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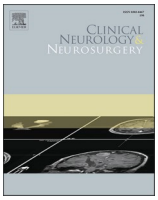

Factors associated with post-stroke depression in the acute phase of ischemic stroke: A cross-sectional study

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ABSTRACT

Objectives: Ischemic stroke is a remarkable cause of death and disability worldwide. Post-stroke depression (PSD) is the most common psychiatric disturbance after stroke. Despite PSD being a potentially treatable condition, it still requires approaches to improve the early diagnosis. The present study aims to investigate the factors associated and correlated variables associated with PSD during hospitalization.

Materials and methods: A retrospective cross-sectional study was conducted in a specialized center of neurology in Santa Catarina, Brazil. 148 patients with acute ischemic stroke hospitalized between January 2020 and February 2021 were included. Sociodemographic, clinical and radiological variables were assessed during hospitalization. The Hospital Anxiety and Depression Scale (HADS) was applied, as well as the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Factors associated were investigated through binary logistic regression and continuous variables through correlation tests.

Results: The prevalence of PSD during hospitalization was 31.1%. Factors associated with PSD in the acute phase of the stroke were female sex (OR: 2.6; CI 95%: 1.3–5.4; $p < 0.01$) and post-stroke anxiety during hospitalization (OR: 4.9; CI 95%: 2.3–10.3; $p < 0.01$). The variables NIHSS, mRS, and stroke area were positively correlated with HADS – depression values.

Conclusions: This research evidenced a high prevalence of PSD in the acute phase of stroke. Despite the study being conducted during the COVID-19 pandemic, the frequency is similar to the non-pandemic periods. The research provided clues to identify and timely treat patients at greater risk of developing PSD during hospitalization.

1. Introduction

Ischemic stroke is a vascular disorder responsible for the second leading cause of death in the world [1] and Brazil [2] and is an important determinant of dependency, poor quality of life, and disability [3]. Post-stroke depression (PSD) is the main psychiatric disorder after stroke, with a frequency of 34.7% three months after stroke [4] and about 25% one to five years after stroke in a metanalysis [5]. PSD negatively impacts the patients' motor, functional and cognitive rehabilitation [6]. Despite being frequent and causing a significant burden of disease, PSD remains underdiagnosed and undertreated [6].

The main biological hypothesis for PSD is the hypothesis of the amines [7], especially serotonin, norepinephrine, and dopamine, which have reduced bioavailable concentrations due to disconnections in the ascending structures of the CNS due to ischemic injury [7]. Some studies regarding neuroimaging evaluation sought to identify specific areas

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related to the pathogenesis of depressive disorder after stroke, highlighting the prefrontal lobe, the frontal lobe, and the limbic system [7]. The precise pathophysiological mechanisms of PSD still need further investigation Fig. 1.

Studies related to risk factors for PSD identified pre-stroke depression as an important risk factor [8], as well as anxiety during hospitalization [8]. A study evaluated the impact of the diagnosis of PSD in the acute phase of stroke on the development of PSD three years after stroke and demonstrated a remarkable higher risk of fivefold [9]. It highlights the relevance of expending special attention to patients at major risk for PSD in the acute phase, which might impact the long-term recovery. Furthermore, other risk factors were identified regarding the severity aspects as well as the degree of disability after stroke evaluated by high modified Rankin Scale (mRS) and the National Institute of Health Stroke Scale (NIHSS) [10]. Another tool to quantify stroke severity can be performed utilizing radiological criteria such as measuring the stroke area, which has been used in limited studies.

Considering these aspects, the present study aimed to investigate the sociodemographic, clinical, and radiological profile of patients with acute ischemic stroke (AIS) admitted to a referral center for stroke treatment (Stroke-Unit of the Hospital Governador Celso Ramos -Stroke-Unit HGCR), to identify the prevalence of PSD during hospitalization and to elucidate the factors associated with this outcome. To our knowledge, this is the first cross-sectional study about PSD in the acute phase in Brazil during the COVID-19 pandemic.

2. Methods

2.1. Study design and setting

An observational, analytic, and cross-sectional study was carried out in a tertiary neurology service located in the Stroke-Unit HGCR, Florianopolis, Santa Catarina, Brazil.

2.2. Participants and eligibility criteria

The participants were 148 patients with AIS of the anterior circulation who were consecutively admitted to the HGCR between January 2020 and January 2021.

The inclusion criteria were: 1) diagnosis of AIS in the frontal, temporal or parietal lobe confirmed in a neuroimaging exam (computed tomography [CT]; and/or magnetic resonance imaging, [MRI]) and 2) patients aged $\geq$ 15 years. The exclusion criteria were: 1) global aphasia, Wernicke aphasia, mixed transcortical and/or sensory transcortical aphasia; 2) previous moderate to severe traumatic brain injury (TBI); 3) supratentorial brain tumors; 4) previous diagnosis of epilepsy; 5) medical history of severe cognitive deficit; 6) substance abuse disorder; 7) impaired level of consciousness (Glasgow Coma Scale $<$ 9) during the first week of hospitalization and/or mechanical ventilation and/or 8) patients with cold symptoms.

2.3. Sample size

The sample size was estimated using a previous regional study entitled "Assessment of the influence of the location of the motor and cognitive changes on the development of signs and symptoms of depression after stroke", carried out in southern Brazil ([Rider, C], unpublished data, 1994). The effect size estimated was 0.45 and using the chi-square test, with sample parameters of 10 degrees of freedom (df), α (bilateral) $= 0.05$, and $\beta = 0.20$, a sample size of 81 patients was defined. Sixty patients were added to compensate for eventual losses, totaling 140 individuals.

2.4. Variables and data collection

During the interview, the evaluated data were age in years, sex, self-referred skin color, years of education, marital status, history of hypertension, diabetes mellitus, other previous comorbidities, history of smoking, and alcoholism. During the neurological examination, the NIHSS and the mRS were applied to assess stroke severity. The hospital's electronic database included the TOAST etiological classification, presence or absence of hemorrhagic transformation, thrombolysis, and/or thrombectomy therapy.

The HADS (Hospital Anxiety and Depression Scale) was used to assess depressive disorder and anxiety in patients hospitalized in a non-psychiatric service, at the bedside, up to seven days after admission. The Portuguese version of the scale has already been validated in Brazil [11] and those patients with PSD and post-stroke anxiety (PSA) [12]. HADS has 2 subscales HADS-A for anxiety and HADS-D for depression. Each subscale has 7 items, each item ranging in score from 0 to 3 [13]. The cutoff point widely used for the general population is eight [13], and this value was used in the present study. Mild depression was determined with HADS-D ranging from 8 to 10, moderate depression from 11 to 14 points, and severe depression $\geq$ 15 points [14].

The neuroimaging exams (cranial CT and/or MRI) were evaluated to determine the specific territory of the ischemic lesion based on the anatomical limits of each lobe. The posterior limit of the frontal lobe was the central sulcus, and the inferior limit was the lateral sulcus [15]. The

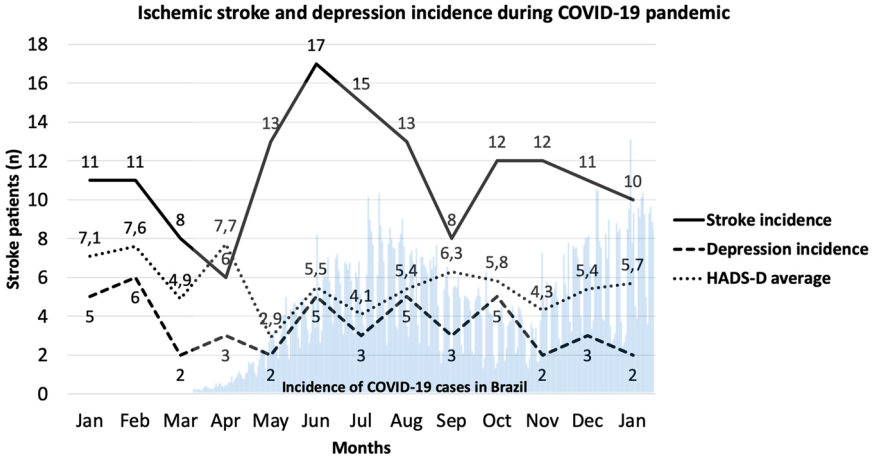

Fig. 1. Representation of the incidence of hospitalizations due to acute ischemic stroke between January 2020 and January 2021 (black line). The dashed line represents the incidence of post-stroke depression during hospitalization in the same period and the dotted line represents the average of the HADS-D during hospitalization. The blue graphic demonstrates the incidence of COVID-19 cases in Brazil, during the same period.

parietal lobe was defined by the central sulcus anteriorly, the lateral sulcus laterally, and the imaginary line between the preoccipital notch and the parieto-occipital fissure posteriorly [15]. The temporal lobe limits were determined superiorly by the lateral sulcus and, posteriorly, by the imaginary line between the preoccipital notch and the parieto-occipital fissure [15]. The insula lobe is limited laterally by the basal ganglia, and medially by the labia of the lateral sulcus [15]. The basal ganglia are located medially to the lobe of the insula and laterally to the thalamus [15]. Furthermore, the exams were analyzed using the WEASIS Medical Viewer program, to perform the area calculation of the lesion in an axial section, considering the largest area in mm^2.

Data were obtained by a medical professional researcher with certification to apply the questionnaire and experience in performing the neurological examination and the process of the data acquisition.

2.5. Data analysis

Data were analyzed using the SPSS 20.0 program and described as relative and absolute frequencies. The magnitude of the association between the dependent variable and the independent variables was measured through the Odds Ratio (OR), with "p" values considered statistically significant when $p < 0.05$. The association between the categorical variables and depression during hospitalization was investigated using a binary logistic regression model. The continuous variables were evaluated using correlation tests (Kendall's Tau-b Test for non-parametric variables and Spearman's Test for ordinal variables). Furthermore, the categorical variables associated with depressive symptoms during hospitalization were included in a multiple logistic regression model. In addition, multivariate linear regression was performed to evaluate the continuous variables associated with the outcome (HADS-D score). Data were described in "R", "R square", and "p" values.

2.6. Ethical considerations

This study was approved by the Ethics Committee of the HGCR (registration number: 3.794.456) and agreed with the Declaration of Helsinki. Informed consent was obtained from all patients and their anonymity was preserved.

3. Results

We interviewed 148 patients with AIS admitted to the Stroke-Unit HGCR between January 2020 and February 2021. Among the 148 participants, 79 (53.4%) were male and the mean age was 64.5 years (SD ± 13.8). The prevalence of PSD in the hospitalization was 31.1%, while PSA was 33.8%. Among the 46 patients with depressive disorder, 26 (56.5%) had mild depression, 12 (26.1%) had moderate depression, and eight (17.4%) had severe depression.

About clinical variables, 70.9% of the patients had hypertension and 30.4% had diabetes mellitus. In addition, 40 (27%) of the participants consumed alcohol and 38 (25.7%) were smokers. Concerning the radiological variables, the right hemispheric was affected in 54.7% of the patients and the main affected topographies were the basal nuclei in 52% and the parietal lobe in 44.6% of the cases. The frequencies of stroke etiologies by TOAST classification were stroke of undetermined etiology in 32.4%; large-artery atherosclerosis in 25.7%; cardioembolism in 24.3%; small-vessel occlusion in 9.5% and stroke of other determined etiology in 8.1%. Regarding the therapeutic variables, 15.5% of the patients underwent intravenous thrombolysis and 9.5% underwent mechanical thrombectomy. About the degree of dependence of patients, 31.8% had a mRS score of 0%, and 26.4% had mRS score of 4. Table 1 shows the sociodemographic, clinical, radiological, and therapeutic data of the participants.

Table 2 shows the factors associated with PSD during hospitalization evaluated in a binary logistic regression model. The sociodemographic

Table 1
Sociodemographic, clinical, and radiological features of patients with acute ischemic stroke hospitalized at the Stroke-Unit HGCR (Santa Catarina, Brazil).

Categorical variables	n	%
Sex	79	53.4
Male	69	46.6
Female		
Ethnicity	30	20.3
No-white	118	79.7
White		
Marital status	27	18.2
Single	62	41.9
Married	26	17.6
Widower	33	22.3
Other		
Psychiatric disorder during hospitalization	46	31.1
Depression	50	33.8
Anxiety	27	18.2
Both		
Previous depressive disorder	118	79.7
No	30	20.3
Yes		
Previous anxiety disorder	135	91.2
No	13	8.8
Yes		
Lesion topography *	61	41.2
Frontal lobe	66	44.6
Parietal lobe	51	34.5
Temporal lobe	45	30.4
Insular lobe	77	52.0
Basal ganglia		
Hemisphere affected **	77	52.0
Left	81	54.7
Right	10	6.8
Both		
Hemorrhagic transformation	126	85.1
No	22	14.9
Yes		
Previous stroke	100	67.6
No	48	32.4
Yes		
mRS[a] ***	47	31.8
Grade 0	30	20.3
Grade 1	15	10.1
Grade 2	14	9.5
Grade 3	39	26.4
Grade 4	3	2.0
Grade 5		
NIHSS[b] stratified	96	64.9
≤ 4	52	35.1
> 4		
Therapeutic approaches	23	15.5
Intravenous thrombolysis	14	9.5
Mechanical thrombectomy		
Comorbidities	105	70.9
Hypertension	45	30.4
Diabetes	40	27.0
Dyslipidemia		
Alcohol consumption	108	73.0
No	40	27.0
Yes		
Smoking	57	38.5
No	38	25.7
Current smoker	53	35.8
Ex-smoker		
Continuous variables	**Median**	**IQ 25–75**
Age	67	56.3 – 74
Time of hospitalization (days)	8	6 – 14
HADS-D[c] during hospitalization	5	2 – 8
HADS-A[d] during hospitalization	5	3 – 8.8
Stroke area (mm^2)	485	222.7 – 1401.4
NIHSS[b]	3	1 – 6

HGCR – Hospital Governador Celso Ramos
[a] *mRS – modified Rankin scale*
[b] *NIHSS -National Institutes of Health Stroke Scale*
[c] *HADS-D – Hospital Anxiety and Depression Scale - Depression*
[d] *HADS-A – Hospital Anxiety and Depression Scale - Anxiety*

* Some patients had lesions in more than one topography
** Some patients had lesions in both hemispheres
*** In-hospital mRS up to 7 days after admission

variables age, ethnicity, and marital status were not associated with intrahospital PSD. The female sex demonstrated to be an important factor associated with PSD (OR: 2.6; CI 95%: 1.3–5.4; $p < 0.01$), as well as PSA during hospitalization (OR: 4.9; CI 95%: 2.3–10.3; $p < 0.01$). Furthermore, anxiety before hospitalization was associated with depression during hospitalization (OR: 2.3; CI 95%: 1.04–5.4; p 0.04). In addition, the presence of hemorrhagic transformation in neuroimaging was shown to be a factor associated with PSD (OR: 2.6; CI 95%: 1.03–6.5; p 0.04). Variables that evaluate stroke severity such as NIHSS and stroke area were not shown to be associated with PSD. Parietal lobe injury was associated with PSD, behaving as a protective factor (OR: 0.3; CI 95%: 0.2–0.7; $p < 0.01$), as well as the previous diagnosis of hypertension (OR: 0.4; CI 95%: 0.2–0.9; p 0.03).

The variables associated with the outcome were included in a multiple logistic regression model. The variables sex ($p = 0.04$), anxiety symptoms during hospitalization ($p < 0.01$), previous diagnosis of hypertension ($p = 0.02$) and parietal lobe involvement ($p < 0.01$) remained independently associated with depression symptoms during hospitalization. Furthermore, in the multivariate linear regression model that included the continuous variables of Table 2, only HADS-A score during hospitalization remained independently associated with HADS-D score during hospitalization ($p < 0.01$).

Table 3 evidence the correlation tests between sociodemographic, clinical, laboratory and radiological variables and the HADS-D values during hospitalization. The clinical variables HADS-A values during hospitalization (R: 0.32; R^2: 0.1024; $p < 0.01$), NIHSS (R: 0.22; R^2: 0.0484; $p < 0.01$) and mRS (R: 0.33; R^2: 0.1089; $p < 0.01$) were positively correlated with HADS-D score. Furthermore, the radiological variable stroke area also demonstrated a positive correlation with the HADS-D score (R: 0.13; R^2: 0.0169; $p < 0.01$). Sociodemographic and laboratory variables were not correlated with HADS-D.

Graphic 1 demonstrates the incidence of hospital admissions for AIS in the Stroke-Unit HGCR from January 2020 to January 2021, as well as the incidence of PSD and the mean of the HADS-D scale in the same period. Also, the graphic represents the incidence of the cases of COVID-19 in Brazil between January 2020 and January 2021. The graphic shows a reduction in the incidence of AIS in April and September 2020 accompanied by an increase in the averages of HADS-D in the same period.

4. Discussion

The present research evidenced a high frequency of PSD during hospitalization for AIS in the period of the study. Female sex and anxiety during hospitalization were identified as strong factors associated with depression during hospitalization. Interestingly, the parietal lobe and previous history of hypertension behaved as a protective factor for the development of PSD during hospitalization. Finally, the NIHSS, mRS, and stroke area were positively correlated with HADS-D in the acute phase of the stroke. To our knowledge, this is the first cross-sectional study about PSD in the acute phase of the ischemic stroke conducted in the COVID-19 pandemic.

The high frequency of PSD identified in the present study is in agreement with the current literature, as rated on a German study that identified a frequency of 31.1% in the early weeks after stroke (median: 6 weeks) [16]. Another study carried out in Australia determined a frequency of 20% 12 months after stroke [17] and one Brazilian study identified a prevalence of 20% after one-to-three months after stroke using 11 as the cutoff point to determine depression by the HADS-D [18]. A meta-analysis that included 61 studies by Hackett et al. evidenced a frequency of 31% at any time up to five years after stroke [5].

Research conducted in Saudi Arabia during the COVID-19 pandemic

Table 2
Predictors of post-stroke depression during hospitalization in a binary logistic regressions analysis.

Variables	HADS-D[a] < 8 N (%)	HADS-D[a] ≥ 8 N (%)	OR (CI 95%)	p value
Age[b]	56 (70.9)	23 (29.1)	1.2 (0.6 – 2.4)	0.58
Age ≤ 67 years	46 (67.7)	23 (33.3)		
Age > 67 years				
Sex	62 (78.5)	17 (21.5)	2.6 (1.3 – 5.4)	< 0.01
Male	40 (58)	29 (42)		
Female				
Ethnicity	21 (70)	9 (30)	0.9 (0.4 – 2.2)	0.89
No-white	81 (68.6)	37 (31.4)		
White				
Marital status	54 (73)	20 (27)	1.5 (0.7 – 2.9)	0.29
No	48 (64.9)	26 (35.1)		
Yes				
Anxiety[c] disorder during hospitalization	79 (80.6)	19 (19.4)	4.9 (2.3 – 10.3)	< 0.01
	23 (46)	27 (54)		
No				
Yes				
Previous depressive disorder	85 (72)	33 (28)	1.2 (0.9 – 1.7)	0.08
	17 (56.7)	13 (43.3)		
No				
Yes				
Previous anxiety disorder	98 (72.6)	37 (27.4)	2.3 (1.04 – 5.4)	0.04
No	4 (30.8)	9 (69.2)		
Yes				
NIHSS[d] stratified	70 (72.9)	26 (27.1)	1.7 (0.8 – 3.4)	0.16
NIHSS[b] ≤ 4	32 (61.5)	20 (38.5)		
NIHSS[b] > 4				
Previous stroke	65 (65)	35 (35)	0.6 (0.3 – 1.2)	0.14
No	37 (77.1)	11 (22.9)		
Yes				
Hemisphere affected	47 (70.1)	20 (29.9)	1.1 (0.6 – 2.3)	0.70
Right hemisphere	55 (69.7)	26 (32.1)		
Left hemisphere				
Basal ganglia topography	53 (74.6)	18 (25.4)	1.7 (0.8 – 3.4)	0.15
No	49 (73.6)	28 (36.4)		
Yes				
Frontal lobe	62 (71.3)	25 (28.7)	1.3 (0.6 – 2.6)	0.46
No	40 (65.6)	21 (34.4)		
Yes				
Temporal lobe	68 (70.1)	29 (29.9)	1.2 (0.6 – 2.4)	0.69
No	34 (66.7)	17 (33.3)		
Yes				
Parietal lobe	48 (58.5)	34 (41.5)	0.3 (0.2 – 0.7)	< 0.01
No	54 (81.8)	12 (18.2)		
Yes				
Insular lobe	74 (71.8)	29 (28.2)	1.6 (0.7 – 3.2)	0.11
No	28 (62.2)	17 (37.8)		
Yes				
Stroke area[e]	70 (72.9)	26 (27.1)	1.7 (0.8 – 3.4)	0.16
Area ≤ 928 mm^2	32 (61.5)	20 (38.5)		
Area > 928 mm^2				
Previous hypertension	24 (55.8)	19 (44.2)	0.4 (0.2 – 0.9)	0.03
No	78 (74.3)	27 (25.7)		
Yes				
Previous diabetes	69 (67)	34(33)	0.7 (0.3 – 1.6)	0.44
No	33 (73.3)	12 (26.7)		
Yes				
Intravenous thrombolysis	87 (69.6)	38 (30.4)	1.2 (0.5 – 3.1)	0.68
No	15 (65.2)	8 (34.8)		
Yes				
Mechanical thrombectomy	95 (70.9)	39 (29.1)	2.4 (0.8 – 7.4)	0.11
No	7 (50)	7 (50)		
Yes				
Hemorrhagic transformation	91 (72.2)	35 (27.8)	2.6 (1.03 – 6.5)	0.04
	11 (50)	11 (50)		
No				
Yes				
Current smoke	73 (66.4)	37 (33.6)	0.6 (0.3 – 1.4)	0.26
No	29 (76.3)	9 (23.7)		
Yes				
Alcohol consumption	74 (68.5)	34 (31.5)	0.9 (0.4 – 2.1)	0.86
No	28 (70)	12(30)		
Yes				

[a] Hospital Anxiety and Depression Scale – Depression (≥ 8 points for depression)
[b] Age was stratified by median
[c] Hospital Anxiety and Depression Scale – Anxiety (≥ 8 points for anxiety)
[d] National Institute Health Stroke Scale
[e] Stroke area was stratified by mean

Table 3
Investigation of sociodemographic, clinical, laboratory and radiological continuous variables and the correlation with HADS-D during hospitalization.

HADS-D during hospitalization	Median (IQ 25 – 75)	R	R^2	p value
Sociodemographic variables				
Age[a]	67 (56.3 – 74)	-0.01	0.0001	0.86
Years of education[a]	6 (4 – 12.8)	-0.05	0.0025	0.44
Clinical variables				
Time of hospitalization in days[a]	8 (6–14)	0.08	0.0064	0.15
HADS-A during hospitalization[a]	5 (3 – 8.8)	0.32	0.1024	< 0.01
NIHSS[a]	3 (1–6)	0.22	0.0484	< 0.01
mRS[b]	1 (0 – 4)	0.33	0.1089	< 0.01
Laboratory variables				
LDL[a]	114 (92 – 139)	-0.05	0.0025	0.42
HDL[a]	43 (34–52)	0.04	0.0016	0.53
HbA1C[a]	5.9 (5.6 – 7)	0.01	0.0001	0.86
Radiological variable				
Stroke area[a]	485 (222.7 – 1401.4)	0.13	0.0169	0.02

[a] Kendall's Tau b correlation was used.
[b] Spearman test was used.

evidenced an elevated frequency (36%) of PSD 90 days after stroke [19], similar data to that observed in previous studies in the non-pandemic period [5,16]. Therefore, according to the authors, the pandemic probably had an unexpressive impact on the PSD frequencies [19]. Furthermore, in the Saudi Arabia study, depression after stroke was associated with the NIHSS and the degree of dependence evaluated by the mRS [19], as observed in the present study, although in our study the PSD has been evaluated during hospitalization. Although the pandemic could have a significant role in the frequency of mood disorders, the data above demonstrate that this fact was not observed when PSD was evaluated in the acute phase. Nevertheless, the average of the HADS-D values evidenced an increase in the months of highest severity of the COVID-19 pandemic, which denotes a possible increase in the severity of depressive symptoms in these months.

Regarding the associated factors with PSD, the present study elucidated the female sex and anxiety as important variables of PSD during hospitalization. A study conducted in the Middle East demonstrated that the female sex had twice the risk of developing PSD in the acute phase of stroke [20]. Another study carried out in Japan revealed no difference between sex when PSD was evaluated in the subacute phase of the stroke [21]. In contrast, a data collection conducted by Mayman et al. pointed to the female sex as a risk factor when PSD was evaluated 1.5 years after the stroke [22]. Besides, the study above mentioned by Mayman et al. identified the history of anxiety as a risk factor for PSD [22]. A systematic review also evidenced anxiety as a factor associated with PSD in the acute phase of the stroke [23]. Our research about PSD in the acute phase of the stroke is in agreement with the previous literature. The therapy for depressive and anxiety symptoms was not initiated in the acute phase of the stroke, due to the evidence in the literature of no improvement in long-term outcomes after stroke [24,25]. However, these data provide clues respecting which patients we need to spend special attention to during follow-up, aiming at early diagnosis, treatment, and better recovery after stroke.

Other neurological conditions are acknowledged to be associated with depression and have related factors previously described in the literature. Regarding TBI, the female sex was identified as a risk factor for developing depression after TBI [26], as observed in PSD. Furthermore, a history of a psychiatric disorder has also been highlighted as a risk factor for depression after TBI [26]. Regarding epilepsy, a metanalysis by Yang et al. demonstrated female sex and anxiety disorder as risk factors for the development of the depressive disorder in the context of epilepsy [27].

Our research elucidated a correlation between PSD in the acute phase of the ischemic stroke and factors that evaluated stroke severity such as NIHSS, mRS, and stroke area calculation. A German study evaluated a small sample of patients with transient ischemic attack and stroke in the acute phase and elucidated that HADS-D levels were not associated with NIHSS [28]. In contrast, a Ghanaian study evidenced that NIHSS and mRS were associated with PSD [10]. The assessment of the stroke severity by measuring the stroke area was applied a few times in previous studies about PSD. Studies by Nys et al. [29] and Sharpe et al. [30] identified an association between stroke volume and depressive symptoms after stroke. In opposition, a study by Herrmann did not show an association between the lesion volume and depression after stroke [31].

Regarding the relationship between the laterality of the lesion and the development of PSD, there is no consensus in the literature. In contrast, when the lesion topography was evaluated, the frontal lobe was pointed out by many studies as a risk factor for PSD in the acute phase [32] and three-to-six months after stroke [33]. Our study revealed no relationship between the frontal lobe lesion and the development of PSD in the acute phase. Interestingly, we have identified the parietal lobe lesion as a protective factor for the development of PSD. No description of this data was found in the previous literature and the mechanisms related to this unforeseen association require investigation in future studies.

Another unexpected protection factor identified in our research was the previous history of hypertension. Most studies that investigated hypertension and its relationship with PSD did not demonstrate a relationship between both conditions [10,34]. The finding of our study demands exploration in further studies, including data about antihypertensive medication compliance.

The present study has limitations to be considered. This research was conducted in a specialized neurology center, which may lead to a selection bias as it included potentially critically ill patients. Moreover, most of the sample consisted of mild to moderate strokes, therefore data could not be generalized to more severe strokes. Furthermore, the relatively small sample size could have diminished the influence of some variables potentially associated with PSD, such as the frontal lobe lesion. To our knowledge, this is the first cross-sectional research about PSD in the acute phase of the ischemic stroke conducted in the COVID-19 pandemic period.

5. Conclusion

This research evidenced a high prevalence of PSD in the acute phase of ischemic stroke. To our knowledge, this study is the first cross-sectional survey that sought to investigate PSD during the hospitalization of AIS patients in the COVID-19 pandemic. Despite the pandemic could have influenced the PSD profile, our data remained similar to the non-pandemic periods, except for the impact of the period with the highest incidence of COVID-19 on the severity of the HADS-D average. Sex female and PSA during hospitalization were factors associated with PSD in the acute phase. The NIHSS, mRS, and stroke area calculation were correlated with HADS-D levels. These findings are important because highlight the patients at greater risk of developing PSD during hospitalization, demanding special attention for early diagnosis and timely treatment. Furthermore, it is relevant to emphasize that stroke is treated in distinct health care settings, which emphasizes the

importance of understanding, with detail, this condition to provide information to similar services and countries. In addition, the protective factors identified in this research necessitate further elucidation in future studies.

CRediT authorship contribution statement

S. Elias: conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted. **M.L. Benevides:** conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted. **A.L.P. Martins**: analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted. **G.L. Martins**: analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted. **A.B.S.W. Marcos**: analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted. **J.C. Nunes:** conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted.

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Declarations of interest

None.

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