Diagnostic yield of magnetic resonance imaging in heart failure with left ventricular dysfunction?

Devemos Realizar Ressonância Magnética Cardíaca em Pacientes com Insuficiência Cardíaca e Disfunção Ventricular sem Diagnóstico Etiológico Definido?

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Abstract

Background: Heart failure with reduced ejection fraction is responsible for half of heart failure cases worldwide and implicates in substantial morbidity and mortality. However, even with clinical history and physical examination associated with conventional complementary exams, many patients remain without etiological diagnosis. Cardiac magnetic resonance has offered the possibility to clarify a variable proportion of these cases.

Objective: To verify how much cardiac magnetic resonance contributes to etiologic diagnosis of heart failure with left ventricular ejection fraction <50% in a specialized service.

Methods: We included individuals referred to cardiac magnetic resonance with heart failure and left ventricular ejection fraction <50% by transthoracic echocardiogram, without defined etiology, from January, 2017 to June, 2018 in a tertiary hospital.

Results: The sample consisted of 87 patients, with average age of 45±16 years, 49% male and left ventricular ejection fraction 32%±13. Of the patients, 55,3% had etiological diagnosis through cardiac magnetic resonance: 33,4% myocarditis, 11.5% non-compaction cardiomyopathy, 6.8% Chagas disease, and for hypertensive heart disease, amyloidosis and arrhythmogenic right ventricle dysplasia, 1,2% each. Late gadolinium enhancement was positive in 61% and non-ischemic pattern predominated (50,5%). Reverse remodeling occurred with normalization of ventricular function in 13% of patients.

Conclusion: The performance of cardiac magnetic resonance in patients without etiologic diagnosis of HF with left ventricle dysfunction is clinically significant, since it contributed more than 50% of the time to the etiology and prognosis of patients. This positive impact occurred in a tertiary cardiology teaching service, so it is possible that in other circumstances the role of the cardiac magnetic resonance may be even greater than that here presented.

Keywords: Heart failure; Cardiomyopathy, dilated; Diagnostic imaging; Magnetic resonance.

Resumo

Fundamento: A insuficiência cardíaca com fração de ejeção reduzida é responsável por metade dos casos de insuficiência cardíaca no mundo e associada à morbidade e à mortalidade substanciais. Contudo, mesmo com história clínica e exame físico associados a exames complementares convencionais, muitos pacientes permanecem sem diagnóstico etiológico. A ressonância magnética cardíaca oferece a possibilidade de esclarecer esses casos.

Objetivo: Verificar em que medida a ressonância magnética cardíaca contribui com o diagnóstico etiológico da insuficiência cardíaca com fração de ejeção do ventrículo esquerdo <50% em um serviço especializado.

Métodos: Foram incluídos indivíduos encaminhados para ressonância magnética cardíaca com insuficiência cardíaca e fração de ejeção do ventrículo esquerdo <50% ao ecocardiograma transtorácico, sem etiologia definida, de janeiro de 2017 a junho de 2018, em hospital terciário.

Resultados: A amostra foi constituída de 87 pacientes, com idade média de 45±16 anos, sendo 49% do sexo masculino e fração de ejeção do ventrículo esquerdo 32%±13. Tiveram diagnóstico etiológico por meio da ressonância magnética cardíaca 55,3% dos pacientes: 33,4% miocardite, 11,5% cardiopatia não compactada, 6,8% cardiopatia chagásica e 1,2% para cardiopatia hipertensiva, amiloidose e displasia

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arritmogênica do ventrículo direito, cada. O realce tardio miocárdico foi positivo em 61%, e predominou o padrão de realce tardio não isquêmico (50,5%). Houve remodelamento reverso com normalização da função ventricular em 13% dos pacientes.

Conclusão: O rendimento da ressonância magnética cardíaca em pacientes sem diagnóstico etiológico da insuficiência cardíaca com disfunção ventricular é significativo do ponto de vista clínico, pois contribuiu, em mais de 50% das vezes, com a etiologia e o prognóstico dos pacientes. Esse impacto positivo ocorreu em serviço terciário e de ensino em cardiologia, sendo possível que, em outras circunstâncias, o papel da ressonância magnética cardíaca seja inclusive maior do que o aqui apresentado.

Palavras-chave: Insuficiência cardíaca; Cardiomiopatia dilatada; Diagnóstico por imagem; Ressonância magnética.

Introduction

Heart failure with reduced ejection fraction (HFREF) is responsible for half of the cases of hospitalization for heart failure (HF). Ischemic heart disease is the main cause of HFREF, but several other conditions can result in systolic ventricular dysfunction.[1-6] The initial evaluation (physical, laboratory, and echocardiography) elucidates the cause in most cases, but many patients remain undiagnosed and are often classified as having idiopathic dilated cardiomyopathy (IDC).[7]

IDC is defined as left ventricular (LV) dilation and systolic dysfunction with no coronary artery disease (CAD) or abnormal ventricular overload.[1] The social and economic impact of adverse events caused by this cardiomyopathy is amplified by more often affecting people in the first few decades of life.[2] In this context, the establishment of a defined etiology can not only drive different therapeutic management, it can also provide prognostic information for the patient, family, and society.

Cardiac magnetic resonance (CMR) imaging can determine the etiology of certain cardiomyopathies through morpho-functional evaluation and delayed gadolinium enhancement (DGE) presence and pattern.[8-11] The detection of a nonischemic DGE pattern can exclude coronary angiography, saving resources and avoiding complications inherent to an invasive procedure with significant potential for contrast nephropathy. This screening may be even more relevant in HFREF patients since more than half have no significant CAD.[3,4]

This study aimed to evaluate the potential contribution of CMR in the diagnosis of HF with systolic ventricular dysfunction without a defined etiology in a referral hospital for cardiovascular diseases.

Methods

This study involved the retrospective selection of all CMR examinations performed between January 2017 and June 2018 at Ana Nery Hospital, a tertiary reference center of the Unified Health System in Salvador, BA, Brazil. This service has a Medical Residency Program in Cardiology. The study population consisted of patients with HF and an ejection fraction < 50% (previously determined on transthoracic echocardiography [ECHO]), with no etiology defined at the initial evaluation who were referred to the CMR for diagnostic research (Figure 1).

The exclusion criteria were known history of CAD, myocardial infarction, or previous revascularization; primary valve disease; known history of hypertrophic cardiomyopathy or congenital heart disease; and previously defined cardiomyopathy diagnoses.

Magnetic resonance imaging

All patients underwent CMR using a 1.5 T device (Avanto, Siemens Medical Solutions, Germany). An eight-channel coil was used to receive the signals. Exploratory images were obtained to guide four-, three-, and two-chamber image acquisitions. Ventricular short-axis cine steady-state free precession magnetic resonance imaging (MRI) synchronized with electrocardiography was obtained in apnea, with 20 images per cardiac cycle. The acquisition parameters included 8-mm slice thickness, 300 of field of view, and 128 × 128 matrix. Image sets were acquired using 8–12 short-axis slices (8-mm slice thickness with 2 mm between cuts) to cover the entire cardiac volume. After the administration of a bolus of contrast (gadoteric acid 0.5 mmol/mL) at a dose of 0.2 mmol/kg, T1-weighted images were acquired using an inversion-recovery sequence and a rapid gradient-echo with small angle excitation (4.8-ms echo; 1.4 × 2.4 × 7 mm voxel size, 20º flip angle).

Morpho-functional and tissue findings

Dynamic images were acquired using the cine MRI technique with gradient-echo sequence to study the functional and morphological aspects of the heart. DGE was used to evaluate the regions affected by myocardial fibrosis, which were classified into two patterns, ischemic (subendocardial or transmural DGE in coronary territory) and nonischemic (other patterns).

Diagnostic criteria

Myocarditis and pericarditis: The presence of myocardial DGE of meso- or epicardial pattern associated or not with T2 hypersignal (edema) was considered the criterion for myocarditis, while the presence of DGE and T2 hypersignal in pericardial topography was the criterion for pericarditis, often associated with pericardial effusion.

Non-compaction cardiomyopathy (NCC): Suggested by the presence of trabeculation, with a non-compaction to compaction myocardium thickness ratio > 2.3 and a non-compaction myocardium mass > 15 g/m² or > 25% of the LV mass.

Hypertensive cardiomyopathy: The diagnosis was suggested by the clinical association of hypertension with concentric LV hypertrophy and minimal or no DGE.

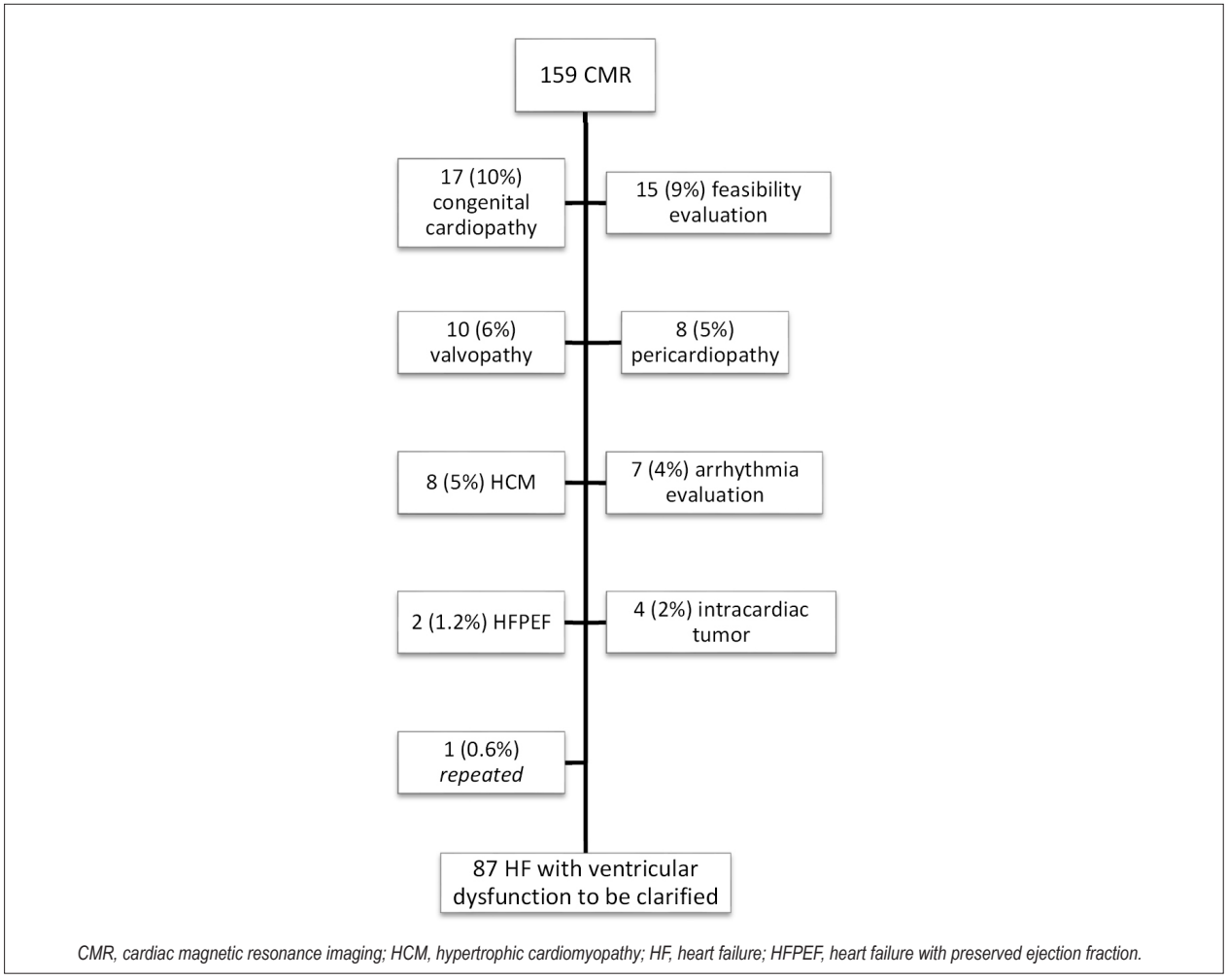


Figure 1 – *Patient selection flowchart.*

Amyloidosis: Presence of concentric ventricular hypertrophy, often associated with biatrial enlargement, with global circumferential subendocardial DGE or difficulty canceling the myocardial signal in this sequence.

Arrhythmogenic right ventricular cardiomyopathy: The imaging Task Force Criteria were followed.[12]

Chagas cardiomyopathy: The pattern of inflammatory cardiomyopathies (such as myocarditis) was followed, with the peculiarity of presenting apical and lateral aneurysms in addition to predominant fibrosis in basal and/or apical inferolateral segments, often extensive and large, associated with any DGE patterns (subendocardial, endocardial, subepicardial, and transmural), making the diagnosis highly suggestive of the disease.

Ethical aspects

The present study was observational and retrospective and in no way influenced any patient's clinical management. Despite this, it was approved by the Ethics Committee since it guaranteed privacy in the use of medical record data and respecting the best practices of use of medical information. Any information considered potentially important for clinical practice would be passed on to the attending physicians, who would decide the best course of action.

Statistical analysis

Categorical data are expressed as number and percentage, while continuous data are shown as mean ± standard deviation. The test version of the Statistical Package for Social Science software (IBM) was used for the analyses.

Results

A total of 159 patients underwent CMR in the referral period. Of them, 87 (54%) had an indication for diagnostic evaluation of cardiomyopathy (Figure 1).

The study population was predominantly young, with a mean age of 45 ± 16 years and equally distributed by sex. The presence of risk factors for CAD showed that 35% had hypertension, 9% had diabetes, 8% had dyslipidemia, 8% were smokers, and none had a history of stroke or acute myocardial infarction.

As for the functional evaluation by CMR, the mean LV ejection fraction was 32%. There was a high occurrence of regional motility dysfunction and moderate to severe mitral regurgitation. Desynchrony (inter- and intraventricular) was present in 10% of cases, with three patients in functional class (FC) III (with LVEF by CMR of 16–32% in resynchronizer preimplantation evaluation, with one of extensive fibrosis, one of septal fibrosis, and one of absent fibrosis). The others were asymptomatic or had an FC II at the time of the CMR (LVEF by CMR of 48–60% with little or no fibrosis).

Other variables such as mean left atrial diameter and indexed LV diastolic volume are described in Table 1.

Table 1 – Function, delayed enhancement research, and ventricular diameter determined on cardiac magnetic resonance (N = 87).

Variable	
Left ventricular ejection fraction	32±13
Indexed final diastolic volume, mL/m²	156±84
Left atrium, mm	40±8.8
Moderate to severe mitral regurgitation	36.9
Abnormal cine magnetic resonance imaging (regional wall motility)	90.2
Desynchrony	10

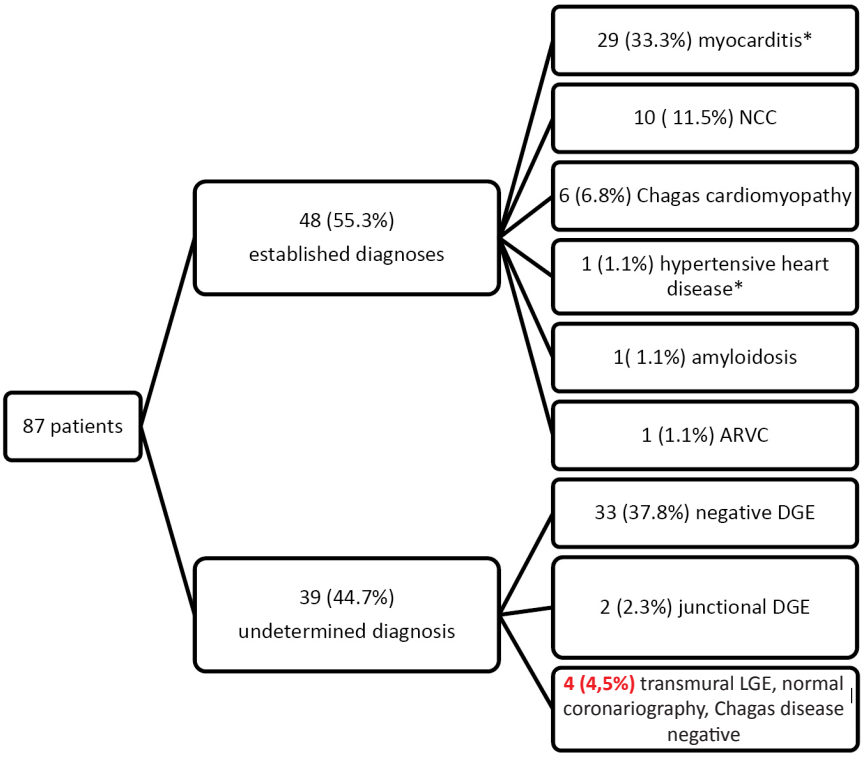
Results are expressed as mean ± standard deviation or %.

A total of 53 (61%) patients had a positive DGE. Of them, the DGE pattern was nonischemic in 44 (50.5%) and ischemic (subendocardial or transmural) in nine (10.3%), three of whom normal coronary arteries, five of whom had presumed Chagas heart disease, and one of whom had amyloidosis.

CMR identified a specific or very suggestive pattern of the HF etiology with ventricular dysfunction in 48 patients (55.3%) (Figure 2). Of the established diagnoses, 38.6% corresponded to diseases with a presumed less unfavorable prognosis (myocarditis, normal CMR, and hypertensive heart disease).

LVEF normalization by CMR (reverse remodeling) was seen in 12 (13.8%) patients who had a previous mean LVEF on ECHO of 40% (the mean interval between the ECHO and CMR exams was 5.5 months). CRM diagnoses in this group were represented by three myocarditis cases and nine undiagnosed cases (four progressed from a dysfunctional ECHO to a normal CMR, one had ischemic DGE with normal scintigraphy, and four had no fibrosis). All reverse remodeling cases were treated with optimized HF medical therapy.

In 39 (44.7%) patients, CMR information was insufficient for a significant diagnostic contribution, of which 33 (37.8%) had a negative DGE, two had junctional DGE, and four ischemic DGE, but with significant CAD excluded by complementary tests and negative Chagas



**Presumed less unfavorable prognosis. ARVC, arrhythmogenic right ventricular heart disease; DGE, delayed gadolinium enhancement; NCC, non-compaction cardiomyopathy.*

Figure 2 – *Diagnostics established by cardiac magnetic resonance in 87 patients with heart failure and ventricular dysfunction under etiological investigation.*

serology (Figure 2). In this group, 15 (46.8%) patients underwent previous coronary angiography, which revealed no coronary obstructions.

Discussion

This study highlights the importance of CMR in elucidating the etiopathogenesis of IDC without a defined etiological diagnosis. Despite the undetermined initial clinical and complementary tests, CMR helped identify the etiology in 55.3% of cases. In Brazil, there are no data that assertively address this issue. Maron et al.[8] and Parsai et al.[9] claim that approximately 50% of cardiomyopathy etiologies remain unknown, with 20–30% being possibly attributable to genetic causes. In such circumstances, CMR can be a useful diagnostic tool in the decision-making process as an intermediate or even definitive step.

The presence of DGE was consistent with the data on with HFREF patients.[3,11,13] It should be noted that the presence of DGE alone is associated with a threefold increase in mortality and hospitalization rates regardless of LVEF.[13] However, the predominance of the nonischemic DGE pattern did not corroborate the findings of other studies.[3,14,15,16] This may be partly related to the predominance of young patients without CAD as well as the large percentage of patients with myocarditis.

The considerable occurrence of diagnoses with a presumed less unfavorable prognosis highlights the relevance of CMR as an instrument to guide the progressive characteristics of diseases in HF. Defined or suggested diagnoses can assist doctors, patients, and family members with therapeutic/social planning and improve prognostic information.

The NCC diagnosis in 11.5% of patients may not necessarily constitute a specific etiological diagnosis. According to some authors, it can correspond to the common final pathway of several heart diseases[18] and indicate hypertrabeculation instead of genetic disease (which must be associated with other clinical data). Thus, even if it does not show other secondary causes of HF, distinguishing between adaptive hypertrabeculation and true NCC (familial or sporadic, primary or triggered by overlapping heart disease) is a challenge.

Patients without a defined diagnosis and negative DGE may have idiopathic IDC. This is partly because IDC shows no fibrosis on CMR (it classically presents as septal wall linear mesocardial DGE).[19] However, it is worth recalling other causes of ventricular dysfunction and dilation that usually present no DGE, such as alcoholic, peripartum, and Takotsubo cardiomyopathy.[1,8] The correlation with clinical history is greatly important to excluding such secondary cardiomyopathies. The absence of DGE, despite contributing little to the diagnosis, is an important piece of information in the clinical follow-up. These patients have a lower chance of adverse events and a better response to ventricular resynchronization therapy when necessary.[2]

As for other cases without defined etiology, the junctional DGE found in two patients can be justified by pressure overload secondary to IDC or, less likely, final-stage HCM with dilation.

In this study, CAD was previously excluded by the attending physicians as a cause of cardiomyopathy, but 11% of the tests presented ischemic DGE. Most of them suggested Chagas cardiomyopathy (six patients, later confirmed by new serology); however, four patients had negative serological tests despite positive epidemiology. These cases may correspond to serological false negatives or the lack of a second serology confirmation since there are no other classical causes of segmental fibrosis besides myocardial infarction and Chagas cardiomyopathy, especially in patients from endemic areas.

The absence (or little extension) of fibrosis is associated with a greater chance of reverse remodeling.[1,2] This premise was verified in the present study, with 13.8% of patients presenting normalized ventricular function and, of them, only two had small-sized positive DGE.

In addition to the more favorable prognosis inherent to this group of patients, the relevant role of optimized drug treatment in HF stands out in all patients.

The proportion of patients with normal CMR despite a previous ECHO revealing a reduced ejection fraction and a past history of HF symptoms corresponds to cases of myocarditis with good progression and ventricular function recovery. According to the risk classification of myocarditis, patients with low-risk syndromes (mild to moderate dysfunction without associated ventricular arrhythmias) usually present no symptoms and recover function in 1–4 weeks.[17] However, the great operator-dependency of ECHO was maximized in the present context since these tests were received from different services.

The patients in the present study were a decade younger and had fewer risk factors for CAD than what has been described in the literature for HF patients.[3-6] These data corroborate the probable definition of undetermined diagnoses as being idiopathic IDC, as it is established that this cardiomyopathy often affects people in the first few decades of life.[2]

In the context of IDC research, CMR may play a restrictive (gatekeeper) role in indicating coronary angiography in HFREF patients, since more than half have no significant CAD.[3,4] Thus, coronary angiography would not be necessary in patients without a defined etiology and nonischemic DGE. In HF, in addition to being susceptible to vascular complications and bleeding, the risk of nephrotoxicity and relevant morbidities should be considered, especially in patients with more severe disease.

The relevance of CMR in the proposed patient profile was researched in a specialized tertiary center. Its usefulness is likely to be even greater in clinical practice, in which non-specialists manage HF.

Limitations

The limitations of the present study include its small sample size and retrospective characteristics. In addition, patients with a borderline ejection fraction were included, as many showed an improved ejection fraction on CMR, a finding that requires highlighting. Other limiting factors are basal ECHO data being provided by several echocardiography laboratories, while CMR

was performed only at the studied reference center by a team of three cardiologists.

Due to call failure, it was not possible to conduct new serological studies for Chagas disease in the four patients with ischemic DGE and negative coronariography who had only one previous negative serology result.

It is noteworthy that, within the analyzed period, our bioimaging service faced two prolonged equipment breakdowns, with tests paused for 8 months, in addition to another 4 months due to medical team changes in the sector, which justified the reduced mean examination production. After these situations were normalized, a mean 30 CMR procedures were performed each month.

Conclusion

The performance of CMR in patients without etiologic diagnosis of HFREF is clinically significant since it contributed to the etiology and prognosis of more than 50% of cases. This positive impact was reported in a tertiary cardiology teaching service; thus, CMR may have an even greater role in circumstances other than those presented here since non-specialists often manage HF.

Authors' contributions

Research concept and design: ATF Barreto, MLBG Bezerra, and RMV Melo; data collection: ATF Barreto, BO Isabella, VA Reis, ATF Barreto, MLBG Bezerra, and VA Reis; data analysis and interpretation: ATF Barreto, MLBG Bezerra, BO Isabella, and VA Reis; statistical analysis: ATF Barreto and RMV Melo; manuscript writing: ATF Barreto, MLBG Bezerra, RMV Melo, BO Isabella, and LCS Passos; critical review of the manuscript for important intellectual content: MLBG Bezerra, RMV Melo, and LCS Passos.

Conflict of interest

The authors have declared that they have no conflict of interest.

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