ORIGINAL ARTICLE

Prevalence and Association Between Cognition, Anxiety, and Depression in Patients Hospitalized with Heart Failure

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Abstract

Background: Cognitive impairment, anxiety, and depression are present in patients with heart failure (HF), but their mutual correlation in hospitalized patients is not well established.

Objectives: The aims of this study were to identify the presence of cognitive impairment and the most affected domain, to investigate possible associations of cognitive impairment with depression and/or anxiety, and to observe whether they correlated with occurrence of readmission within 30 days following hospital discharge.

Methods: This is a prospective observational study including patients with HF from a private hospital. Psychological distress and cognition were evaluated by the Hospital Anxiety and Depression Scale (HADS) and by the Mini Mental State Exam (MMSE), respectively. Clinical data were obtained from the medical record at the time of inclusion, and outpatient follow-up was performed 30 days after discharge via telephone calls.

Results: This study included 71 patients (83% men, 75 \pm 11 years). Cognitive impairment was present in 53.5% of the patients, and recall memory was the most altered cognitive domain. The proportion of possible/probable anxiety and depression was 21.1% and 34.2% in patients with cognitive impairment, respectively. However, only depression demonstrated association with cognitive impairment (p = 0.018). Cognitive impairment, anxiety, and depression showed no relationship with the occurrence of readmission within 30 days.

Conclusions: Cognitive impairment and depressive symptoms are prevalent and associated, and recall memory was the most altered cognitive domain in patients hospitalized with HF. However, there was no relationship between these factors and readmission within 30 days.

Keywords: Heart Failure; Cognitive Dysfunction; Depression; Anxiety.

Introduction

Heart failure (HF) is a debilitating and progressive disease, defined as an inability of the heart to supply oxygen demands to peripheral organs.¹ It is a major cause of morbidity and mortality that affects an increasing number of patients due to increased life expectancy.² The prevalence of HF, even in the young population, is expected to increase approximately 46% from 2012 to 2030, resulting in more than 8 million individuals affected by this disease in the United States.³ It has a great socioeconomic impact with major healthcare costs due to hospitalization, rehospitalization, and decline in patients' quality of life.

Ineffective self-care or medication prescription adherence contributes to progression of the disease and recurrent hospitalizations that can reach 20% in the first 30 days after discharge.⁴ In this scenario, successful communication between multidisciplinary health teams and patients depends on full understanding of the instructions and their reason. This requires that two major components be carefully observed: the cognitive function and mental health of these patients.⁴

Mailing Address: Luciana Diniz Nagem Janot de Matos

Hospital Israelita Albert Einstein – Av. Albert Einstein, 627, bloco D - 3ºandar, Centro de Reabilitação. Postal code: 05652-900. Morumbi, São Paulo, SP – Brazil. E-mail: luciana.matos@einstein.br Cognitive function alterations are usually diagnosed on neuropsychological testing comparing performance across various cognitive domains including learning and memory, language, visuospatial, executive function, and psychomotor. Cognitive impairment is defined by decline or loss of one of the five domains of cognitive function.^{5,6} Additionally, emotional conditions, such as anxiety and depression, are other factors that may affect attention and learning capacity in patients with HF. In these patients, symptomatic scenarios such as anxiety and depression are often observed,^{7,8} and these disorders contribute to worse health-related quality of life and increased hospitalizations.⁹ All these conditions may have direct impact on patients' ability to manage their treatment, poor medication adherence, poor self-care, and impaired functional activities of daily life.^{10,11}

Knowing the state of cognitive function and the presence of anxiety and depression in patients with HF is essential for better adaptation and control of the educational process and, consequently, greater adherence to treatment. The aims of this study were to assess the presence of disorders in cognitive function, to identify the most affected domain in patients hospitalized with HF, and to investigate possible associations between cognitive function and anxiety or depression in these patients. In addition, we evaluated whether cognitive impairment, anxiety, and depression were correlated with occurrence of readmission within 30 days following hospital discharge.

Material and methods

Study design

This is a prospective observational study conducted with 71 patients with diagnosis of HF who were hospitalized in a private hospital between May 2015 and July 2018. The individuals were routinely enrolled in the Institutional Heart Failure Protocol, and those older than 18 years, with less than 30 days hospitalization, who were clinically stable, were selected as potential subjects to be included in the study. The evaluations were carried out at through simple validated questionnaires applied by health professionals from the research team, approximately 72 hours before the day scheduled for hospital discharge.

The exclusion criteria were left ventricular ejection fraction (LVEF) greater than 50%, previous diagnosis of dementia, previous psychiatric disorders, inability to fill out the questionnaire, and refusal of participation.

Measures

Cognition evaluation

Cognition was measured by the Mini Mental State Exam (MMSE), which allows a quick assessment of cognitive functions by exploring two types of verbal and non-verbal responses.12 Verbal subtests assess temporal and spatial orientation, memory, attention, recognition, and concentration with a maximum score of 21 points. Non-verbal subtests assess visual-motor coordination and the ability to perform a specific task with a maximum score of 9 points. The results were adjusted according to the patient's years of schooling, as described by Brucki,13 applying the following criteria: 20 points for patients who were illiterate; 25 points for those with 1 to 4 years of schooling; 26.5 points for 5 to 8 years; 28 points for 9 to 11 years, and 29 points for over 11 years. The instrument is easy to apply, requires a short administration time (5 to 20 minutes), and shows a good sensitivity in screening global cognitive impairment. The score ranges from 0 to 30, and higher score values indicate higher cognitive performance.13

Anxiety and depression evaluation

Anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS), which assesses levels of anxiety and depression in a hospital setting. This is a self-assessment questionnaire that contains 14 multiple choice questions, of which 7 refer to anxiety and 7 to depression. Subscales of anxiety and depression assess the severity of emotional disorder and each item can be scored from 0 to 3, reaching a maximum of 21 points, and the higher the score, the more present the disorder. Numerical variables can be categorized as: 0- improbable (0 to 7), 1- possible (8 to 11), and 2- probable (12 to 21). In our analysis we considered the subscales grouped into improbable and possible + probable.¹⁴

Demographic, clinical, and medication data

Demographic, clinical, and medication data were collected and further verified with reviews of medical records. LVEF values were obtained from the most recent echocardiogram reports. New York Heart Association (NYHA) classification of HF class (I to IV) was applied at the time of the patient's enrolment in the study.

Readmission within 30 days

We evaluated the relationship of cognitive impairment, anxiety, and depression with the occurrence of readmission within 30 days. Patients were contacted by phone 30 days after hospital discharge to verify hospital readmission in this period.

Statistical analysis

Qualitative variables were described in general and by groups using absolute and relative frequencies. Quantitative variables were assessed for sample distribution using histograms, boxplots, and quantilequantile plots, and they were described by means and standard deviations or by medians and quartiles, depending on the presence or absence of significant asymmetry. For comparisons between groups, chisquare tests or Fisher's exact tests were used for qualitative variables, and Student's t tests (with or without correction for unequal variances) or Mann-Whitney tests were used for quantitative variables. Comparisons between domains of the MMSE were performed with the Friedman nonparametric test for paired samples, and the Spearman correlation coefficient was used to measure the association between each domain and the total score.

To assess the relationship between anxiety and depression and cognitive impairment by controlling for other variables, we adjusted binary logistic regression models in multiple approaches, which were subsequently subjected to the selection of variables by Wald's criterion. The results of the models were presented by estimated odds ratios, 95% confidence intervals, and p values. The analyses were performed with the aid of the SPSS program, considering a significance level of 5%.

Results

Baseline measurements of selected patients divided in groups by presence or absence of cognitive function impairment

We included 71 patients in the present study; of these, 58 had 12 years of schooling, and 32 were classified as having cognitive impairment. One patient had 11 years of schooling and cognitive impairment; of the 9 patients with 5 to 8 years of schooling, 4 had cognitive impairment, and, of the 3 patients with 4 years of schooling, 1 had cognitive impairment. Thus, of the total of 71 cases, 38 were classified as having cognitive impairment.

The baseline characteristics of patients with and without cognitive impairment are show in Table 1. Cognitive impairment was present in 53.5% of patients, and most of them were men. We observed that patients with cognitive impairment were older than those without. Although the most prevalent etiology of myocardiopathy in both groups was ischemic, the group without cognitive impairment had a higher proportion of individuals with idiopathic etiology (30.3%), while the group with cognitive impairment had a higher proportion of individuals with hypertensive etiology (15.8%). The main cause of hospitalization in both groups was clinical decompensation of HF. The group with cognitive impairment had a higher proportion of individuals using statin, and the group without cognitive impairment using amiodarone. There were no differences between groups in relation to body mass index, years of schooling, presence of previous acute myocardial infarction, hypertension, diabetes mellitus, and functional class (Table 1).

MMSE domains affected in hospitalized patients with HF

In addition to assessing the cognitive function of hospitalized patients with HF, we also analyzed the most affected domain in this population. We observed a statistically significant correlation of MMSE domains between themselves, but the domain with greatest impact on MMSE total score was "recall memory", which is short-term memory (Table 2).

Association of cognitive impairment and anxiety/ depression in hospitalized patients with HF

The relationship of anxiety and depression (HADS questionnaire) with the presence of cognitive impairment is shown in Table 3. We did not observe evidence of a significant association of the classification (qualitative variables) of anxiety and depression with cognitive impairment. The proportion of possible/ probable anxiety in the group without cognitive impairment was 33.3%, and in the group with cognitive impairment it was 21.1%. The proportion of possible/probable depression was 18.2% in the group without cognitive impairment and 34.2% in the group with cognitive impairment.

Table 1 - Clinical characteristics of selected patients

	Cognitive impairment			
	No (n=33)	Yes (n=38)	Total	
Sex				0.3170
Female	4 (12.1%)	8 (21.1%)	12 (16.9%)	
Male	29 (87.9%)	30 (78.9%)	59 (83.1%)	
Age (years)				0.0061
Mean ± SD	71 (12)	78 (9)	75 (11)	
Minimum to maximum	30 - 90	55 - 96	30 - 96	
BMI (kg/m²)				0.741
Mean ± SD	28.5 (4.9)	28.1 (5.1)	28.3 (4.9)	
Minimum to maximum	20.0 - 40.8	18.5 - 41.5	18.5 - 41.5	
Schooling (years of study)				0.510
Mean ± SD	12 (12; 12)	12 (12; 12)	12 (12; 12)	
Minimum to maximum	4 - 12	4 - 12	4 - 12	
Previous AMI				0.3090
No	17 (51.5%)	15 (39.5%)	32 (45.1%)	
Yes	16 (48.5%)	23 (60.5%)	39 (54.9%)	
Hypertension				0.0910
No	13 (39.4%)	8 (21.1%)	21 (29.6%)	
Yes	20 (60.6%)	30 (78.9%)	50 (70.4%)	
Diabetes mellitus				0.5699
No	17 (51.5%)	17 (44.7%)	34 (47.9%)	
Yes	16 (48.5%)	21 (55.3%)	37 (52.1%)	
HF etiology				0.005 ¹
Idiopathic	10 (30.3%)	1 (2.6%)	11 (15.5%)	
Ischemic	20 (60.6%)	26 (68.4%)	46 (64.8%)	
Hypertensive	2 (6.1%)	6 (15.8%)	8 (11.3%)	
Valvular	1 (3.0%)	3 (7.9%)	4 (5.6%)	
Others	0 (0.0%)	2 (5.3%)	2 (2.8%)	
NYHA functional class				0.179 ¹
Ι	6 (18.2%)	2 (5.3%)	8 (11.3%)	
II	15 (45.5%)	25 (65.8%)	40 (56.3%)	
III	9 (27.3%)	10 (26.3%)	19 (26.8%)	
IV	3 (9.1%)	1 (2.6%)	4 (5.6%)	

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Causes of hospitalization				0.317 ^Q
Clinical decompensation	29 (87.9%)	30 (78.9%)	59 (83.1%)	
Others	4 (12.1%)	8 (21.1%)	12 (16.9%)	
LVEF				0.036 ^M
Mean (first; third quartile)	0.35 (0.25; 0.40)	0.40 (0.30; 0.44)	0.35 (0.27; 0.41)	
Minimum to maximum	0.20 - 0.50	0.23 - 0.50	0.20 - 0.50	
Medications				
ACEI/ARA				0.788 ^Q
No	12 (36.4%)	15 (39.5%)	27 (38.0%)	
Yes	21 (63.6%)	23 (60.5%)	44 (62.0%)	
Beta-blocker				0.240 ^Q
No	13 (39.4%)	10 (26.3%)	23 (32.4%)	
Yes	20 (60.6%)	28 (73.7%)	48 (67.6%)	
Statin				0.028 ^Q
No	15 (45.5%)	8 (21.1%)	23 (32.4%)	
Yes	18 (54.5%)	30 (78.9%)	48 (67.6%)	
Aldosterone antagonist				0.244 ^Q
No	22 (66.7%)	30 (78.9%)	52 (73.2%)	
Yes	11 (33.3%)	8 (21.1%)	19 (26.8%)	
Diuretic				>0.99 ^F
No	3 (9.1%)	3 (7.9%)	6 (8.5%)	
Yes	30 (90.9%)	35 (92.1%)	65 (91.5%)	
Amiodarone				0.027 ^Q
No	19 (57.6%)	31 (81.6%)	50 (70.4%)	
Yes	14 (42.4%)	7 (18.4%)	21 (29.6%)	

ACEI/ARA: angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist; AMI: acute myocardial infarction; BMI: body mass index; F: Fisher's exact test; HF: heart failure; LVEF: left ventricular eject fraction; M: Mann-Whitney test; NYHA: New York Heart Association; Q: chi-square test; SD: standard deviation; T: Student's t test.

Table 2 – Affected Mini-Mental domains in hospitalized patients with HF

	Spatial orientation	Immediate memory	Attention and calculation	Recall memory	Language
Temporal orientation	0.689	>0.99	0.989	<0.001	>0.99
Spatial orientation		>0.99	0.002	<0.001	>0.99
Immediate memory			0.006	<0.001	>0.99
Attention and calculation				0.014	0.619
Recall memory					< 0.001

HADS state -				
	No	Yes	Total	P value
Anxiety				0.244 ^Q
Improbable (0-7)	22 (66.7%)	30 (78.9%)	52 (73.2%)	
Possible + probable (8-21)	11 (33.3%)	8 (21.1%)	19 (26.8%)	
Anxiety				0.438 ^M
Median (first; third quartile)	4 (2; 9)	6 (4; 7)	5 (3; 8)	
Minimum to maximum	0 - 17	0 - 16	0 - 17	
Depression				0.128 ^Q
Improbable (0-7)	27 (81.8%)	25 (65.8%)	52 (73.2%)	
Possible + probable (8-21)	6 (18.2%)	13 (34.2%)	19 (26.8%)	
Depression				0.010 ^M
Median (first; third quartile)	4 (1; 6)	6 (4; 8)	5 (2; 8)	
Minimum to maximum	0 - 13	1 - 18	0 - 18	

When we consider anxiety and depression scores as quantitative variables, we have evidence of differences between groups just for depression, with the depression score being higher among those with cognitive impairment (p = 0.010).

To investigate the association between cognitive impairment and anxiety or depression, we performed multiple logistic regression models by controlling non-homogeneous characteristics between the groups, such as age, etiology of HF, and LVEF, and we found no evidence of a significant association between the presence of cognitive impairment and anxiety (Table 4). For the model that considers the chance of a possible/probable outcome for depression, we found that there was evidence of a significant association between the presence of cognitive impairment and depression (p = 0.018)

Relationship of cognitive impairment, anxiety and depression with the occurrence of readmission within 30 days

As a secondary objective, we evaluated the relationship of cognitive impairment, anxiety, and depression with the occurrence of readmission within 30 days, and we found no evidence of a significant association in the proportion of hospitalization within 30 days in the categories (Table 5).

Discussion

The main findings of this study were that 53.5% of the hospitalized patients with HF had cognitive function impairment, and the most affected MMSE domain was recall memory. There was a significant association between cognitive impairment and depression in these patients, evaluated by the HADS questionnaire. Moreover, we found no evidence of a significant association of cognitive impairment, anxiety, and depression with the occurrence of readmission within 30 days.

Cognitive impairment has been described in patients with HF in several studies over the past decades, with strong association between these factors and a negative impact on engagement in self-care and medication management.^{5,15} We found the prevalence of cognitive deficit in individuals with HF to be 53.5%, values similar to those found in the literature, which can vary from 25% to 84%¹⁶⁻¹⁹ depending on the population evaluated. Some factors may explain this wide prevalence range, such as the definition of cognitive impairment, the NYHA

Table 4 – Multiple model adjusted for anxiety and depression

	Odds ratio Possible/probable anxiety (95% CI)	P value
Initial model		
Cognitive impairment		
No	Reference	
Yes	1.215 (0.304; 4.850)	0.783
Age (years)	0.928 (0.859; 1.002)	0.055
Etiology of HF		
Idiopathic	Reference	
Ischemic	0.173 (0.032; 0.949)	0.043
Hypertensive	0.611 (0.062; 5.990)	0.672
Valvular	1.100 (0.083; 14.558)	0.942
LVEF	0.992 (0.921; 1.068)	0.830

Model after variable selection			
Age (years)	0.918 (0.863; 0.978)	0.008	
	Odds ratio Possible/probable depression (95% CI)	P value	
Initial model			
Cognitive impairment			
No	Reference		
Yes	7.752 (1.532; 39.233)	0.013	
Age (years)	0.944 (0.884; 1.009)	0.090	
Etiology of HF			
Idiopathic	Reference		
Ischemic	0.622 (0.089; 4.357)	0.633	
Hypertensive	0.998 (0.079; 12.616)	0.999	
Valvular	0.525 (0.025; 11.132)	0.679	
LVEF	0.938 (0.870; 1.012)	0.100	
Model after variable selection			
Cognitive impairment			

No	Reference	
Yes	5.076 (1.320; 19.524)	0.018
Age (years)	0.930 (0.875; 0.989)	0.020

CI: confidence interval; HF: heart failure; LVEF: left ventricular ejection fraction.

	Readmission within 30 days		Р
	No	Yes	value
Cognitive impairment			0.737 ^Q
No (n=30)	21 (70.0%)	9 (30.0%)	
Yes (n=38)	28 (73.7%)	10 (26.3%)	
Anxiety			>0.99 ^F
Improbable (n= 51)	37 (72.5%)	14 (27.5%)	
Possible + probable (n=17)	12 (70.6%)	5 (29.4%)	
Depression			0.986 ^c
Improbable (n=50)	36 (72.0%)	14 (28.0%)	
Possible + probable (n=18)	13 (72.2%)	5 (27.8%)	
Total	49 (72.1%)	19 (27.9%)	

functional class at the time of the test, the age of the patients, their educational level, and the difference in the hospitalization status of the patients, whether in- or outpatients.⁴ Unlike our cohort, most studies included outpatients, who may be more clinically stable. Patients with HF have 4 times more risk of having cognitive impairment compared with normal controls.¹⁶ Furthermore, we found that the most impaired cognitive domain was recall memory. These data corroborate data from other studies with patients with HF, in which memory was the most affected domain.^{16,17,20} This could possibly be explained and influenced by the patients' mean age.

Different mechanisms may explain the role of the cognitive impairment seen in patients with HF, and it is not totally clear whether the increased risk is due to the clinical syndrome of HF itself or to vascular risk factors.²¹ Some of the well-known factors include impaired or reduced vascular blood flow, chronic or intermittent cerebral hypoperfusion, or microembolisms, leading to ischemic damage and altered function.^{21, 22} Thus, the coexistence of systemic vascular disease is linked to poor cognition, and it is reasonable to suspect that the higher proportion of individuals with hypertensive and ischemic HF etiology observed in our sample is related to this decline. Another possible explanation is the low levels of albumin observed in cachexia in end-stage HF, which is already known to be independently associated with poor cognition.²³ Hypoxia, inflammatory cytokines, and cardioembolic disease with atrial fibrillation, which are often seen in end stages of HF, may also be another explanation for cognitive decline in patients with HF.²⁴⁻²⁵ Indeed, it is known that there is a strong association between the presence of atrial fibrillation and an increased risk of cognitive decline.²⁶ In our sample, we observed more frequent use of amiodarone in the patients without cognitive impairment. Intuitively, it is possible to think that the use of this medication may have controlled the atrial fibrillation in these patients. Another important point is that we observed a higher use of statin in the patients with cognitive impairment. There is a certain concern regarding the use of statin and cognitive impairment since some studies report forgetfulness, confusion, and other forms of cognitive impairment. However, none of these symptoms have been shown to be severe, and most reversed with interruption of statin therapy.²⁷⁻²⁹ Other investigators reported no evidence that statin caused cognitive impairment.^{30,31} It is worth noting that the real link between these effects and the use of statin is not well established.²⁹ Explanations for this question are outside the scope of our study; nonetheless, we believe that the cause of this cognitive impairment is not unifactorial, and it may be related to cerebral hypoperfusion, decompensation of HF, and hospitalization of the patients.

Psychiatric disorders such as anxiety and depression are symptomatic scenarios common observed in patients with cognitive impairment, and they have been shown to be a determining factor in memory impairment in HF. In the adequate care for patients with HF, it is important to detect these symptoms, as they can contribute to poor health-related quality of life, exacerbating HF symptoms, hospitalizations, readmissions, and even mortality rates.³²⁻³⁴ Depression is considered an independent risk factor of cardiac incidents and death, as well as a strong predictor of readmission. Anxiety seems to be an adequate predictor only in conjunction with depression.35 In the literature, it has been shown that depressive and anxious symptoms often coexist in patients with HF, with a 35% prevalence of depressive symptoms and a 56% prevalence of anxiety.36

It is conceivable that hospitalization may add to depressive and anxious mood states. This is supported by a study showing that only 10% of outpatients with HF presented depressive symptoms. On the other hand, studies that included inpatients, detected 40% to 70% of patients as being in depressive mood.^{37,38} Acute states of illness interfere negatively with mood and, consequently, cognition, since they may coexist, be related,³⁹ and affect self-care.⁴⁰ In this study, we observed that there was evidence of a significant association between the presence of cognitive impairment and depression in hospitalized patients with HF. In contrast, we found no evidence of a significant association with anxiety.

Despite the possible interference of hospitalization with the high prevalence of depression, the correlation between depressive symptoms and cognitive impairment in patients with HF has been described,^{20,39} and it is associated with worse clinical outcome, especially related to exercise capacity, disease progression, and recurrent hospitalizations. Depression symptoms are predictive factors for developing HF or other cardiovascular diseases.^{35,41} HF decompensation can promote barriers to self-care, poor medication adherence, low physical activity,40 and increased mortality,41 triggering impaired mental health.42 These findings make evident the importance of considering patients with HF holistically, identifying mood disorders and their associated causes to provide support according to their needs. Thus, mental health cannot be viewed as secondary; rather, it must be evaluated and treated in the general context of the disease, as it has an impact on short- and long-term self-care, as well as on economic aspects.

Although both anxiety and depression are related to higher risk of readmission, we did not see any association of these factors and cognitive impairment with the occurrence of readmission within 30 days. In our hospital, all pharmacological and non-pharmacological recommendations are offered in writing to patients and their caregivers. This practice may have been responsible for greater involvement of patients in their care after hospital discharge. Furthermore, it is important to highlight that the studied population had a high social level, with great access to health and, probably, assistance support.

However, it can be considered that the screening for mood disorders, such as depression and anxiety, during hospitalization for HF, as well as recognition of cognitive deficits are fundamental to patients' longterm well-being. The guidance offered is important to obtain good results in the continuous treatment after hospital discharge and to reduce hospital readmissions, promoting higher quality of life.

Study Limitations

We recognize many limitations in our study. We highlight that this study was conducted in a private hospital, and the participants had higher educational and socioeconomic characteristics with more access to assistance support. Moreover, we are aware that MMSE is not considered an effective diagnostic evaluation for cognitive impairment; however, it is a quick and easy measure that does raise important information about the participants' cognition status, and it can help to screen early possible alterations to their global cognitive status, which is extremely important for maintaining the treatment and well-being of patients. Finally, there was a short follow-up time of 30 days after hospital discharge.

Conclusions

This study highlighted the importance of cognitive impairment and its prevalence in the population with HF, with recall memory being was the most affected domain. This deficit appears to more specifically associated with depressive symptoms. However, this study demonstrated that the cognitive decline was not associated with the occurrence of readmission within 30 days.

Author contributions

Conception and design of the research: Soares VL, Pereira C, Carvalho AC, Mota TP, de Matos LDNJ; acquisition of data: Soares VL, Pereira C, Carvalho AC, Mota TP; analysis and interpretation of the data: Soares VL, Pereira C, Carvalho AC, Mota TP, Groehs RV, Bacal F, de Matos LDNJ; statistical analysis: Groehs RV; writing of the manuscript: Groehs RV, de Matos LDNJ; critical revision of the manuscript for intellectual content: Groehs RV, Bacal F, de Matos LDNJ.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Research Ethics Committee at the Hospital under the protocol number CAAE: 68426117.3.0000.0071.

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