

## Doppler Echocardiographic Follow-Up of Mitral and Aortic Regurgitation in Children and Adolescents with Subclinical and Mild Rheumatic Carditis

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### Abstract

**Background:** Mild rheumatic carditis (MRC) and subclinical rheumatic carditis (SRC) are basically differentiated through auscultation of mitral regurgitation murmur. The evolution of these forms is not well established in the literature.

**Objective:** To evaluate the evolution of mild and subclinical rheumatic carditis, considering mitral and aortic regurgitation (acute phase) and regression, maintenance or worsening of these diseases at the end of follow-up (chronic phase).

**Methods:** Retrospective, longitudinal study, including patients with mild and subclinical rheumatic carditis. The echocardiographic evolution of mitral and aortic regurgitation was compared in both groups, considering the analysis at the end of follow-up. The Chi-square test and Kaplan-Meier survival curves were used, with significance level established at  $p < 0.05$ .

**Results:** A total of 125 patients were included, 69 (55.2%) with subclinical rheumatic carditis and 56 (44.8%) with mild rheumatic carditis, with a mean age in the acute phase of  $10.4 \pm 2.6$  years and, at the end of study,  $19.9 \pm 4.6$  years. The time of follow-up ranged from 2 to 23 years (mean:  $9.38 \pm 4.3$  years). In the acute phase, mild/moderate or moderate mitral regurgitation was more frequent in patients with mild rheumatic carditis ( $p = 0.001$ ). Mild or mild/moderate aortic regurgitation was also more common in the mild rheumatic carditis group ( $p = 0.045$ ). In the chronic phase, we observed that both mitral ( $p < 0.0001$ ) and aortic regurgitation ( $p = 0.009$ ) were more frequent in patients with mild rheumatic carditis, and survival free of rheumatic heart disease was higher in the subclinical rheumatic carditis group ( $p = 0.010$ ). Residual mitral regurgitation was higher in the mild rheumatic carditis group ( $p < 0.0001$ ), and residual aortic regurgitation was similar in both groups ( $p = 0.099$ ).

**Conclusion:** Mitral regurgitation resolution was higher in patients with subclinical rheumatic carditis, and the involution of aortic regurgitation was less frequent and similar in both groups. (Int J Cardiovasc Sci. 2017;30(5):391-400)

**Keywords:** Myocarditis; Rheumatic Heart Disease; Mitral Valve / abnormalities; Aortic Valve / abnormalities; Echocardiography, Doppler; Child; Adolescent.

### Introduction

Rheumatic fever (RF) is still responsible for high morbidity and mortality in young individuals in developing countries, despite the decline in Acute RF (ARF) and Chronic Rheumatic Cardiopathy (CRC) in developed countries.<sup>1-4</sup> Brazil is considered a country with a medium prevalence of the disease, with a rate of

3.6/1,000.<sup>2</sup> Echocardiographic (echo) screening studies carried out in schoolchildren in the metropolitan area of Belo Horizonte, state of Minas Gerais, Brazil, showed a prevalence of around 40/1,000.<sup>5,6</sup>

It is known that carditis is the most severe manifestation of ARF, being the only one that can leave sequelae. Carditis may be subclinical - normal cardiac auscultation – or clinical – auscultation of Mitral Regurgitation (MR)

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and/or aortic regurgitation murmurs, with or without signs and symptoms of heart failure. Mild carditis is characterized by MR murmur auscultation, whereas in the subclinical form, cardiac auscultation is normal, and the echocardiographic alterations are similar to those observed in mild carditis. The evolution of these two forms of carditis is not well established in the literature, particularly in relation to subclinical carditis. In moderate or severe carditis, a higher frequency of residual valve lesions is expected. However, in mild and subclinical cardiac involvement, the possibility of resolution of these lesions is not known, or even if evolution to more severe regurgitation or mitral stenosis will occur.<sup>7-9</sup>

In the last review of the Jones criteria,<sup>10</sup> subclinical carditis was considered the major manifestation in all patients, whether from countries with high or low prevalence. In our service, echocardiography has been performed since 1992 in all patients diagnosed with ARF, with or without cardiac auscultation, and during patient follow-up.

The aim of this study was to evaluate the evolution of mild and subclinical rheumatic carditis, considering mitral and/or aortic valve regurgitation (acute phase) and disease regression, maintenance or worsening at the end of follow-up (chronic phase).

## Methods

This was a retrospective, longitudinal, observational study (concurrent cohort), carried out in an outpatient clinic specific for the care of patients with RF. The patients were recruited from data recorded in the service, from 1992 to 2014.

Patients with a diagnosis of ARF according to the Jones criteria,<sup>10,11</sup> with subclinical carditis (normal cardiac auscultation and mitral and/or aortic regurgitation in the echocardiography) and mild carditis (MR murmur and mitral and/or aortic regurgitation in the echocardiography) making regular use of secondary prophylaxis were included. All patients had echocardiographic examination performed in the acute and chronic phases, after a follow-up period of 2 or more years.

Patients were allocated to two groups, namely those with subclinical rheumatic carditis (SRC) and mild rheumatic carditis (MRC).

The degree of valvular regurgitation at the echocardiographic Doppler examination in the acute

and chronic phases was classified as absent, mild, mild/moderate, and moderate according to criteria established by the American Society of Echocardiography (ASE)<sup>12</sup>. The morphological and Doppler echocardiographic criteria used for the definition of MR and non-physiological Aortic Regurgitation (AoR) were based on a consensus established by the World Health Organization working group and other authors.<sup>11-15</sup>

In the analysis of the evolution of the valvular lesions, the first echocardiography of the acute phase and the last one of the chronic phase were considered. Residual valvulopathy was defined as the presence of any degree of MR associated with AoR or greater than mild MR. The good evolution was defined as absence of valvular dysfunction or permanence of mild MR in the last evaluation.

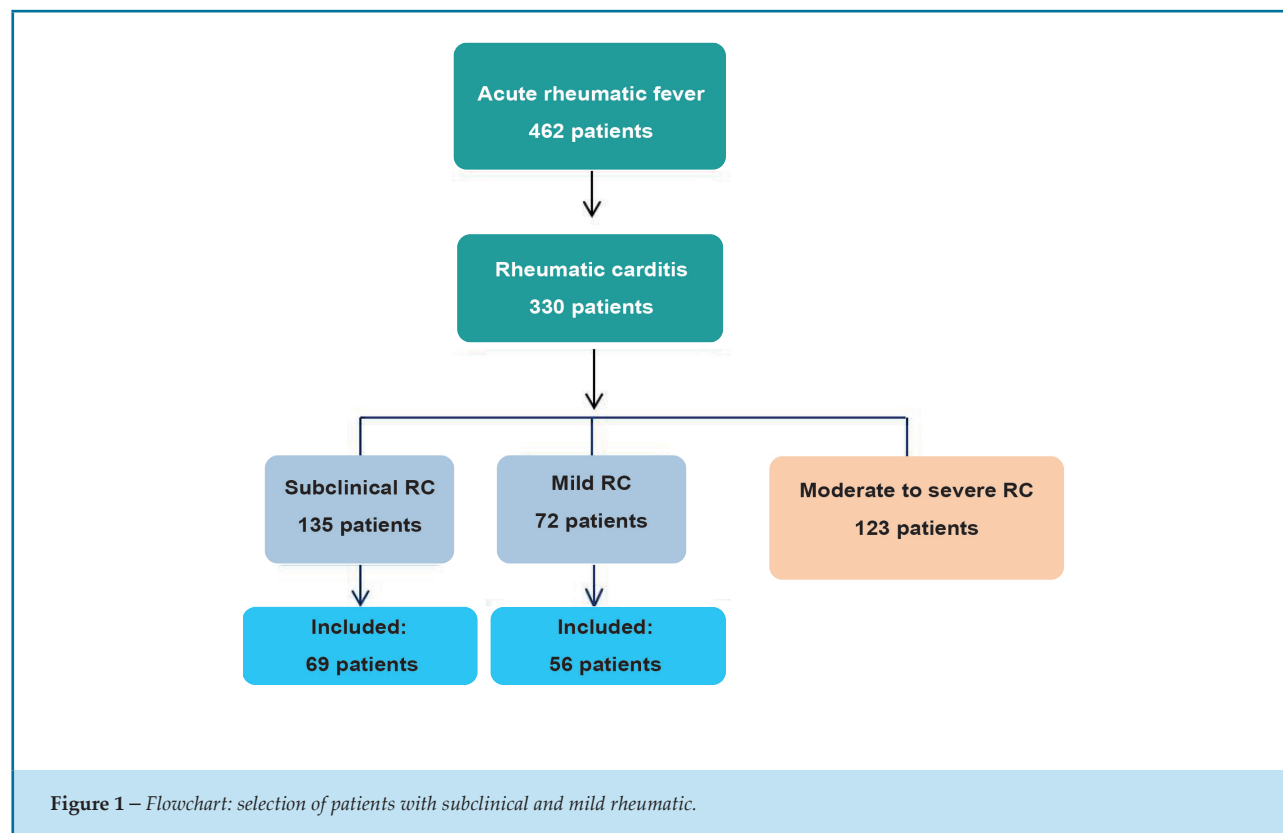
The research protocol was approved by the UFMG Research Ethics Committee (CAAE 31821614.0.0000.5149).

## Statistical Analysis

The analyses were processed using the Statistical Package for Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of the variables was tested by the Shapiro-Wilkstest. The continuous quantitative variables with normal distribution were shown as mean and standard deviation, and the variables with non-parametric distribution, as median and their maximum and minimum values. Categorical variables were described as numbers and/or percentages. The unpaired Student's *t* test was used to compare age means. For the categorical variables, Pearson's chi-square test or Fisher's test was used, as appropriate. For the evaluation of survival free of residual valvulopathy, the Kaplan-Meier curve was used with the log-rank test. All tests were performed considering a significance level of 5%, two-tailed probability and 95% Confidence Interval (95% CI).

## Results

Of the 462 patients who were regularly followed at the service and underwent echocardiography assessments in the acute and chronic phases, 330 had carditis, of which 135 (40.9%) were classified as having mild rheumatic carditis and 72 (21.8%) as subclinical rheumatic carditis. Of these, 125 patients met the inclusion criteria, of which 69 (55.2%) were allocated in the MRC Group and 56 (44.8%) in the SRC Group (Figure 1).



The age of presentation of the acute phase was 5 to 15 years (mean of  $10.4 \pm 2.6$  years). The age at the end of the study was 10 to 34 years (mean  $19.9 \pm 4.6$  years), and follow-up ranged from 2 to 23 years (mean of  $9.38 \pm 4.3$  years). At the end of the study, 51.2% patients were aged between 10 and 20 years and 47.2% between 21 and 30 years. There was a predominance of females (64%) and ARF was more frequent in the age range of 5 to 10 years (54.4%).

There was a higher association of chorea with subclinical carditis ( $p < 0.0001$ ) and of arthritis with

mild carditis ( $p < 0.0001$ ). The general characteristics of the population of the two groups are shown in table 1.

None of the patients in the MRC and SRC groups used corticosteroids in the acute phase, even those in which moderate valve regurgitation was observed at the echocardiography. According to the current therapeutic protocol in the service, corticosteroids were used only in patients with moderate or severe carditis. All patients were receiving regular secondary prophylaxis with penicillin G benzathine every 21 (most) or 28 days. No recurrence was reported in any of the patients.

**Table 1** – General characteristics of patients with subclinical (n = 69) and mild (n = 56) carditis

Characteristics	Rheumatic carditis		p value
	Subclinical	Mild	
Female gender	44	36	0.551
Presence of chorea	53	16	< 0.0001
Presence of arthritis	24	47	< 0.0001
Age at the acute phase, mean, years	$10.3 \pm 2.6$	$10.4 \pm 2.7$	0.913
Age at the end of the study, mean, years	$19.2 \pm 4.1$	$20.7 \pm 5.0$	0.071

### Echocardiographic analysis of rheumatic mitral and aortic valve disease (acute phase)

All patients with mild rheumatic carditis had MR at the echocardiography performed in the acute phase. Only one patient with subclinical rheumatic carditis did not have MR, but showed altered mitral valve morphology and mild non-physiological AoR. In the MRC Group, there was a higher frequency of mild/

moderate or moderate MR when compared to the SRC Group ( $p = 0.001$ ).

AoR was present in 20 (29%) patients with subclinical rheumatic carditis and 27 (48%) with mild rheumatic carditis. In the SRC group, all AoR cases were mild ones, but in the MRC group, there were four cases of mild/moderate AoR ( $p = 0.045$ ). The mitral and aortic valve involvement in each group is shown in table 2.

**Table 2 – Valvular involvement in subclinical and mild rheumatic carditis**

Valve involvement	Rheumatic carditis	
	Subclinical	Mild
Isolated MR	49	29
Isolated AoR	1	1
RM + AoR	19	26

MR: mitral regurgitation; AoR: aortic regurgitation.

### Echocardiographic analysis of rheumatic mitral and aortic valve diseases (chronic phase)

In the chronic phase of RF (Figure 2), according to the echocardiographic evaluation, MR was present in 47 (68%) patients of the SRC Group, and in only two the degree of the lesion was mild / moderate. In the MRC group, MR persisted in 54 (96.4%), of which 15 (28.8%) had mild / moderate or moderate degree ( $p < 0.0001$ ).

Regarding the echocardiographic assessment of the aortic valve in the chronic phase (Figure 3), AoR was mild in nine (13%) patients of the SRC Group and in 19 (34%) patients in the MRC Group, whereas mild/moderate AoR was found in four patients from the MRC Group ( $p = 0.009$ ).

The type of mitral and aortic valve involvement in each group is described in table 3.

### Evolutionary analysis of valve lesions

The time of echocardiography in the chronic phase ranged from 2 to 23 years, with a mean of  $9.38 \pm 4.3$  years (median of 9 years).

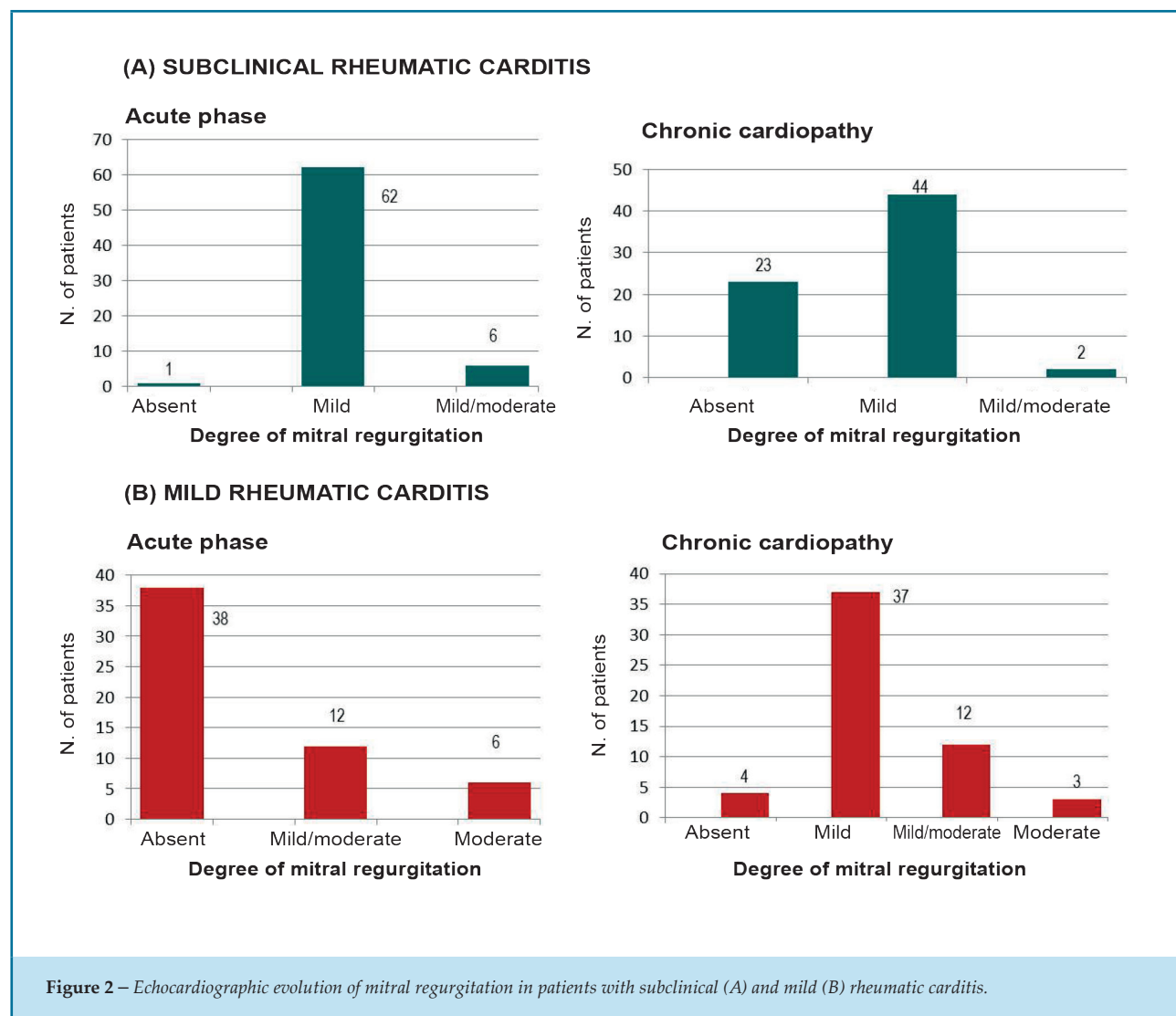
Regarding the MR evolution, it was observed that of the 69 patients in the SRC Group, 22 (31.9%) had full resolution. Among those who had full resolution, in 18 (81.8%) the MR was mild and in four (18.2%) the MR was mild / moderate in the acute phase. Of the 56 patients in

the MRC Group, only four (7.1%) had full MR resolution, one (25%) mild MR and three (75%) moderate MR in the acute phase. A higher rate of MR resolution was observed in the SRC Group ( $p < 0.0001$ ). MR also regressed more frequently when it was isolated and not associated with AoR ( $p < 0.0001$ , odds ratio 2.51, 95%CI: 1.53-4.09) in both groups. None of the patients showed evolution to stenotic lesions. Only two patients from the SRC group had mild worsening of the MR: from mild in the acute phase to mild/moderate in the chronic phase.

Regarding the evolution of the AoR, in patients with subclinical rheumatic carditis, resolution occurred in 13 (18.8%) of them, all of them with previously mild AoR. In patients with mild rheumatic carditis, AoR resolution was observed in nine (16.1%) patients, all of them also with previously mild lesions. There was no difference between the groups ( $p = 0.099$ ). Neither of the two groups showed mild to moderate AoR resolution.

Data on the echocardiographic evolution of mitral and aortic valve lesions are shown in Figures 2 and 4.

The evaluation of Kaplan-Meier survival curves regarding survival free of residual valvulopathy (CRC), defined as the presence of MR greater than mild or mild MR associated with AoR, showed a difference between the two groups ( $p = 0.010$ ), being higher in SRC patients, due to the higher MR resolution. When considering the AoR-free survival, there was no difference between the two groups ( $p = 0.099$ ).



The survival curves for residual valvulopathy (CRC) and for residual aortic valvulopathy are shown in Figures 3 and 5.

## Discussion

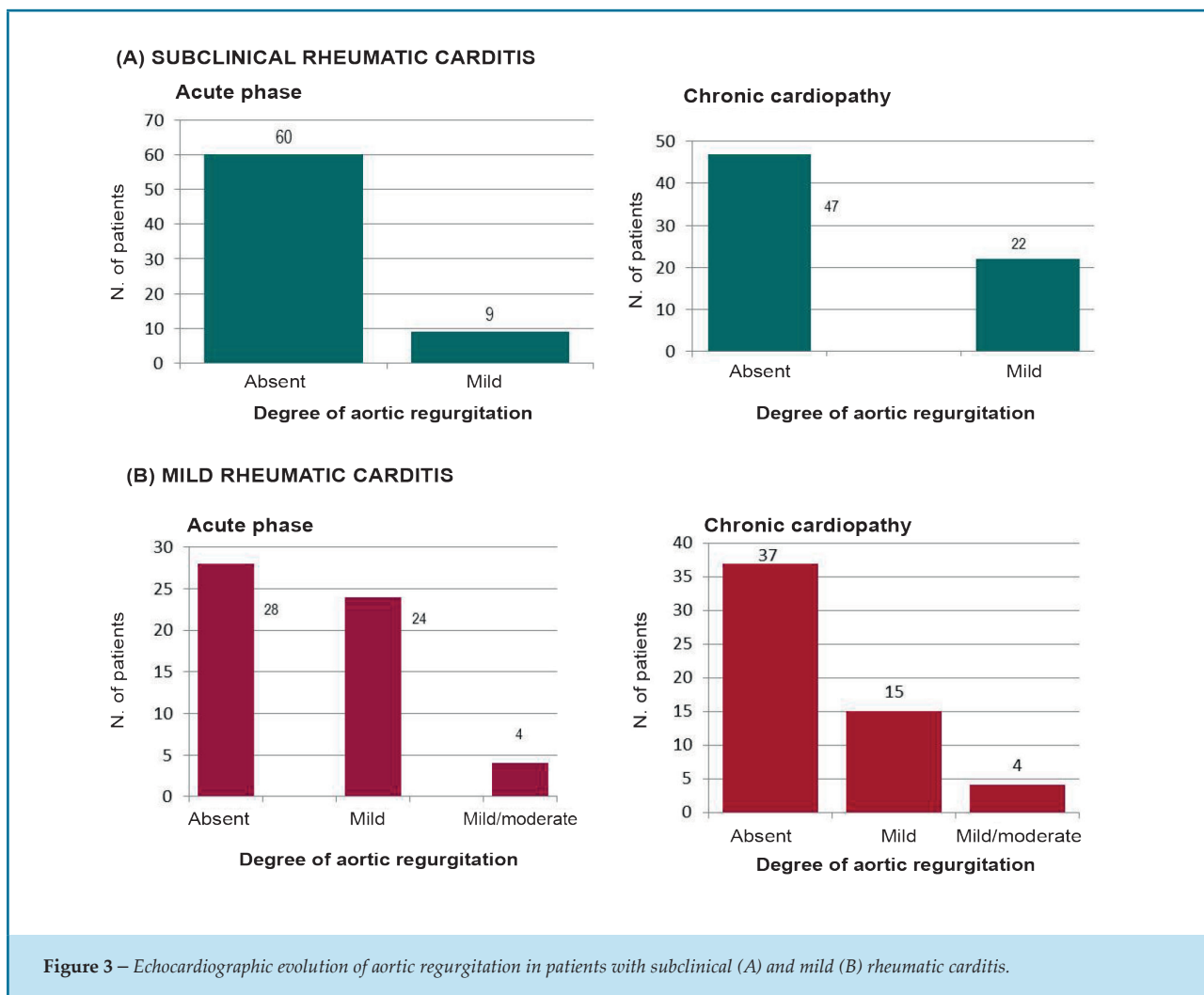
The frequency of mild and subclinical rheumatic carditis in the study population was 40.9% and 21.8%, respectively. The literature shows great variation in the frequency of subclinical rheumatic carditis, varying from 16.7 to 43.3%,<sup>7,16-20</sup> the same occurring in relation to mild rheumatic carditis, which can be explained by the difference in the classification criteria.<sup>7,8,16,19</sup>

The highest observed association frequency between arthritis with mild rheumatic carditis and of chorea with subclinical rheumatic carditis agrees with that described by other authors.<sup>8,19-24</sup> There was also agreement on

the predominance of mitral valve involvement in both groups, both in the acute and chronic phases.<sup>7-9,25</sup>

Previous studies have concluded that CRC progression is proportional to the severity of carditis: the more severe the valve lesion in the initial outbreak, the worse the valve damage in the chronic phase.<sup>7</sup> However, the echocardiographic evolution of valvular lesions (mitral and aortic) observed in patients with SRC and MRC regarding progression to greater severity or onset of stenotic lesions, or whether they remain stable or regress, remains to be elucidated.

Historically, prior to the use of the echocardiographic examination, Décourt<sup>26</sup> described that, in patients with mild carditis, approximately 80% of clinical manifestations disappeared, as well as residual valvular lesions. Thomas,<sup>27</sup> in the 1960s, also reported that the



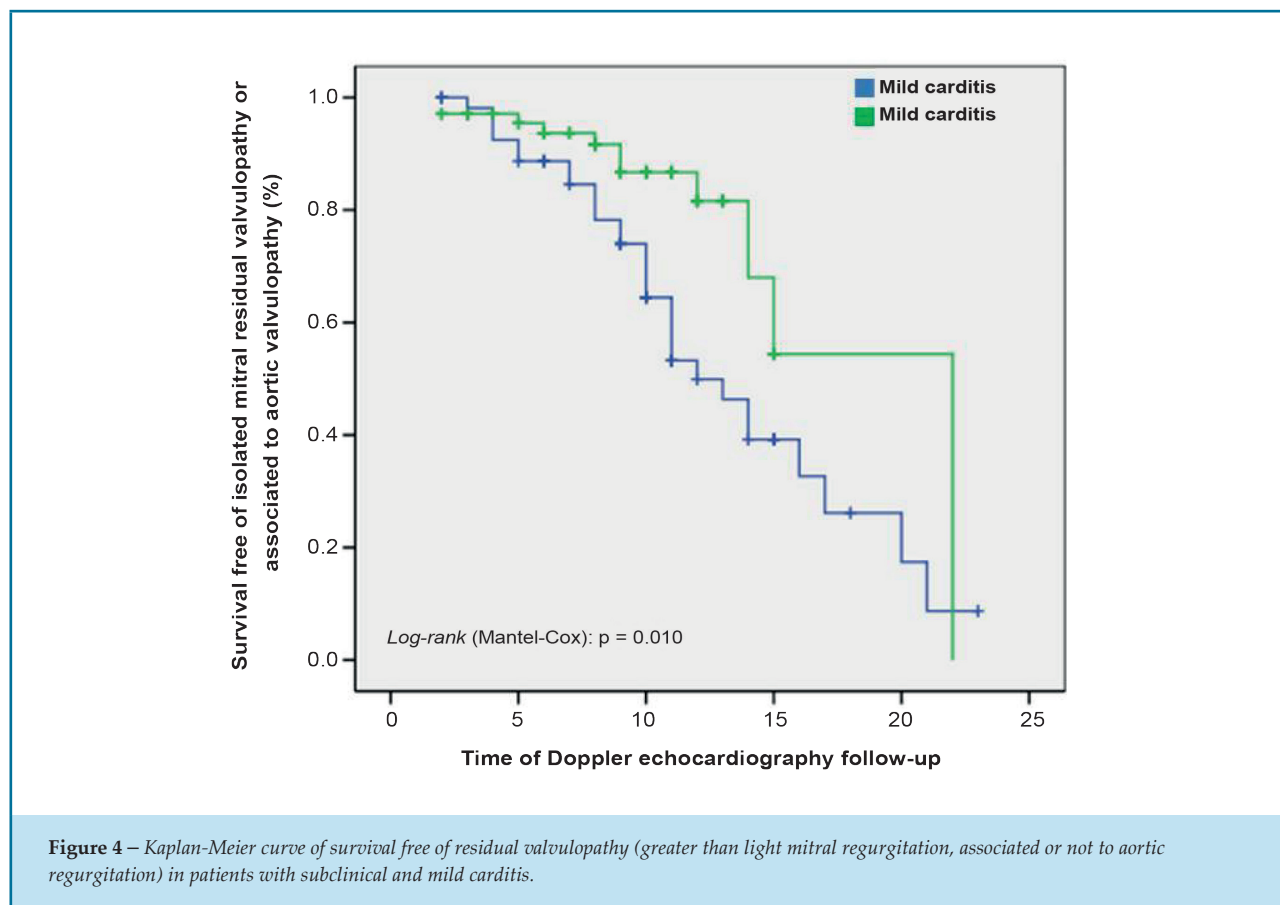
**Table 3 – Chronic rheumatic valve disease in patients with subclinical and mild carditis**

Valve involvement	Rheumatic carditis	
	Subclinical	Mild
Absent	20	1
Isolated MR	38	36
Isolated AoR	2	1
MR + AoR	9	18

MR: mitral regurgitation; AoR: aortic regurgitation.

clinical examination remained normal in the follow-up of patients who had no cardiac abnormalities in the acute phase, without murmurs. Differently from this pre-echocardiographic era, when only the clinical evolution (murmur persistence) was considered, later studies

showed that the valvular lesion persists at a higher frequency. Of the 56 patients with mild rheumatic carditis evaluated here, only four (7%) showed MR regression, according to the echocardiographic evaluation. In the 69 patients with subclinical rheumatic carditis, 22 (31.9%)



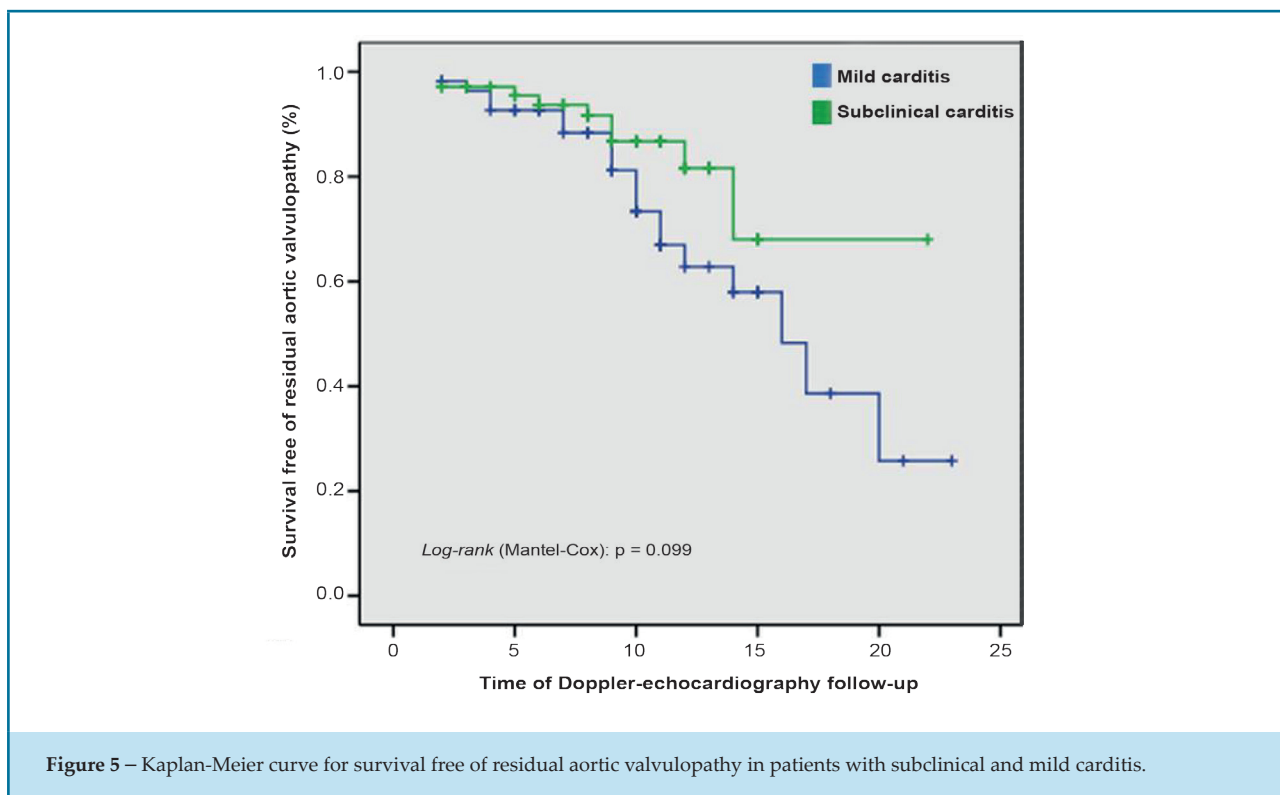
had total MR resolution. These data corroborate the findings of a previous study, in which MR resolution was observed in 28% of patients with subclinical rheumatic carditis.<sup>8</sup>

Several authors have concluded that subclinical valvular lesions may persist for a long time. Figueroa et al.<sup>18</sup> observed that half of the patients, at the end of 5 years of follow-up, remained with valvular lesions at the echocardiographic examination, with no evolution being observed to severe regurgitation or stenotic lesion. Of the 40 patients with subclinical rheumatic carditis from the Ozkutho and Hallioglu study,<sup>28</sup> 33 had MR, 6 has AoR and only one had MR associated with AoR. After a mean follow-up period of 18 months, it was observed that the valvular lesion disappeared in 23 patients (57.5%). However, in the present study, considering a mean evolution of 10 years, there was a lower frequency of total MR regression, which occurred in 22/69 patients (31.9%). Karaaslan et al.<sup>29</sup> followed 23 patients with subclinical rheumatic carditis (19 with MR, one with AoR and three with MR and AoR), for a mean follow-up period of 9.91 months.

The echocardiographic analysis in this period showed that the degree of MR improved in 13 patients (59.1%) and disappeared completely in six (27.3%). The AoR improved in two and disappeared completely in two.

Meira et al.,<sup>7</sup> in a comparative study of the echocardiographic evolution of valvular lesions in 258 children and adolescents with RF during a follow-up period of 2 to 15 years, observed the regression of the lesions in 25% in the patients with mild rheumatic carditis, 2.5% of those with moderate carditis and in none of those with severe carditis. When compared to the present study, regression in the MRC group occurred in 7% of patients.

Pekpak et al.,<sup>30</sup> when assessing 56 patients with ARF, observed that 103 (66%) had carditis, of which 29 (28.2%) had subclinical rheumatic carditis. After 1 year or more of follow-up, none of the patients had worsening of the valvular lesion; in four (15%), valvular dysfunction remained unaltered; and in 25 (85%), the lesion regressed. The regression rate was higher than that observed in the present study (37.6%).



**Figure 5** – Kaplan-Meier curve for survival free of residual aortic valvulopathy in patients with subclinical and mild carditis.

Basturk et al.<sup>31</sup> followed 30 patients with subclinical rheumatic carditis and compared their echocardiographic evolution with that of 82 patients with clinical carditis after at least 2 years of disease. They observed that the regression rate was similar in both groups and there was no resolution of isolated AoR, but there was a significant recovery of the isolated MR or when associated with AoR.

The current study is the first to compare the echocardiographic evolution of subclinical with mild rheumatic carditis, during a mean period of almost a decade. The most favorable evolution was that of MR in the SRC Group and was associated with the occurrence of MR alone in ARF. A greater persistence of alterations was observed in patients with an association of MR and AoR. In this association, there is a lower probability that the mitral and aortic dysfunctions will be physiological. This fact allows us to infer it may be difficult to differentiate non-physiological mild MR from physiological MR. When murmur corresponding to MR occurs, there is more significant valve dysfunction at the echocardiographic examination, and the possibility of confusion with physiological MR is also less likely. Physiological AoR is rare at the assessed age range, and neither patients with mild rheumatic carditis nor those with subclinical rheumatic carditis had a corresponding murmur in the acute phase.

In patients with other major manifestations in the acute phase (chorea and / or arthritis), the echocardiographic assessment at this phase does not influence the diagnosis or the therapeutic approach, but it is important to determine if there is persistence or worsening of valve involvement during the follow-up of these patients, with echocardiographic assessment being carried out at the end of the period proposed for secondary prophylaxis. Patients with normal auscultation at 25 years of age or after 10 years of secondary prophylaxis may present with greater than mild valvular dysfunction or even progress to mitral stenosis (valve area  $< 4 \text{ cm}^2$  and  $> 2.5 \text{ cm}^2$ ).<sup>8</sup>

### Limitations

This study has limitations inherent to a longitudinal study, with a long follow-up period. In the initial phase of the study, the echocardiographic criteria of valvular disease/ mitral and aortic valvulopathy were not well established yet. This may have influenced the findings, especially regarding the differentiation between physiological mild MR and non-physiological MR. Echocardiographic evaluations of mitral and aortic valve dysfunctions carried out after the publication of the World Heart Federation criteria in 2012 might have been more accurate after this date.<sup>32</sup>



## Conclusion

The best evolution of subclinical rheumatic carditis was attributed to the lower frequency of residual mitral regurgitation. However, considering the evolution of aortic regurgitation, there was no difference between patients who had subclinical or mild rheumatic carditis. This fact may be related to the difficulty in the echocardiographic differentiation between mild physiological and non-physiological mitral regurgitation. Despite well-established echocardiographic criteria for the determination of mild non-physiological mitral regurgitation, there is still the influence of the echocardiographer's experience. Considering the evolution of aortic regurgitation, both in patients with subclinical rheumatic carditis and in those with mild rheumatic carditis, the medical conduct regarding the duration of secondary prophylaxis should be similar in the two groups, that is, up to 25 years of age or more, if there is worsening of the valve lesion. Thus, patients with subclinical or mild rheumatic carditis and aortic regurgitation alone or associated with mild mitral regurgitation would undergo prophylaxis for a similar period of time. As for patients in the subclinical rheumatic carditis group with isolated mild mitral regurgitation, whose evolution is more favorable, prophylaxis could

be maintained up to 21 years, as currently recommended, unless there is worsening of the valve lesion.

## Author contributions

Conception and design of the research: Meira ZMA. Acquisition of data: Meira ZMA, Araújo FDR, Almeida LMC. Analysis and interpretation of the data: Meira ZMA, Araújo FDR, Almeida LMC. Statistical analysis: Araújo FDR, Almeida LMC. Writing of the manuscript: Meira ZMA, Araújo FDR, Almeida LMC. Critical revision of the manuscript for intellectual content: Meira ZMA.

## Potential Conflict of Interest

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

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## Study Association

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