode of referral or the length of hospital stay, illustrating the sample's homogeneity.

Regarding the effects of specific symptoms of LHS and RHS, they did not influence arrival time to an emergency room, neither time from hospital admission to first CT. Even after excluding wake-up strokes, in an attempt to remove potential bias on the time of symptom recognition, once it is not possible to establish a distinct time of symptoms onset[20], the results remained unchanged. This is not in line with our initial hypothesis, that RHS present later to an ED, and therefore could have less chances to be treated, but supports the idea that stroke laterality may not influence the appreciation of symptoms of the ischemic event by patients or bystanders, as already proven by other investigators [15-17,21] [22,23]. On the other hand, patients with minor RHS, particularly those without major motor disability, may not have been captured in our study as they did not come to hospital as stroke code activations.

When assessing the time from hospital admission to first treatment, we observed that RHS took longer to be treated with thrombectomy. This finding was not observed in patients submitted to thrombolysis, as already reported by other authors[18,21], but this is not a consistent finding in literature[24]. Interestingly, this delay to thrombectomy was only present in RHS that were referred to our CSC from another hospital. The decision to pursue thrombectomy in an acute ischemic event is complex, based, not only on specific criteria, that include prestroke mRS, NIHSS score, Alberta Stroke Programme Early (ASPECT) score and time from symptoms' onset to treatment[6], but also relies on the clinical interpretation and the experience of the assessing doctor. A possible explanation is that the majority of the transferred strokes come from less differentiated hospitals where patient assessment is not always performed by a neurologist or stroke specialists. Our CSC is a tertiary care hospital, so every patient admitted to our acute stroke pathway, independently of the time of the day, is observed by a stroke neurologist. Since the intervention neurorradiology team is the same, the observed difference is probably due to the first assessment at the admission hospital. This is further supported by the fact that when we calculated time since admission at our CSC to thrombectomy in patients transferred from other hospitals, this difference between LHS and

RHS ceased, confirming that delay occurs at the referring hospital. A possible explanation may be NIHSS valorization and interpreting thrombectomy criteria literally, at the referring hospital, undervaluing strokes in the right hemisphere. Consequently, these factors could retard the decision to transfer or not to the CSC, leading to a delay in time to thrombectomy in RHS. Such findings support the need to implement tele-consultation or improve education of non-specialized medical staff caring for acute stroke patients, regarding specificities and discrepancies between strokes affecting left and right brain hemisphere. This gains further relevance since RHS and LHS patients exhibit overlapping disability at discharge and the delay in RHS treatment may have contributed to our observation. There are several studies addressing the impact of laterality on thrombolysis, but there's a paucity of data concerning the impact on mechanical thrombectomy. *Desai and colleagues* [25] found no differences between hemispheres in time from patient was last know well to thrombectomy, however the authors did not specify the origin of their stroke patients, if they were transferred from another hospital or not, which is in contrast to our center that includes patients referred from other hospitals.

Concerning decision to treat, laterality did not influence these rates. In our cohort, a large proportion of patients underwent acute stroke treatment: 40% patients where eligible for intravenous thrombolysis, whereas 60% gathered criteria for intra-arterial reperfusion. Previous evidence suggested that patients with RHS are less likely to be submitted to thrombolysis[12,13] and to mechanical thrombectomy[26] when compared to LHS. In contrast, in this cohort, the number of patients treated with IV rt-PA as first treatment and thrombectomy was not affected by laterality. This is consistent with data from other studies with regard to the proportion of thrombolysis[17,18] Regarding the effect of the affected stroke hemisphere in the decision to pursue thrombectomy, *Desai et al*[25] observed significant lower thrombectomy rates in RHS than LHS, but only on less severe ischemic events, with NIHSS score of 6-12. They support that a possible explanation for this mismatch in clinical decision could rely on the symptomatic differences between hemispheres.

We observed that LHS had higher mean NIHSS scores at admission and post-treatment. It is known that right strokes score less than left ones due to the inherent bias of the NIHSS for left hemispheric function.[10] [11,18,27]. However, at discharge, such difference ceased. Also, when evaluating mRS score at discharge in all patients and in the subgroup of treated ones, there were no differences between hemispheres. This is a major point in terms of education of the health care professionals. Although right lesions score less on the assessment tools used at admission than the left ones, they have the same scores at discharge and, therefore, similar outcomes. Ischemic events of the right side can be as disabling as the ones affecting the left side. There is a lack of agreement regarding the effect of laterality on the outcome of stroke patients. Some authors defend an association of LHS with a better clinical outcome when compared to RHS[21,26,28,29] while others [18,24],

found no difference between hemispheres. However, we concluded that RHS can be as severe as LHS. A systematic review conducted by *Rastogi et al*[30] even described a higher rate of mortality in right middle cerebral artery territory, but this was not observed in our cohort.

Lastly, the presence of one of the three cortical symptoms (extinction, asomatognosia, and anosognosia) was evaluated only on right hemisphere strokes, namely on the time from symptom onset to hospital admission, admission to CT, admission to first treatment, on the decision to treat and type of selected treatment. There were no statistically significant differences to report, which illustrates that the presence of cortical symptoms did not seem to influence the management of RHS. Then we compared time from admission to first treatment in RHS between patients with and without cortical symptoms, subdividing in patients that were first admitted at CHUPorto and not, concluding that there was no statistically significant difference. *Di Legge et al*[12] demonstrated that the presence of neglect, when recognized, doubled the chance of the patient to be treated with thrombolysis. Future studies on this topic are needed in order to validate these results.

The major strengths of this study are the prospective and consecutive nature of the study and the homogeneity of groups regarding demographic, clinical and vascular territory stroke characteristics, and type of acute stroke treatment.

Our study has some limitations, like admission NIHSS scores not obtained by neurologists in patients that were first observed in other hospitals. Another potential limitation was that we only considered patients who led to an activation of the acute stroke pathway, so we may have missed those who were not recognized, either by patients or by the professional responsible for that activation at hospital admission. Lastly, this cohort was obtained from a biomarker study (BioStroke) so it only includes patients whose blood samples were collected.

CONCLUSION

In conclusion, our study showed that RHS had a greater delay in admission-to-treatment time, on the subset of patients that were transferred from secondary care hospitals, to be submitted to thrombectomy at our CSC. However, when we evaluated time since admission at our CSC to thrombectomy, in this subgroup of patients, the difference was not present. Thus, it is plausible to conclude that this delay occurs at the referring hospital, where the first assessment of a stroke may not be performed by a neurologist or a stroke specialist. Such finding gains further relevance since LHS and RHS had the same outcome at discharge, reflecting that RHS can be as disabling as LHS. These results support the importance of implementing tele-consultation or educating non-specialized medical staff that work with acute stroke patients, regarding specificities of right hemisphere strokes.

TABLES

Table I. Baseline characteristics for acute ischemic stroke patients with left and right hemispheric strokes

	All (n=278) n (%)	**Left** (n=145) n (%)	**Right** (n=133) n (%)	***P***
Mean age (±SD), years	76.0 ± 12.2	76.0 ± 12.1	76.0 ± 12.3	0.974
Male sex	125 (45)	67 (46)	58 (44)	0.664
Risk Factors and Comorbidities				
Hypertension	206 (74)	110 (75)	96 (72)	0.484
Dyslipidemia	151 (54)	85 (58)	66 (50)	0.133
Atrial Fibrillation	84 (30)	38 (26)	46 (35)	0.129
Diabetes Mellitus	70 (25)	41 (28)	29 (22)	0.214
Heart Failure	64 (23)	31 (21)	33 (35)	0.497
Smoking	58 (23)	32 (25)	26 (22)	0.534
Alcohol	51 (21)	27 (21)	24 (20)	0.882
Previous Stroke	46 (17)	27 (19)	19 (14)	0.331
Chronic Obstructive Pulmonary Disease	31 (11)	14 (10)	17 (13)	0.408
Dementia	28 (10)	13 (9)	15 (11)	0.522
Peripheral artery disease	27 (10)	16 (11)	11 (8)	0.437
Chronic Kidney Disease	24 (9)	14 (10)	10 (8)	0.526
Myocardial Infarction	19 (7)	12 (8)	7 (5)	0.320
Migraine	7 (3)	4 (3)	3 (2)	0.783
Chronic Medication				
Antihypertensive	192 (69)	102 (70)	90 (68)	0.630
Statin	128 (46)	71 (49)	57 (43)	0.307
Anticoagulant	69 (25)	29 (20)	28 (29)	0.095
Antiplatelet	69 (25)	40 (27)	29 (22)	0.265
Antidiabetic	58 (21)	31 (21)	27 (20)	0.825
Lived Alone*	43 (18)	22 (18)	21 (19)	0.734
Education Level ⊥				0.849
None	10 (9)	4 (7)	6 (12)	
1st-4th grade	72 (65)	40 (65)	33 (65)	
5th-9th grade	13 (12)	8 (13)	5 (10)	
10th-12th grade	8 (7)	4 (7)	4 (8)	
>12th grade	8 (7)	5 (8)	3 (6)	
Mode of referral				0.500
Medical Emergency Centre	148 (53)	80 (55)	68 (51)	
Another Hospital	103 (37)	47 (32)	56 (42)	
Walking	27 (10)	18 (13)	9 (7)	
Wake-up stroke	76 (27)	35 (24)	41 (31)	0.211
Baseline mRankin				0.510
0-3	256 (92)	135 (93)	122 (92)	
4-5	22 (8)	10 (7)	11 (8)	

*44 missing values

⊥ 167 missing values

Table II. Comparison of stroke etiology, NIHSS, mRanking score and type of acute treatment between right and left hemispheric strokes

	All (n=278) n (%)	**Left** (n=145) n (%)	**Right** (n=133) n (%)	***P***
Etiology (according to TOAST)				0.435
Cardioembolic	147 (53)	75 (51)	73 (55)	
Atheroscletoric	51 (18)	28 (19)	23 (17)	
Cardioembolic & atherosclerotic	7 (3)	2 (1)	5 (4)	
Prothrombotic	5 (2)	4 (3)	1 (1)	
ESUS	30 (11)	15 (10)	15 (11)	
Incomplete	6 (2)	2 (1)	4 (3)	
Undetermined	30 (11)	18 (12)	12 (9)	
Other	2 (1)	2 (1)	0 (0)	
Affected artery				**0.027**
Middle cerebral artery	266 (96)	135 (93)	131 (99)	
Internal carotid artery	12 (4)	10 (7)	2 (1)	
Median NIHSS (IQR)				
At admission	12 (8-20)	14 (7-22)	12 (8-17)	**0.035**
After treatment	9 (4-17)	11 (4-20)	8 (4-13)	**0.015**
At discharge	5 (2-12)	5 (1-12)	5 (2-12)	0.847
Treated strokes *	196 (72)	97 (68)	99 (75)	0.220
First treatment				0.321
Thrombolysisθ	78 (40)	42 (43)	36 (36)	
Thrombectomy	118 (60)	55 (57)	63 (64)	
mRS at discharge ς				0.409
0-3	144 (52)	81 (56)	63 (48)	
4-5	105 (38)	47 (33)	58 (44)	
6	26 (10)	16 (11)	10 (8)	
mRS at discharge treated patients⊥				0.590
0-3	111 (57)	57 (60)	54 (55)	
4-5	69 (36)	31 (32)	38 (39)	
6	14 (7)	8 (8)	6 (6)	

*- 4 missing values about treatment

θ- Includes patients who were first treated with thrombolysis

ς- 3 missing values

⊥- 2 missing values

Table III. Influence of laterality in acute stroke pathway time intervals

	All n= 278	**Left** n=145	**Right** n=133	***P***
Overall Patients				
Mean time ± SD min				
Symptoms to Admission	304.4 ± 309.1	282.3 ± 306.5	327.9 ± 311.3	0.240
Excluding wake-up strokes	198.7 ± 239.8	188.4 ± 223.7	210.7 ± 239.4	0.496
Admission to CT-scan γ	43.0 ± 42.2	41.3 ± 38.1	44.8 ± 46.3	0.493
Median length of stay, days (IQR)	3 (2-9)	3 (2-8)	3 (2-12.75)	0.678
Treated Patients				
Mean time ± SD min				
Admission to 1st Treatment φ	215.0 ± 264.3	169.1 ± 185.5	261.6 ± 319.5	**0.015**
Thrombolysis ⊥	49.1 ± 33.4	45.4 ± 22.5	53.5 ± 42.7	0.286
CHUPorto (n= 63)	45.0 ± 31.3	42.0 ± 19.1	50.8 ± 41.8	0.274
Other hospital (n=15)	62.8 ± 39.3	62.3 ± 31.6	63.3 ± 47.2	0.964
Thrombectomy	323.5 ± 294.3	259.1 ± 200.4	386.4 ± 250.3	**0.018**
CHUPorto (n=41)	189.1 ± 885.2	192.2 ± 92.9	184.4 ± 74.8	0.788
Other hospital (n=77)	392.9 ± 335.4	307.19 ± 241.1	453.8 ± 379.7	**0.042**

Ω 24 missing values of time of symptom onset
γ 6 missing values of time of CT in patients transferred from another hospital
φ 2 missing values of time of first treatment in patients transferred from another hospital
⊥ includes patients whose first treatment was thrombolysis

Table IV. Comparison of time intervals, decision to treat and type of treatment between RHS with and without cortical symptoms

	RHS with cortical symptoms mean ± SD n= 87	**RHS without cortical symptoms** mean ± SD n=46	***P***
Symptoms to Admission (min)	350.8 ± 317.2	287.0 ±299.6	0.278
Admission to CT (min)	45.2 ± 45.9	44.0 ± 47.5	0.882
Admission to 1st Treatment (min)	226.9 ± 272.0	335.6 ± 397.5	0.175
CHUPorto	100.8 ± 87.2	99.3 ± 92.3	0.940
Other hospital	339.3 ± 326.8	339.0 ± 330.1	0.997
Decision to treat, n (%)	67 (79)	32 (68)	0.172
Thrombolysis	25 (37)	11 (34)	0.776
Thrombectomy	42 (63)	21 (66)	

FIGURES

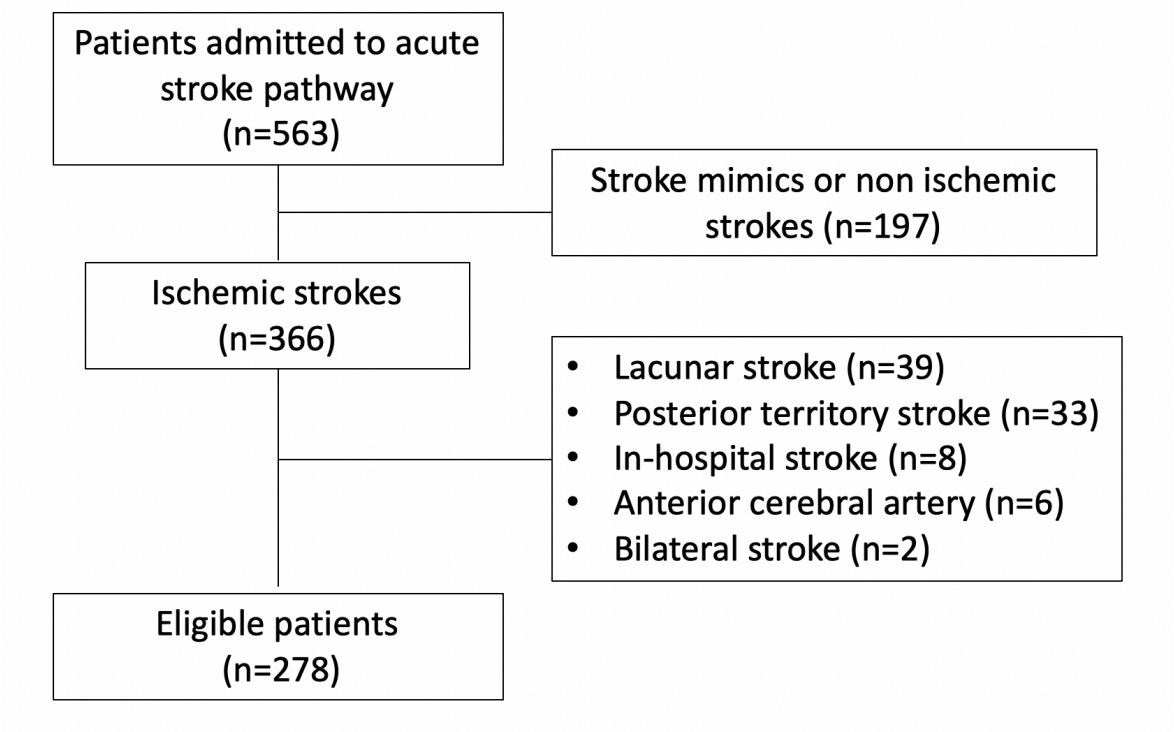


Figure 1. Flow-chart of patients' selection.

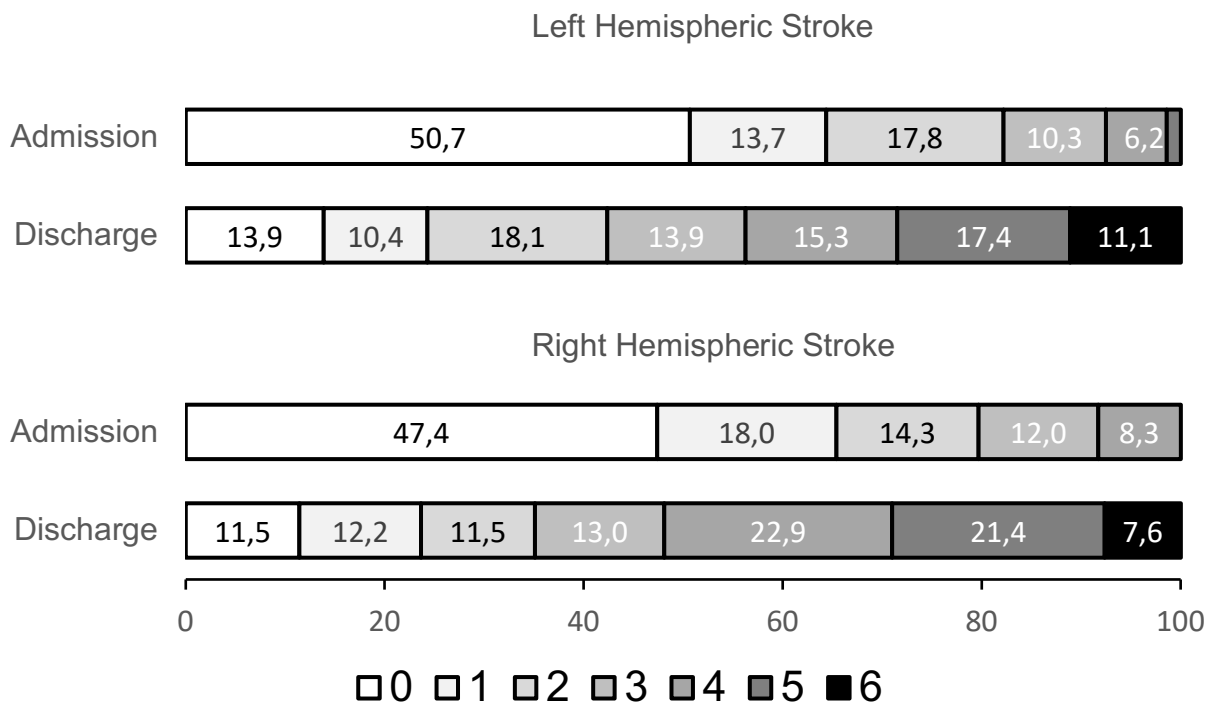
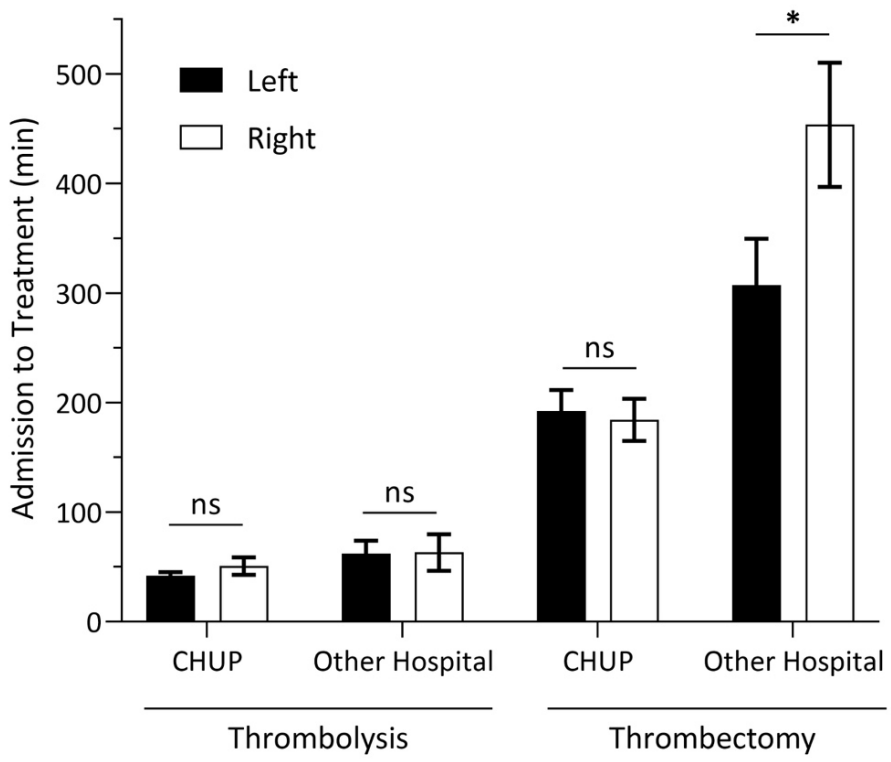


Figure 2. Admission and discharge modified Ranking scale score in left and right hemispheric stroke



Other hospital includes patients from Centro Hospitalar S. João, Centro hospital Tâmega e Sousa, Hospital da Senhora da Oliveira, Centro Hospitalar De Trás-Os-Montes E Alto Douro, Centro Hospitalar Do Nordeste, Centro Hospitalar do Médio Ave, Unidade Local de Saúde de Matosinhos, Unidade Local Saúde Alto Minho, Centro Hospitalar de Vila Nova de Gaia/Espinho

Figure 3. Time from hospital admission to first treatment in different subgroups: LHS and RHS first admitted at CHUPorto vs other hospital

REFERENCES

1. INE. Causas de Morte 2019. 2021; https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_destaques&DESTAQUESdest_boui=458514604&DESTAQUESmodo=2.
2. WHO G. The top 10 causes of death. 2020; https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
3. Krishnamurthi RV, Ikeda T, Feigin VL. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology.* 2020;54(2):171-179.
4. Moser DK, Kimble LP, Alberts MJ, et al. Reducing Delay in Seeking Treatment by Patients With Acute Coronary Syndrome and Stroke. *Circulation.* 2006;114(2):168-182.
5. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology.* Apr 24 2001;56(8):1015-1020.
6. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* Dec 2019;50(12):e344-e418.
7. Mayasi Y, Helenius J, Goddeau RP, Jr., Moonis M, Henninger N. Time to Presentation Is Associated with Clinical Outcome in Hemispheric Stroke Patients Deemed Ineligible for Recanalization Therapy. *J Stroke Cerebrovasc Dis.* Oct 2016;25(10):2373-2379.
8. Orfei MD, Robinson RG, Prigatano GP, et al. Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: a systematic review of the literature. *Brain.* 2007;130(12):3075-3090.
9. Fink JN. Underdiagnosis of right-brain stroke. *Lancet.* Jul 30-Aug 5 2005;366(9483):349-351.
10. Woo D, Broderick JP, Kothari RU, et al. Does the National Institutes of Health Stroke Scale favor left hemisphere strokes? NINDS t-PA Stroke Study Group. *Stroke.* Nov 1999;30(11):2355-2359.
11. Fink JN, Selim MH, Kumar S, et al. Is the association of National Institutes of Health Stroke Scale scores and acute magnetic resonance imaging stroke volume equal for patients with right- and left-hemisphere ischemic stroke? *Stroke.* Apr 2002;33(4):954-958.
12. Di Legge S, Fang J, Saposnik G, Hachinski V. The impact of lesion side on acute stroke treatment. *Neurology.* Jul 12 2005;65(1):81-86.
13. Foerch C, Misselwitz B, Sitzer M, Berger K, Steinmetz H, Neumann-Haefelin T. Difference in recognition of right and left hemispheric stroke. *The Lancet.* 2005;366(9483):392-393.
14. Portegies MLP, Selwaness M, Hofman A, Koudstaal PJ, Vernooij MW, Arfan Ikram M. Left-sided strokes are more often recognized than right-sided strokes: The rotterdam study. *Stroke.* 2015;46(1):252-254.

15. McCluskey G, Wade C, McKee J, McCarron P, McVerry F, McCarron MO. Stroke Laterality Bias in the Management of Acute Ischemic Stroke. *J Stroke Cerebrovasc Dis.* Nov 2016;25(11):2701-2707.
16. Agyeman O, Nedeltchev K, Arnold M, et al. Time to admission in acute ischemic stroke and transient ischemic attack. *Stroke.* Apr 2006;37(4):963-966.
17. Blondin NA, Staff I, Lee N, McCullough LD. Thrombolysis in right versus left hemispheric stroke. *J Stroke Cerebrovasc Dis.* Jul-Aug 2010;19(4):269-272.
18. Fink JN, Frampton CM, Lyden P, Lees KR. Does hemispheric lateralization influence functional and cardiovascular outcomes after stroke?: an analysis of placebo-treated patients from prospective acute stroke trials. *Stroke.* Dec 2008;39(12):3335-3340.
19. Desai SM, Rocha M, Starr M, et al. Laterality is an Independent Predictor of Endovascular Thrombectomy in Patients With Low National Institute of Health Stroke Scale. *J Stroke Cerebrovasc Dis.* Nov 2018;27(11):3172-3176.
20. Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* Jan 1993;24(1):35-41.
21. Peter-Derex L, Derex L. Wake-up stroke: From pathophysiology to management. *Sleep Med Rev.* Dec 2019;48:101212.
22. Di Legge S, Saposnik G, Nilanont Y, Hachinski V. Neglecting the difference: does right or left matter in stroke outcome after thrombolysis? *Stroke.* Aug 2006;37(8):2066-2069.
23. Faiz KW, Sundseth A, Thommessen B, Rønning OM. Prehospital delay in acute stroke and TIA. *Emerg Med J.* Aug 2013;30(8):669-674.
24. Derex L, Adeleine P, Nighoghossian N, Honnorat J, Trouillas P. Factors influencing early admission in a French stroke unit. *Stroke.* Jan 2002;33(1):153-159.
25. Almekhlafi MA, Hill MD, Roos YM, et al. Stroke Laterality Did Not Modify Outcomes in the HERMES Meta-Analysis of Individual Patient Data of 7 Trials. *Stroke.* Aug 2019;50(8):2118-2124.
26. Hedna VS, Bodhit AN, Ansari S, et al. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? *J Clin Neurol.* Apr 2013;9(2):97-102.
27. Lyden P, Claesson L, Havstad S, Ashwood T, Lu M. Factor analysis of the National Institutes of Health Stroke Scale in patients with large strokes. *Arch Neurol.* Nov 2004;61(11):1677-1680.
28. Aszalós Z, Barsi P, Vitrai J, Nagy Z. Lateralization as a factor in the prognosis of middle cerebral artery territorial infarct. *Eur Neurol.* 2002;48(3):141-145.
29. Ween JE, Alexander MP, D'Esposito M, Roberts M. Factors predictive of stroke outcome in a rehabilitation setting. *Neurology.* Aug 1996;47(2):388-392.
30. Rastogi V, Lamb DG, Williamson JB, et al. Hemispheric differences in malignant middle cerebral artery stroke. *J Neurol Sci.* 2015;353(1-2):20-27.