

## Assessment of Right Ventricle Function and Myocardial Fibrosis by Cardiovascular Magnetic Resonance in Patients with Inferior Wall Myocardial Infarction

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### Abstract

**Background:** Right ventricular dysfunction (RVD) can be found in 30-50% of patients with inferior wall myocardial infarction (I-MI) and predicts early mortality. Myocardial fibrosis is associated with progressive ventricular dysfunction and severe prognosis. In these patients, cardiovascular magnetic resonance (CMR) is an important risk stratification method.

**Objectives:** This study sought to evaluate the association between RVD and myocardial fibrosis in patients with I-MI, using CMR.

**Methods:** Cohort study conducted in a prominent center of cardiology. Forty individuals with I-MI were included in the study. CMR was performed during hospitalization to estimate parameters of right ventricle function and to quantify myocardial fibrosis through late gadolinium enhancement (LGE) technique. Patients were stratified by ventricular function, and clinical characteristics were compared between study groups.

**Results:** Forty patients were included in the study, 75% were male and 43% elderly (age  $\geq$  60 years). Hypertension (45%) and smoking (33%) were the most prevalent cardiovascular risk factors. RVD was found in 33% of patients. Mean fibrosis mass was  $22 \pm 12$  g in patients with RVD compared with  $15 \pm 8$  g in patients with preserved ventricular function ( $p = 0.051$ ).

**Conclusions:** The findings of our study indicate a possible association between RVD and myocardial fibrosis in patients with I-MI. However, further studies with larger series are needed to confirm our findings. (Int J Cardiovasc Sci. 2017;30(2):109-116)

**Keywords:** Myocardial Infarction; Spectroscopy; Magnetic Resonance Imaging; Fibrosis.

### Introduction

Right ventricular dysfunction (RVD) can be observed in 30% to 50% of patients with inferior wall myocardial infarction (I-MI) and it might be associated with atrioventricular block, hemodynamic instability and in-hospital mortality.<sup>1,2</sup> In these patients, early detection of right ventricle involvement plays a key role in planning the most appropriate treatment strategy and in determining favorable prognosis.<sup>1-3</sup>

The assessment of right ventricle (RV) by echocardiography is technically difficult due to the lack of an adequate acoustic window and its peculiar anatomical conformation.<sup>3,4</sup> The capability to precisely visualize the RV makes cardiac magnetic resonance (CMR) the method of choice for estimating the extent of myocardial damage and the functional impairment by means of highly accurate and reproducible measures of RV.<sup>3-6</sup>

Following myocardial infarction, cardiac remodeling involves an inflammatory reaction followed by scar

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formation at the site of infarction.<sup>7</sup> However, sustained fibrotic activity results in stiffening of the myocardium and is associated with progressive ventricular dysfunction and severe prognosis.<sup>7,8</sup> Late-gadolinium enhancement (LGE) CMR has been used extensively in a large number of studies as the technique of choice for detection and measurement of myocardial fibrosis.<sup>9-12</sup>

In patients with I-MI, therefore, CMR has been established as the gold standard imaging method for the assessment of RV function and myocardial fibrosis.<sup>9-12</sup> This study aimed to evaluate the association between myocardial fibrosis and RVD in patients with I-MI, using CMR.

## Methods

### Study population

A total of fifty-seven patients with acute ST segment elevation myocardial infarction with inferior wall involvement (ST segment elevation in D2, D3 and aVF derivations on the electrocardiography) were prospectively recruited at Ana Neri Hospital, Brazil, between January and December 2014. Patients were excluded if they had metallic implants incompatible with CMR, glomerular filtration rate (GFR) < 30 ml/min, severe claustrophobia or gadolinium hypersensitivity.

Clinical data including age, sex, family history, comorbidities and cardiovascular risk factors were retrospectively collected from patients' medical records. CMR was performed during hospitalization to estimate parameters of RV function and to quantify myocardial fibrosis. Right ventricular ejection fraction (RVEF), end-systolic volume and end-diastolic volume were measured to estimate ventricular function. LGE-CMR technique was used to measure myocardial fibrosis in the inferior wall. Patients were stratified by ventricular function, considering RVD if RVEF < 40%.

The study was approved by the ethical, institutional review board (Ana Nery Hospital Ethics Committee) and the National Ethics Committee and all patients provided written informed consent.

### CMR acquisition

Patients were scanned in the supine position and CMR studies were performed using a 1.5 T whole-body scanner (Avanto, Siemens Medical Solutions, Germany).

An 8 channel cardiac coil was used for signal reception. Scout images were obtained to plan the four-chamber, three-chamber and two-chamber views, as well as short axis cine imaging. ECG-gated steady-state free precession (SSFP) short-axis images of the ventricles were acquired during breath holds with 20 image frames per cardiac cycle. Acquisition parameters were: 8-mm slice thickness, FOV 300, matrix 128 x 128.

A stack of images, using a minimum of 8 and a maximum of 12 slices in short-axis plane (slice thickness 8-mm; gap 2-mm) was acquired, allowing coverage of the entire cardiac volume. Every effort was made to obtain adequate images with a satisfactory right ventricle depiction.

LGE-CMR enabled the assessment of myocardial fibrosis, as presented in Figure 1. After a bolus of 0.2 mmol/kg of contrast agent (Gadodiamide, Omniscan™, GE Healthcare), images were acquired using a T1-weighted segmented inversion-recovery turbo fast low-angle shot sequence (echo time 4.8 ms; voxel size 1.4×2.4×7 mm; flip angle, 20°). The inversion time was meticulously adjusted for optimal nulling of normal myocardium. A non-viable segment was one in which delayed enhancement comprised more than 50% of wall thickness.

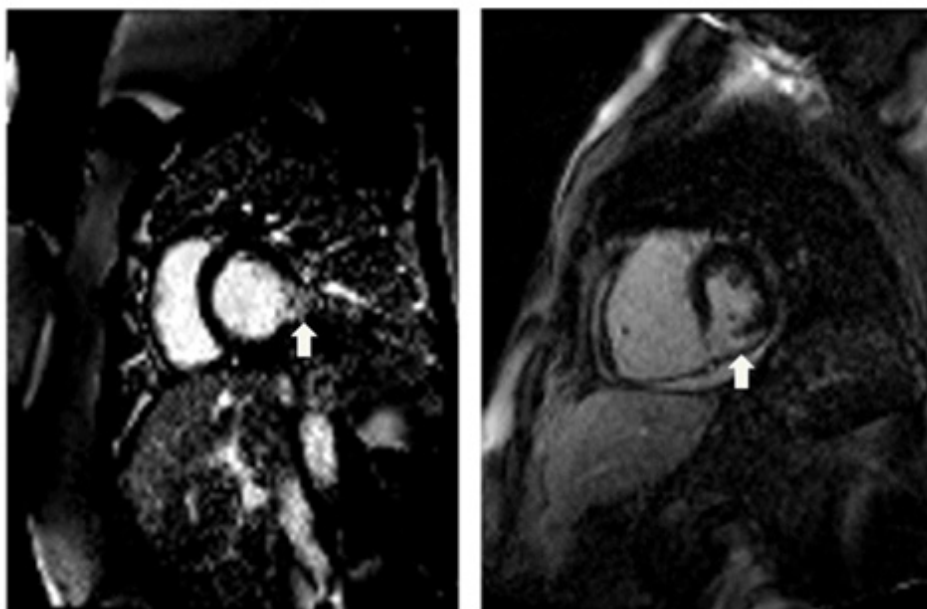
### CMR analysis

Ventricular mass, volume, and systolic function, including RVEF, were analyzed using the cine MR images and ARGUS 4D VF software. End-systolic and end-diastolic frames were identified by the smallest and largest cavity area, respectively. Ventricular contours were manually traced in both systolic and diastolic frames, for at least 8 slices from base to apex.

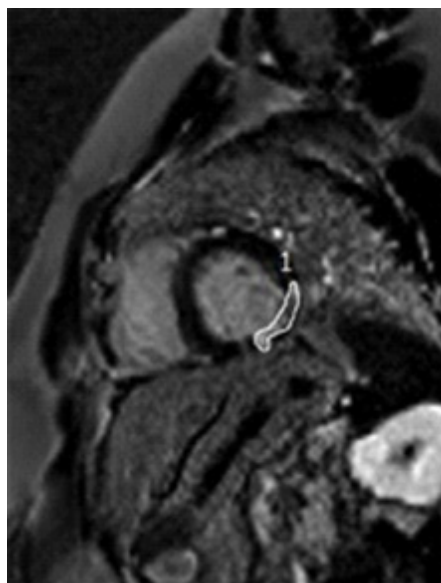
The regions of interest were manually traced along the areas of fibrosis (Figure 2). Fibrosis mass was obtained by multiplying this area by the slice thickness and by myocardium density (1.05 g/ml).

### Statistical analysis

Continuous variables were expressed as mean ± SD if normally distributed and otherwise as median and range. The *Kolmogorov-Smirnov* test was used to test variable normality. Categorical variables were given as counts and percentages of total. Continuous variables were compared by Student's t-test for independent samples and comparisons of categorical variables



**Figure 1** – Late gadolinium enhancement-cardiac magnetic resonance images from patients with inferior wall myocardial infarction (white arrows show myocardial fibrosis in the inferior wall).



**Figure 2** – Measurement of fibrosis by late gadolinium enhancement (1 represents the area of fibrosis).

were made using Fisher's exact test. The Pearson's correlation test was applied to examine the association between RVD and fibrosis. Multivariate logistic regression was performed to determine predictors

of RVD. P-values of less than 0.05 were considered significant. Statistical analysis was performed using Statistical Package for the Social Sciences software, version 17.0.

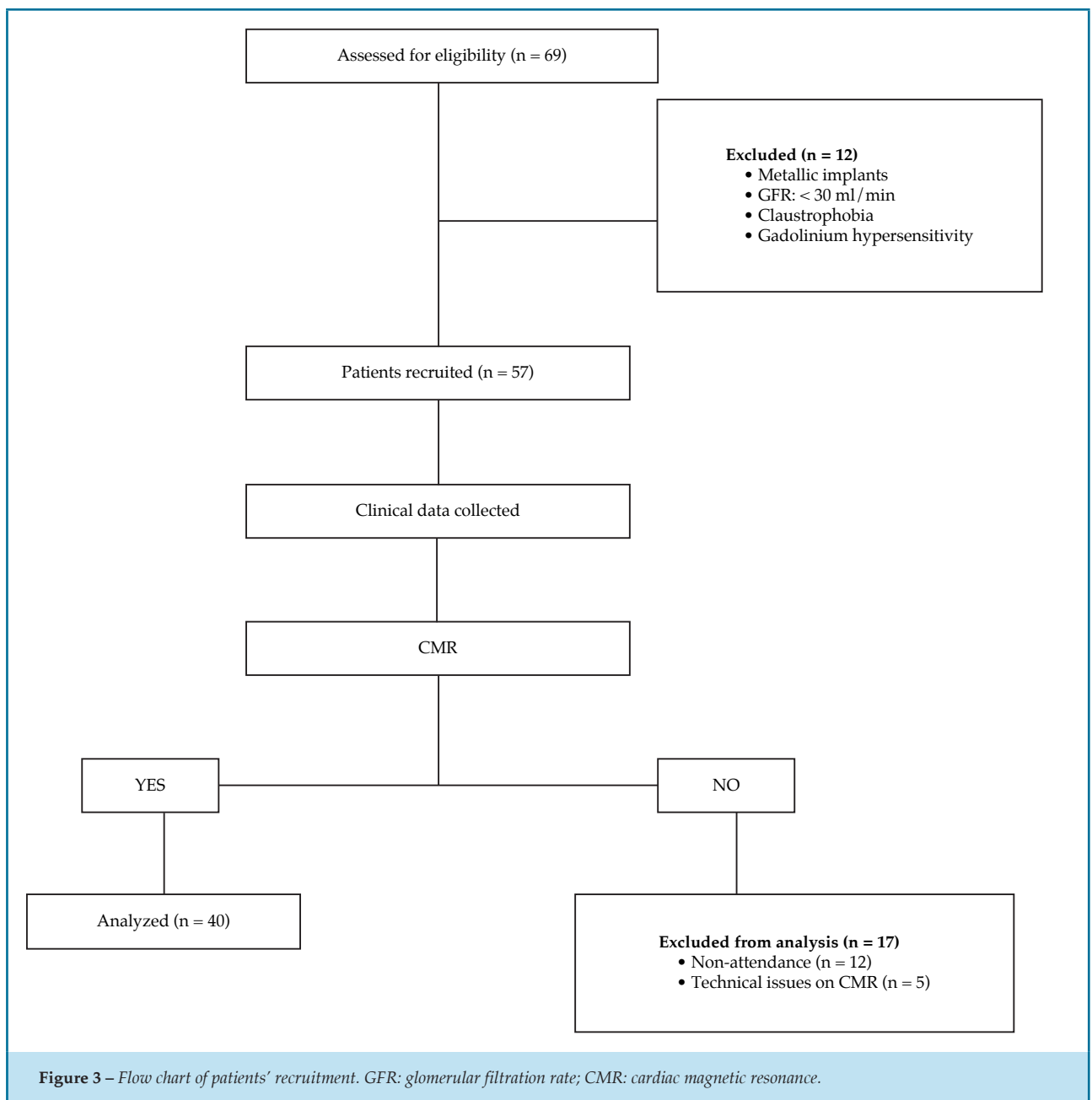
## Results

Fifty-seven patients were selected between January and December 2014 according to our inclusion criteria. CMR imaging exam was performed in forty individuals, and seventeen participants were excluded due to impossibility of performing the exam or technical issues on their CMR (Figure 3).

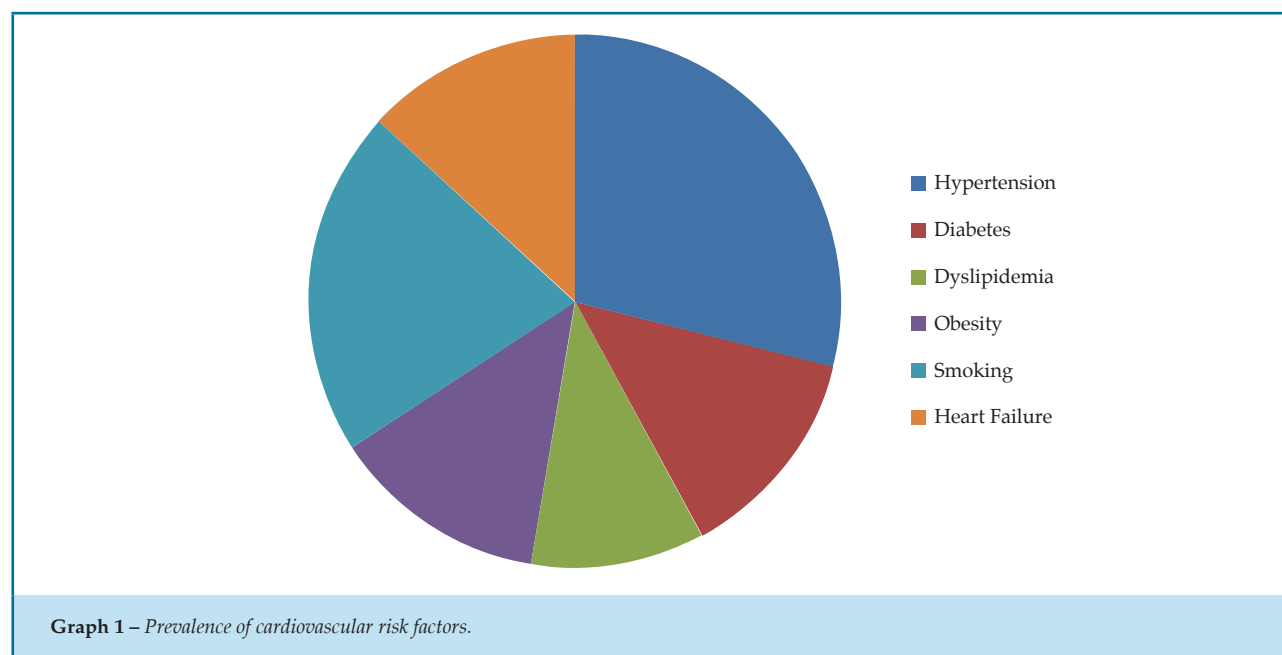
Of the forty patients included in the study, 30 (75%) were male and 18 (45%) were elderly (age  $\geq 60$  years) (Table 1). Twenty-two patients (55%) had hypertension, 12 (30%) had

coronary artery disease, 10 (25%) had diabetes mellitus, 10 (25%) had heart failure, 10 (25%) had obesity and 8 (20%) had dyslipidemia. Moreover, 16 patients (40%) had a history of smoking and 3 patients (8%) a history of stroke (Graph 1).

Table 2 describes RV function and the variables analyzed by LGE-CMR. Mean end-systolic volume was  $45 \pm 24$  mL, mean end-diastolic volume was  $84 \pm 34$  ml and mean ejection fraction was  $44 \pm 12\%$ . Thirteen (33%) patients had RVD. Mean fibrosis area obtained by CRM was  $20 \pm 12$  mm<sup>2</sup>, mean fibrosis mass was  $17 \pm 10$  g and mean of non-viable segments was  $3 \pm 2$ .



**Figure 3** – Flow chart of patients' recruitment. GFR: glomerular filtration rate; CMR: cardiac magnetic resonance.



**Table 1 – Clinical characteristics of the study population**

Variables	n = 40
<b>Demographic</b>	
Age (mean ± SD)	58 ± 8
Age ≥ 60 (n, %)	18 (45)
Male (n, %)	30 (75)
<b>Clinical</b>	
Systemic arterial hypertension (n, %)	22 (55)
Diabetes mellitus (n, %)	10 (25)
Dyslipidemia (n, %)	8 (20)
Obesity (n, %)	10 (25)
Smoking (n, %)	16 (40)
Heart failure (n, %)	10 (25)
Stroke (n, %)	3 (8)
Coronary artery disease (n, %)	12 (30)

According to Pearson's correlation, fibrosis mass and RVEF were indirectly correlated, although there was no statistical significance ( $r = -0.3$ ;  $p = 0.08$ ). Furthermore, multivariate logistical regression analysis showed that age, gender and hypertension were positively correlated, while smoking, dyslipidemia and diabetes

**Table 2 – Ventricular function and variables analyzed by late gadolinium enhancement technique**

Variables	n = 40
Ejection fraction (%)	44 ± 12
Ejection fraction < 40 (n, %)	13 (33)
End-systolic volume (ml)	45 ± 24
End-diastolic volume (ml)	84 ± 34
Non-viable segments	3 ± 2
Fibrosis area (mm <sup>2</sup> )	20 ± 12
Fibrosis mass (g)	17 ± 10

were negatively correlated with RVEF, without statistical significance (Table 3). Moreover, there was a negative correlation between RVEF and fibrosis mass ( $p = 0.05$ ).

Patients were stratified by RV function and both study groups had similar clinical characteristics (Table 4). Student's t-test showed that mean fibrosis area and mean fibrosis mass were higher in the group of patients with RVD ( $p = 0.092$ ,  $p = 0.051$  respectively). There were no statistically significant differences in the number of non-viable segments between groups.

**Tabela 3 – Regression model for predictors of right ventricular dysfunction**

Variable	B	P
Fibrosis mass	-0.167	0.05
Age	0.048	0.503
Gender	0.148	0.927
Smoking	-3.883	0.075
Hypertension	0.579	0.676
Dyslipidemia	-21.984	0.999
Diabetes	-0.401	0.794

**Table 4 – Comparison of clinical characteristics and cardiac magnetic resonance variables between study groups**

Variable	Right ventricular dysfunction		P
	YES (n = 13)	NO (n = 26)	
<b>Demographic, n (%)</b>			
Age ≥ 60	5 (38)	12 (46)	0.473
Gender (male)	9 (69)	20 (77)	0.613
<b>Clinical, n (%)</b>			
Systemic arterial hypertension	5 (39)	16 (61)	0.358
Diabetes mellitus	2 (15)	7 (27)	0.475
Dyslipidemia	0 (0)	8 (30)	0.154
Obesity	2 (15)	5 (19)	0.953
Smoking	4 (31)	12 (46)	0.481
Heart failure	3 (23)	6 (23)	0.559
Stroke	1 (7)	2 (7)	0.537
Coronary artery disease	3 (23)	8 (31)	0.543
<b>CMR variables (Mean ± SD)</b>			
Non-viable segments	4 ± 3	3 ± 2	0.464
Fibrosis area (mm <sup>2</sup> )	25 ± 14	18 ± 10	0.092
Fibrosis mass (g)	22 ± 12	15 ± 8	0.051

CMR: cardiac magnetic resonance

## Discussion

Recent studies have been focused in the negative impact of RVD in patients with I-MI, as it is considered an important independent predictor of mortality in these patients.<sup>13</sup> The assessment of RV function and its predictors enables early identification of individuals who tend to have worse outcomes and poor prognosis. The present study, in agreement with previous reports,<sup>14-17</sup> confirms the ability of CMR to precisely evaluate RV function and quantify myocardial fibrosis.

In our study group, composed mostly of male and elderly patients, hypertension was the most prevalent cardiovascular risk factor (55%) followed by smoking (40%), diabetes mellitus (25%) and heart failure (25%). Smarz et al.<sup>18</sup> have reported a similar prevalence of these cardiovascular risk factors in 90 patients with I-MI, except for the prevalence of dyslipidemia of 70%, which was different from that found in our study (20%).

In the present study, RVD was evident in 33% of cases with I-MI, which was similar to the prevalence of 32% reported in previous studies on 50 patients with I-MI.<sup>19,20</sup> Considering that similar clinical features were observed between patients with RVD and patients with preserved ventricular function, our study could investigate, with relative precision, the association between RV function and myocardial fibrosis.

Our study revealed a negative correlation between RVEF and variables such as smoking, dyslipidemia, diabetes and fibrosis mass. The analysis showed a strong trend towards the association between RVEF and fibrosis mass ( $p = 0.05$ ), indicating that greater mass of fibrosis is related to lower RVEF. This finding suggests that fibrosis is a possible predictor of RVD.

Furthermore, the current study showed an important trend towards higher mean fibrosis mass in patients with RVD compared to patients with preserved ventricular function ( $22 \pm 12\text{g}$  vs  $15 \pm 8\text{g}$ ,  $p = 0.051$ ). This result indicates a possible association between RVD and myocardial fibrosis within inferior wall, with clinical and prognostic significance in patients with I-MI. A similar association has been reported in a study

by Kaandorp et al.,<sup>21</sup> which results showed higher values of RV end-diastolic volume in the group of patients with higher mean fibrosis mass.<sup>3</sup>

The small sample size of our study population is the main limitation to the present findings. Moreover, the amount of patients excluded (30%) due to the lack of CMR imaging data is an important limitation of the present study. Therefore, further studies with larger series are needed to confirm our findings.

## Conclusions

The CMR seems to be an adequate method for risk stratification of patients with I-MI and RV dysfunction. The findings of our study indicate a possible association between myocardial fibrosis in the left ventricular inferior wall and RVD in patients with I-MI. Nevertheless, further studies with larger series are needed to confirm our findings.

## Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Lacerda PN, Macêdo CRB, Aras Júnior R, Fernandes AMS; Acquisition of data: Gomes Júnior AM, Lacerda PN, Pinto FGF, Almeida RF, Santos JM; Analysis and interpretation of the data: Lacerda PN, Pinto FGF, Almeida RF, Gomes Júnior AM, Santos JM, Fernandes AMS; Statistical analysis and Writing of the manuscript: Lacerda PN, Pinto FGF, Almeida RF, Gomes Júnior AM, Santos JM, Macêdo CRB, Aras Júnior R, Fernandes AMS.

## 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.

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