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Outcomes of Echocardiography-detected Rheumatic Heart Disease: Validating a Simplified Score in Brazilian Schoolchildren

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Outcomes of Echocardiography-detected Rheumatic Heart Disease: Validating a Simplified Score in Brazilian Schoolchildren

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On behalf of the PROVAR (*Programa de Rastreamento da Valvopatia Reumática*) investigators.

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Abstract:

Objectives: Echocardiographic (echo) screening is an important tool to estimate rheumatic heart disease (RHD) prevalence, but the natural history of screen-detected RHD remains unclear. The aim of this study was to assess the accuracy of the simplified score using the WHF criteria in predicting mid-term RHD outcomes in Brazilian schoolchildren. We present mid-term follow-up of patients with subclinical RHD from the PROVAR study, which uses non-experts, telemedicine and portable echo to screen for RHD.

Setting: Public schools of underserved areas and private schools in Minas Gerais, southeast Brazil.

Participants: Total 197 patients (170 borderline and 27 definite RHD) with follow-up of 29±9 months were included. Median age was 14 (12–16) years, and 130 (66%) were female. Only 4 patients in the definite group were regularly receiving penicillin.

Primary and secondary outcome measures: Unfavorable outcome was based on the 2-years follow-up echo, defined as worsening diagnostic category, remaining with mild definite RHD or development/worsening of valve regurgitation/stenosis.

Results: Among patients with borderline RHD, 29 (17.1%) progressed to definite, 49 (28.8%) remained stable, 86 (50.6%) regressed to normal and 6 (3.5%) were reclassified as other heart diseases. Among those with definite RHD, 13 (48.1%) remained in the category, while 5 (18.5%) regressed to borderline, 5 (18.5%) regressed to normal and 4 (14.8%) were reclassified as other heart disease. The simplified echo score was a significant predictor of RHD unfavorable outcome (hazard ratio [HR] 1.197, 95% confidence interval 1.098-1.305, $p<0.001$).

Conclusion: The simple risk score provided an accurate prediction of RHD status at 2-year follow-up, showing a good performance in Brazilian schoolchildren, with a potential

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3 value for risk stratification and monitoring of echocardiography-detected RHD.
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5 **Trial registration:** N/A.
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10 **Key-words:** Rheumatic heart disease; screening; echocardiography; follow-up;
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12 prognosis.
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14 **Word count:** 2,341
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19 **Strengths and limitations of this study:**
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- 21
- 22 • PROVAR is the first longitudinal program evaluating the impact of
23 echocardiographic screening in Latin America and the mid-term prognosis of
24 subclinical RHD in the Brazilian context.
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 - 26 • Unprecedented follow-up data from Latin America data suggest that screen-
27 detected RHD in Brazil is not benign: patients with definite RHD are likely to
28 remain in this category (48.1%), while progression rates of borderline disease are
29 considerable (17.1%).
30
 - 31 • A newly developed five-component point-based echo score showed considerable
32 accuracy in this population for discriminating children at risk for unfavorable echo
33 outcome at 2 years.
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 - 35 • The program had low-participation and high attrition: 40% of students consented
36 to school-based screening and only 36% of screen-positive children were enrolled
37 in follow-up.
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 - 39 • No child progressed to clinically significant RHD, suggesting the progression
40 timeline may be longer in the Brazilian context and limiting further conclusions
41 on the long-time prognosis of subclinical RHD.
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Article summary:

- PROVAR is the first Rheumatic Heart Disease (RHD) screening program in Brazil.
- Here we present mid-term follow-up of Brazilian schoolchildren with subclinical RHD.
- Half of patients with definite RHD are likely to remain in this category (48.1%)
- Over half of patients with borderline RHD regressed to normal and 17.1% progressed.
- A simplified 5-variable echo score was a powerful predictor of unfavorable outcome.

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Introduction

Rheumatic heart disease (RHD) is the major cause of acquired cardiovascular disease in children and young adults worldwide. Its global burden is noteworthy, affecting 39 million people and causing 319,400 deaths annually^{1 2}. The disease is more prevalent in low and middle-income countries and it's still mostly diagnosed in advanced stages of the disease, in symptomatic patients¹. Thus, the latent period between the first episode of acute rheumatic fever (ARF) and cardiovascular symptoms is not being readily identified nor used as an opportunity to implement early interventions.

In this context, echocardiographic screening in endemic areas has emerged as an effective approach to identify patients in early, subclinical stages of RHD³⁻⁶. Diagnostic criteria for subclinical RHD— asymptomatic patients with echocardiographic findings suggestive of RHD without history of ARF – have been standardized by the World Heart Federation (WHF) consensus in 2012. Three categories are defined: definite, borderline and normal⁷. The morphological findings of RHD and the criteria for pathologic valve regurgitation are also established. This standardization allowed for comparison between studies carried out in different populations.

Although criteria are standardized, prognosis and natural history of latent RHD, and the impact of clinical interventions – such as secondary prophylaxis – still require further evaluation. The first studies that evaluated the follow-up of patients with subclinical RHD have several limitations, including relatively short follow-up times, small sample size and lack of standardized criteria for echocardiographic and clinical progression⁸. However, data suggests that RHD progression in children with latent RHD is not negligible⁹. Therefore, we aimed to assess the mid-term evolution of Brazilian schoolchildren (5-18 years) with subclinical RHD findings observed in echocardiographic screening^{4 5 10} and to assess the performance of a simplified score

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3 developed by Nunes *et al*⁹, consisting of 5 components of the WHF criteria, as a predictor
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5 of unfavorable echocardiographic outcomes.
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10 **Methods:**

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12 This is a prospective cohort study with systematic clinical and echocardiographic
13 follow-up of children with subclinical RHD. It was derived from a RHD screening
14 program, established in Brazil in 2014 - the PROVAR+ (*Programa de Rastreamento da*
15 *Valvopatia Reumática*) study - a collaboration between the Children's National Health
16 System, Washington – DC, US, the Universidade Federal de Minas Gerais and the
17 Telehealth Network of Minas Gerais¹¹, Belo Horizonte, Minas Gerais, Brazil. This
18 screening program has already screened more than 12,000 children and adolescents from
19 21 schools in Minas Gerais, Brazil, between October 2014 and December 2016^{4 5 10}. The
20 study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and
21 ethics approval was obtained from the institutional review boards of the participant
22 institutions as well as from the local Boards of Health and Education.
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37 In brief, public schools and primary care centers from low income areas of
38 metropolitan Belo Horizonte, Brazil, were selected to participate in the screening
39 program, based on socioeconomic data (Human Development Index (HDI)) and priorities
40 of the health authorities. Selected private schools (2) were also invited in order to
41 characterize RHD in high-income youth. All asymptomatic students, without history of
42 ARF or RHD, were eligible for screening^{4 5}. All participants were informed about the
43 study and had the informed consent signed by their parents or by themselves, if in legal
44 age.
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55 The echocardiographic screening was performed from 2014 to 2016 by
56 previously trained non-physicians (nurses and imaging technicians) and later uploaded to
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3 dedicated cloud storage systems and interpreted through telemedicine by cardiologists in
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5 Brazil and the US¹², applying the WHF criteria. Detailed screening methodology has been
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7 previously published^{4,5}.
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10 Participants with abnormal screening were invited for the UFMG Pediatric
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12 Cardiology outpatient clinics, and were prospectively enrolled. All patients included in
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14 the follow-up from Belo Horizonte had the baseline screening diagnosis confirmed by
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16 standard echocardiography, scheduled in the University Hospital. The ones from Montes
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18 Claros had the diagnosis based on consensus reads of VSCAN studies. Specific care of
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20 these patients was left to the discretion of the caring cardiologist with experience in RHD.
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22 Follow-up consisted of clinical examination by a pediatrician (BB, AD), with
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24 standardized clinical history and physical examination, and standard echocardiogram by
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26 an experienced pediatric cardiologist (SR) (Vivid IQ®, GE Healthcare, Milwaukee, WI,
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28 USA), blinded to the findings of the previous exam, and based on the WHF criteria. A
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30 standardized imaging protocol was applied. Patients were then reclassified by consensus
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32 in the 4 pre-established categories. Specific care of these patients and indication of
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34 secondary prophylaxis – not mandatory for any category – was left to the discretion of
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36 the caring cardiologist (ZM, FA and MCN). All echo variables were systematically
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38 collected in a dedicated online database.
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45 The simplified echocardiographic score proposed by Nunes *et al*, consisting of 5
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47 variables (mitral valve anterior leaflet thickening, excessive leaflet tip motion, and
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49 regurgitation jet length ≥ 2 cm, and aortic valve focal thickening and any regurgitation)⁹
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51 was applied to this population. Disease unfavorable outcome assessed by
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53 echocardiogram was defined as worsening in diagnostic
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55 category (borderline to definite), remaining with mild definite RHD
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57 or worsening in the grade of mitral or aortic valve
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3 regurgitation or development/worsening grade of mitral
4 stenosis. Favorable outcome was defined as disease regression – considered when an
5 improvement in diagnostic category was observed or in case of reduction of regurgitation
6 severity – or remaining with stable borderline disease.
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11 ***Patient and public involvement***

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14 The study participants were not involved in the design of this study. No patient
15 involvement.
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18 ***Data analysis and statistics***

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21 Data were systematically entered to the RedCap® online database¹³. Statistical
22 analysis was performed using SPSS® software version 23.0 for Mac OSX (SPSS Inc.,
23 Chicago, Illinois). Continuous variables were expressed as mean ± standard deviation
24 (SD) or as median and interquartile range (IQR, [Q1/Q3]) when appropriate. Categorical
25 variables were expressed as absolute values and percentages. The between-group
26 comparison (progression vs regression/stable) was performed using the Fisher's Exact
27 Test for categorical variables.
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38 The simplified echo score⁹ was applied to this population of schoolchildren to
39 assess its discrimination and calibration in predicting disease unfavorable outcome using
40 logistic regression. The predictive value of the score was assessed as a time-dependent
41 variable in the Cox proportional hazards model. RHD favorable outcome rates of the 3
42 risk categories (low/intermediate/high) were estimated by the Kaplan–Meier method and
43 compared by the log-rank test. A two-tailed significance level of 0.05 was considered
44 statistically significant.
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56 **Results:**

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58 Total 197 patients were included, being 114 (36%) out of 317 children with
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3 positive screening echos in Belo Horizonte and 83 (37%) of 224 in Montes Claros, with
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5 a mean 29 ± 9 (range 11 to 48) months follow-up, considering the latest clinical visit. At
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7 baseline, 170 (86.3%) had borderline and 27 (13.7%) definite RHD. Median age was 14.1
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9 (IQR 12.0 – 16.2) years, and 130 (66%) were female. Belo Horizonte and Montes Claros
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11 had similar rates of borderline (85.1% vs. 88.0%) and definite (14.9% vs. 12.0%) RHD
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13 at baseline ($p=0.56$). Only 13 (6.6%) patients were regularly receiving Penicillin (7 with
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15 $<80\%$ adherence), 4 in the definite RHD group. Detailed baseline demographic and
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17 echocardiographic characteristics are depicted in **Table 1**. Compared to the 344 patients
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19 without follow-up, the study sample had similar baseline distribution of
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21 borderline/definite diagnoses (86.3%/13.7% vs. 89.5%/10.5%, $p=0.26$) as well as WHF
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23 subgroups for borderline ($p=0.27$) and definite ($p=0.10$) RHD, human development index
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25 (0.77 [IQR 0.76 – 0.80] vs. 0.77 [IQR 0.76 – 0.80], $p=0.22$, household (4 [IQR 4 – 5] vs.
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27 4 [IQR 4 – 6] inhabitants, $p=0.25$) and age (14.2 [IQR 12.0 – 16.2] vs. 14.1 [IQR 11.8 –
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29 15.8] years, $p=0.46$), but a slightly higher proportion of females (66.3% vs. 57.0%,
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31 $p=0.03$) was observed.
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38 Cardiovascular symptoms were reported by 69 (35%) patients in the follow-up
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40 visits, including dyspnea (15.2%) and palpitations (14.2%). However, clinical evaluation,
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42 physical examination, and echocardiograms did not support a cardiac etiology of these
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44 symptoms. During follow-up, at least 1 episode of pharyngitis was reported by 92
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46 patients, being 62 (67%) adequately treated in primary care, as informed by patients or
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48 parents.
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52 Among patients with borderline RHD, 29 (17.1%) progressed to definite RHD, 49
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54 (28.8%) remained stable, 86 (50.6%) regressed to normal and 6 (3.5%) were reclassified
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56 as other heart diseases. Among those with definite RHD, 13 (48.1%) remained in the
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58 category, while 5 (18.5%) regressed to borderline, 5 (18.5%) regressed to normal and 4
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(14.8%) were reclassified as other heart disease (**Figure 1**). No patients had worsening grade of mitral or aortic regurgitation or development/worsening grade of mitral stenosis.

Among borderline patients who progressed, 26 (89.7%) had mitral regurgitation (MR), 2 had aortic regurgitation and 14 (48.3%) had at least 1 morphological abnormality of the mitral valve as the initial criteria. At follow-up, 12 patients developed morphological abnormalities of the mitral (N=10) and aortic (N=4) valves. No patients developed ventricular dysfunction or enlargement (**Table 2**).

Predictive Performance of the simplified echocardiographic score

The simplified score, based on components of the WHF criteria, was a significant predictor of RHD unfavorable outcome (hazard ratio [HR] 1.197, 95% confidence interval [CI] 1.098 - 1.305, $p < 0.001$). The discrimination of the score was good (C-statistic=0.714, 95% CI 0.627 - 0.801) and the model was well calibrated (**Appendix Figure 1**). A Hosmer-Lemeshow $p = 0.589$ confirmed no significant difference between observed and predicted unfavorable outcome (**Appendix Figure 2, A and B**).

The score classified 121 children in low risk, 48 in the intermediate risk, and 28 in the high-risk groups. Additionally, the score model was able to separate low-, intermediate- and high-risk categories for disease unfavorable outcome (**Figure 2**). Favorable outcome RHD risk rate in the low-risk children at 1-, and 2-years follow-up was 99%, and 97% respectively, compared to 76%, and 47% in the high-risk group.

Discussion:

In agreement with growing international data⁸, subclinical RHD in Brazil has a variable outcome. Approximately 1 in 5 children with borderline RHD progressed to definite RHD and more than 1 in 3 children with definite RHD remained in this category.

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3 A recently developed risk stratification score⁹ was a modest, but significant, predictor of
4 unfavorable echocardiographic outcome in our population.
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8 Since its inception, the PROVAR research program has been studying the use of
9 echocardiography to improve the early detection of RHD¹² in Brazil. Epidemiologically
10 characterization of RHD prevalence, and study of portable and handheld devices, task-
11 shifting, and telemedicine have been undertaken to understand how to improve diagnostic
12 access in low-resource populations in Brazil^{4 10 12 14}. Determining outcomes for children
13 with subclinical RHD is a critical next step to inform program evaluation, as for other
14 screening programs worldwide. These data, with a mean follow-up of 29-months, show
15 that both borderline and definite RHD are dynamic phenotypes, with borderline RHD
16 showing more favorable outcomes^{6 8 15}.
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29 Nearly half (46%) of the youth in this program improved echocardiographically
30 to normal, similar to global rates ranging from 47-67%^{8 16}. Yet borderline RHD was not
31 a benign finding, with one in five (17%) of children progressing to definite RHD, in line
32 with global data which has reported 17-23% progression at 2.5-7.5 years of follow-up^{8 17}
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18. Children with definite RHD at diagnosis had more unfavorable outcomes with 40%
remaining definite, though no child progressed to moderate or severe RHD, reflecting a
mildly phenotype in screen-detected RHD in Brazilian youth compared to global data^{8 15}
^{17 19 20}. This milder phenotype may reflect the relatively stronger public health system in
Brazil, compared to many other RHD-endemic areas, facilitating higher rates of sore
throat and rheumatic fever diagnoses, but more data are needed. The impact of secondary
prophylaxis in this cohort cannot be determined, as few were prescribed prophylaxis and
adherence was not well captured, and we await the results of a large randomized clinical
trial on the impact of penicillin prophylaxis in screen-detected youth, currently ongoing
in Uganda (*Gwoko Adunu pa Lutino*; clinicaltrials.gov No. NCT03346525).

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3 The most novel aspect of this follow-up study was the application of a newly
4 developed score to predict unfavorable outcome among children with screen-detected
5 RHD⁹. Addressing the need to simplify the WHF criteria and improve the applicability
6 for use with handheld echocardiography (lacking spectral Doppler), Nunes et al
7 developed a five-component point-based score that showed considerable accuracy for
8 predicting disease progression in two large African cohorts⁹. The score showed modest
9 discrimination for unfavorable outcome in our population, potentially related to the less
10 aggressive RHD phenotype in Brazil as compared to African cohorts^{8 19}, suggesting wider
11 external validation and recalibration may be necessary for global application. However,
12 still in a population with a relatively low risk of progression – especially to clinically
13 significant disease – its discrimination of subgroups at higher risk of unfavorable
14 echocardiographic outcome point towards an useful public health tool, and urges further
15 investigations.

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33 The PROVAR program has encountered several context-specific limitations and
34 lessons learned. First, the program has struggled with low-participation and high attrition
35 compared to other global populations: only 40% of students have consented to school-
36 based screening⁵ and only 36% of screen-positive children from the schools were enrolled
37 in follow-up. Much higher rates of follow-up were seen in primary healthcare screening
38 (84.4%⁵), suggesting this location is more appropriate in our context. Second, absent a
39 gold standard, initiation of penicillin prophylaxis was left to the discretion of the treating
40 physician. Low rates of prescription were seen compared to those reported globally,
41 suggesting the need for widespread provider education based on the results from the
42 GOAL study (*Gwoko Adunu pa Lutino*; clinicaltrials.gov No. NCT03346525). Finally,
43 no child progressed to clinically significant RHD, suggesting the timeline of progression
44 may be longer in the Brazilian context. This may have important implications on when to
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3 screen and cost-effectiveness evaluations. Despite these limitations, the PROVAR
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5 program is the only longitudinal program evaluating the impact of echocardiographic
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7 screening in Latin America.
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10 11 12 **Conclusion:**

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14 These data suggest that screen-detected RHD in Brazil is not benign; patients with
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16 definite RHD are likely to remain in this category, and progression rates of borderline
17
18 RHD are not negligible. The simplified echocardiography score⁹ assessed in an
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20 independent population with predominantly low-risk for RHD progression was accurate
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22 to predict early disease unfavorable outcome. Additional investigations are needed to
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24 establish the long-term prognosis of subclinical RHD, and the effects of prophylaxis in
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26 high-risk subgroups.
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33 **Conflicts of interest:**

34
35 The authors have no conflicts of interest to declare regarding this manuscript.
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40 **Author contributions:**

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42 Conception and design of the research: Bechtluft, BMF, Nascimento, BR, Sable,
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44 C, Beaton, AZ, Nunes, MCP, Ribeiro, AL; Acquisition of data: Bechtluft, BMF, Fraga,
45
46 CL, Barbosa, MM, Reis, SDP, Meira, ZMA, Castilho, SRT, Arantes, NF, Oliveira, KKB,
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48 Castro, L, Rezende, BDF, Costa, WAA, Mata, MDO, Pereira, AFC; Analysis and
49
50 interpretation of data: Nascimento, BR, Nunes, MCP, Sable, C, Beaton, AZ, Reis, SDP,
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52 Meira, ZMA, Castilho, SRT, Arantes, NF; Statistical analysis: Nascimento, BR, Ribeiro,
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54 AL, Sable, C; Obtaining financing: Beaton, AZ, Sable, C, Nascimento, BR; Writing of
55
56 the manuscript: Bechtluft, BMF, Nascimento, BR, Sable, C, Nunes, MCP; Critical
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3 revision of the manuscript for intellectual content: All authors; Authors responsible for
4 the overall content as guarantors: Bechtluft, BMF, Nascimento, BR, Beaton, AZ,
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revision of the manuscript for intellectual content: All authors; Authors responsible for the overall content as guarantors: Bechtluft, BMF, Nascimento, BR, Beaton, AZ, Ribeiro, AL, Sable, C, Nunes, MCP.

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Data sharing statement:

Data analytic methods and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure, from the corresponding author upon reasonable request.

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Tables:**Table 1:** Baseline characteristics of patients with borderline and definite rheumatic heart disease.

Variable:	Result:
Borderline RHD (N=170)	
Age (years), median (IQR)	14 (11 – 16)
Female gender, N (%)	111 (65.7)
Follow-up period (months), mean \pm SD	28.9 \pm 9.0
1. At least two morphological features of RHD of the MV without pathological MR or MS	1. 5 (2.9)
2. Pathological MR	2. 135 (79.4)
3. Pathological AR	3. 30 (17.6)
Definite RHD (N=27)	
Age (years), median (IQR)	14.0 (12 – 16)
Female gender, N (%)	19 (70.4)
Follow-up period (months), mean \pm SD	29.5 \pm 9.2
1. Pathological MR and at least two morphological features of RHD of the MV	1. 24 (88.9)
2. MS mean gradient \geq 4 mmHg	2. 0
3. Pathological AR and at least two morphological features of RHD of the AV	3. 0
4. Borderline disease of both the AV and MV	4. 3 (11.1)

Abbreviations: AV: aortic valve; AR: aortic regurgitation; IQR: interquartile range (Q1 – Q3); MR: mitral regurgitation; MS: mitral stenosis; MV: mitral valve; RHD: rheumatic heart disease; SD: standard deviation.

Table 2: Baseline echocardiographic variables of patients with progression, stabilization and regression of rheumatic heart disease at 2-year follow-up.

Valve:	Variable:	Progressed: Borderline Definite (N=29)	to Definite (N=11)	Remained stable (borderline) / other (N=156)
Mitral valve, N (%):	Anterior leaflet thickening	18 (62.1)		10 (90.9)
	Chordal thickening	0		2 (18.2)
	Restricted leaflet motion	1 (3.4)		4 (36.4)
	Excessive leaflet tip motion	2 (6.9)		6 (54.5)
	Mitral stenosis	0		0
	Any regurgitation	28 (96.6)		11 (100)
	Regurgitation seen in 2 views	26 (89.7)		10 (90.9)
	Jet length ≥ 2 cm\ddagger	25 (86.2)		9 (81.8)
	Velocity ≥ 3 m/s for 1 envelope\S	9 (31.0)		4 (36.4)
	Pansystolic jet (color Doppler)	15 (51.7)		8 (72.7)
Aortic valve, N (%):	Irregular or focal thickening	0		2 (18.2)
	Coaptation defect	0		1 (9.1)
	Restricted leaflet motion	0		0
	Leaflet Prolapse	0		0
	Any regurgitation	2 (6.9)		3 (27.3)
	Regurgitation seen in 2 views	2 (6.9)		2 (18.2)
	Jet length ≥ 1 cm\ddagger	1 (3.5)		3 (27.3)
	Velocity ≥ 3 m/s in early diastole\S	0		1 (9.1)
		Pandiatolic jet (color Doppler)	0	

Abbreviations: *Congenital mitral valve or aortic valve abnormalities were excluded. \ddagger Abnormal thickening of the anterior mitral valve leaflet ≥ 3 or >4 mm using harmonic imaging. \ddagger In at least 1 view. \S Measurements available with the Vivid-Q exams.

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3 **Figures legends:**
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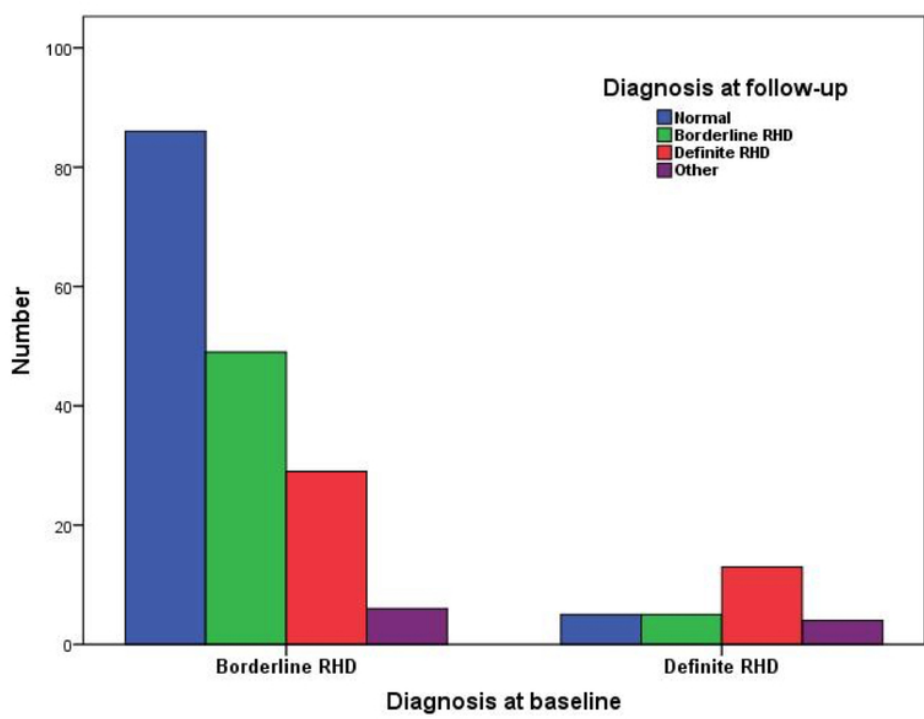
5 **Figure 1:** RHD progression during the follow-up according to diagnosis at baseline.
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7 **Figure 2:** Cumulative incidence of disease unfavorable outcome in children with
8 echocardiography-detected RHD according to according to risk categories of the
9 simplified score.
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17 **Appendix Figure 1:** Receiver operator characteristic curve for echocardiography score
18 showing predicted probability from the model (C-statistic of 0.71).
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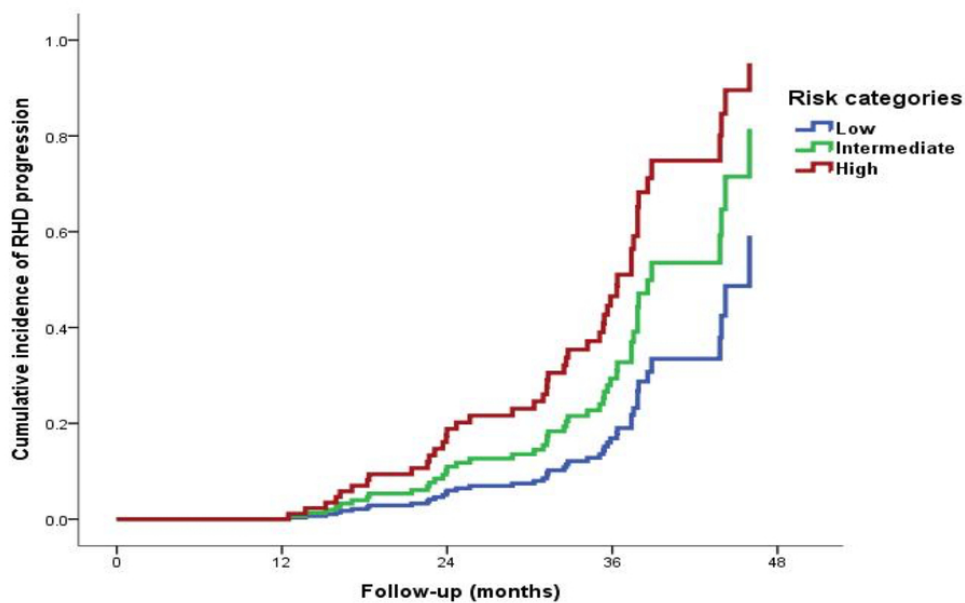
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21 **Appendix Figure 2:** (A) Calibration plots by quintiles for RHD progression risk
22 prediction model in the validation cohort. (B) Calibration plots by quintiles for favorable
23 outcome RHD risk prediction model in the validation cohort.
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RHD progression during the follow-up according to diagnosis at baseline.

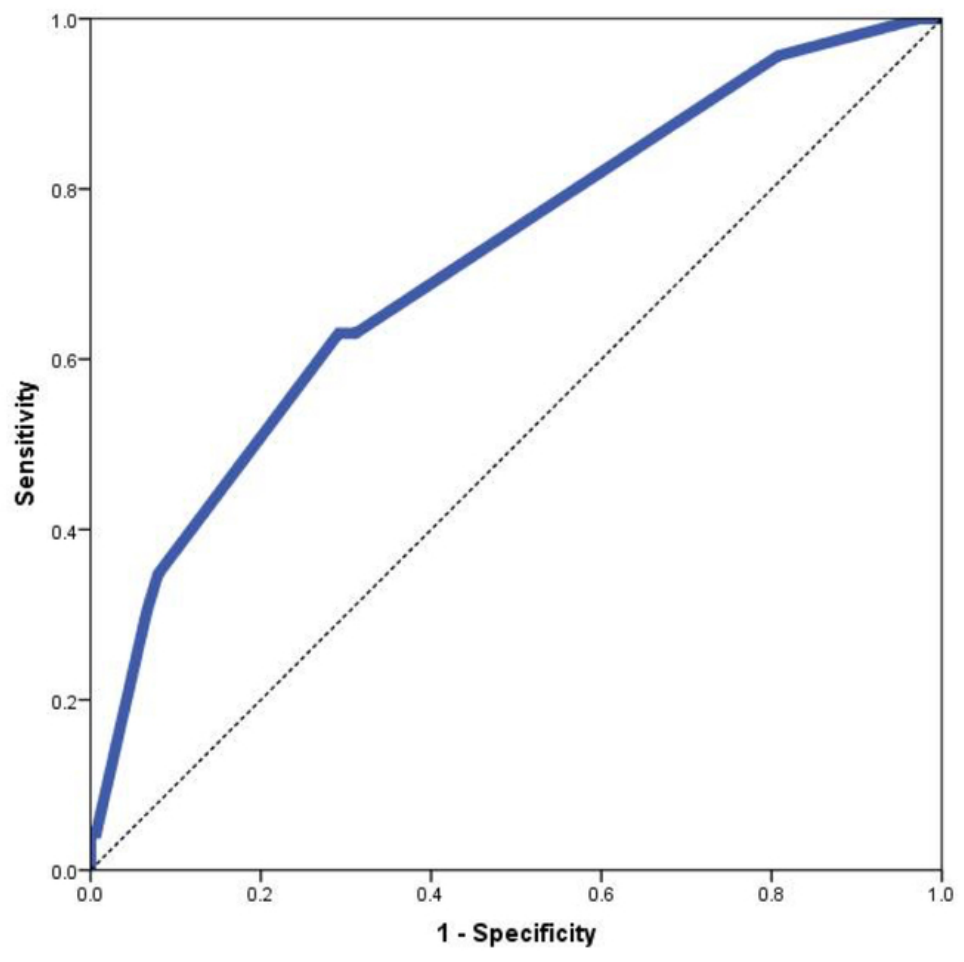
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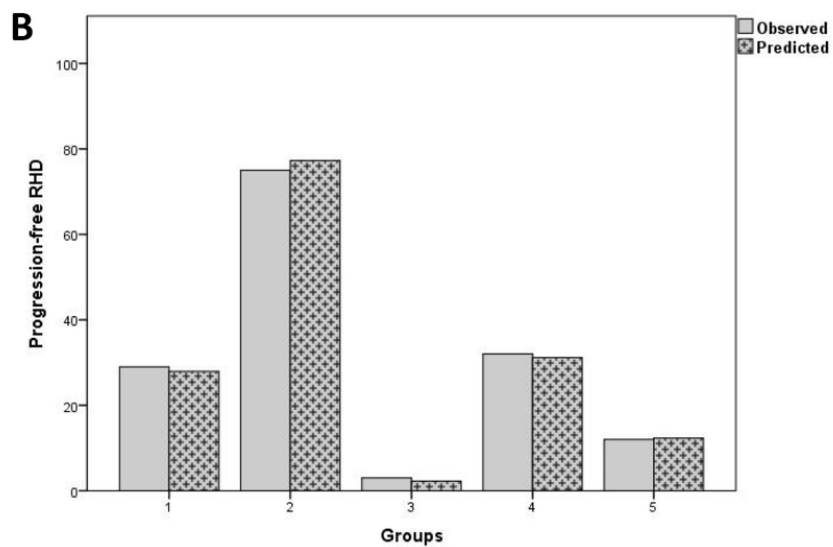
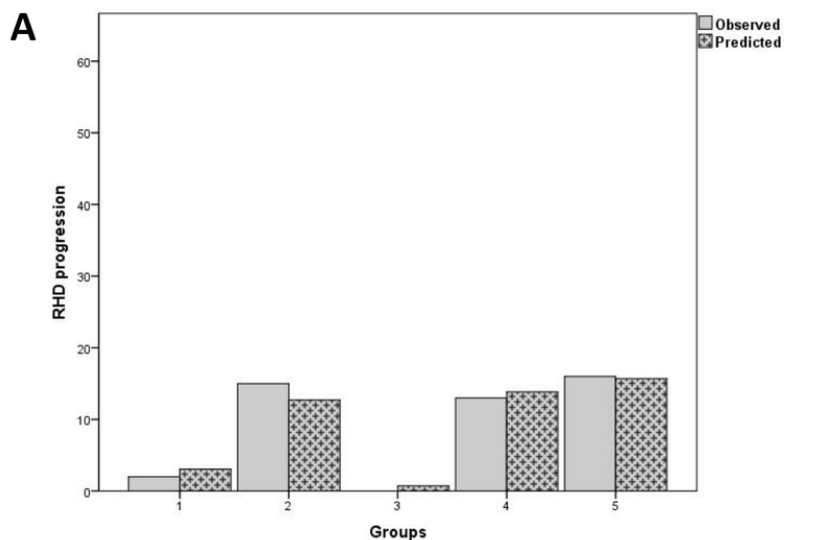
Cumulative incidence of disease unfavorable outcome in children with echocardiography-detected RHD according to according to risk categories of the simplified score.

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Reporting checklist for prediction model development and validation study.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPOD reporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

	Reporting Item	Page Number
Title		
	#1 Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract		
	#2 Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction		
	#3a Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	1, 2
	#3b Specify the objectives, including whether the study describes the	2

development or validation of the model or both.

Methods

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3	Methods		
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5	Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.
6			6, 7
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10	Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.
11			7,8
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14	Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.
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18	Participants	#5b	Describe eligibility criteria for participants.
19			6
20	Participants	#5c	Give details of treatments received, if relevant
21			7
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23	Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.
24			8
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26	Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.
27			N/A
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29	Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured
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34	Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.
35			N/A
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38	Sample size	#8	Explain how the study size was arrived at.
39			9
40	Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.
41			N/A
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45	Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.
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49	Statistical analysis methods	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.
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54	Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.
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58	Statistical analysis	#10d	Specify all measures used to assess model performance and, if relevant,
59			N/A

1	methods		to compare multiple models.	
2	Statistical analysis	#10e	If you are validating a prediction model, describe any model updating	N/A
3	methods		(e.g., recalibration) arising from the validation, if done	
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6	Risk groups	#11	Provide details on how risk groups were created, if done.	N/A
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8	Development vs.	#12	For validation, identify any differences from the development data in	8
9	validation		setting, eligibility criteria, outcome, and predictors.	
10				
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12	Results			
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14	Participants	#13a	Describe the flow of participants through the study, including the	9,10
15			number of participants with and without the outcome and, if applicable,	
16			a summary of the follow-up time. A diagram may be helpful.	
17				
18	Participants	#13b	Describe the characteristics of the participants (basic demographics,	9
19			clinical features, available predictors), including the number of	
20			participants with missing data for predictors and outcome.	
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22	Participants	#13c	For validation, show a comparison with the development data of the	9, 10
23			distribution of important variables (demographics, predictors and	
24			outcome).	
25				
26	Model	#14a	If developing a model, specify the number of participants and outcome	10
27	development		events in each analysis.	
28				
29	Model	#14b	If developing a model, report the unadjusted association, if calculated	N/A
30	development		between each candidate predictor and outcome.	
31				
32	Model	#15a	If developing a model, present the full prediction model to allow	9, 10
33	specification		predictions for individuals (i.e., all regression coefficients, and model	
34			intercept or baseline survival at a given time point).	
35				
36	Model	#15b	If developing a prediction model, explain how to the use it.	10
37	specification			
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39	Model	#16	Report performance measures (with CIs) for the prediction model.	10
40	performance			
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42	Model-updating	#17	If validating a model, report the results from any model updating, if	N/A
43			done (i.e., model specification, model performance).	
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46	Discussion			
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48	Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample,	12, 13
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few events per predictor, missing data).

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3	Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data 12
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6	Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. 11 - 13
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10	Implications	#20	Discuss the potential clinical use of the model and implications for future research 12
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14	Other		
15	information		
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18	Supplementary	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. 20
19	information		
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21	Funding	#22	Give the source of funding and the role of the funders for the present study. 14
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BMJ Open

Validation of a Simplified Score for Predicting Latent Rheumatic Heart Disease Progression Utilizing a Prospective Cohort of Brazilian Schoolchildren

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-036827.R1
Article Type:	Original research
Date Submitted by the Author:	03-Feb-2020
Complete List of Authors:	<p>Bechtluft, Bárbara; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Nascimento, Bruno; Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Sable, Craig ; Children's National Health System Washington, Cardiology Fraga, Clara; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Barbosa, Márcia; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Reis, Susana; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Diamantino, Adriana; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Meira, Zilda Maria; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Castilho, Sandra Regina; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Arantes, Nayana; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Oliveira, Kaciane; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Silva, José Luiz; Universidade Federal de Minas Gerais, Departamento de Estatística Rezende, Breno; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Costa, Waydder Antônio; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Mata, Mariana; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Pereira, Augusto; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Ribeiro, Antonio Luiz; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular Beaton, Andrea; Cincinnati Children's Hospital Medical Center, Cardiology Pereira Nunes, Maria Carmo; Hospital das Clínicas da Universidade Federal de Minas Gerais, Serviço de Cardiologia e Cirurgia Cardiovascular</p>
Primary Subject Heading:	Cardiovascular medicine

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Secondary Subject Heading:	Epidemiology, Paediatrics
Keywords:	Paediatric rheumatology < PAEDIATRICS, Echocardiography < RADIOLOGY & IMAGING, Paediatric cardiology < RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Ultrasound < RADIOLOGY & IMAGING





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3 **1 Validation of a Simplified Score for Predicting Latent Rheumatic Heart Disease**
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5 **2 Progression Utilizing a Prospective Cohort of Brazilian Schoolchildren**
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23 On behalf of the PROVAR (*Programa de Rastreamento da Valvopatia Reumática*) investigators.
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3 31 **Abstract:**
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5 32 **Objectives:** Echocardiographic (echo) screening is an important tool to estimate
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8 33 rheumatic heart disease (RHD) prevalence, but the natural history of screen-detected
9
10 34 RHD remains unclear. The PROVAR+ study, which uses non-experts, telemedicine and
11
12 35 portable echo, pioneered RHD screening in Brazil. We aimed to assess the mid-term
13
14 36 evolution of Brazilian schoolchildren (5-18 years) with echocardiography-detected
15
16 37 subclinical RHD and to assess the performance of a simplified score consisting of 5
17
18 38 components of the WHF criteria, as a predictor of unfavorable echocardiographic
19
20 39 outcomes.
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23
24 40 **Setting:** Public schools of underserved areas and private schools in Minas Gerais,
25
26 41 southeast Brazil.
27

28 42 **Participants:** Total 197 patients (170 borderline and 27 definite RHD) with follow-up of
29
30 43 29±9 months were included. Median age was 14 (12–16) years, and 130 (66%) were
31
32 44 female. Only 4 patients in the definite group were regularly receiving penicillin.
33
34

35 45 **Primary and secondary outcome measures:** Unfavorable outcome was based on the 2-
36
37 46 years follow-up echo, defined as worsening diagnostic category, remaining with mild
38
39 47 definite RHD or development/worsening of valve regurgitation/stenosis.
40
41

42 48 **Results:** Among patients with borderline RHD, 29 (17.1%) progressed to definite, 49
43
44 49 (28.8%) remained stable, 86 (50.6%) regressed to normal and 6 (3.5%) were reclassified
45
46 50 as other heart diseases. Among those with definite RHD, 13 (48.1%) remained in the
47
48 51 category, while 5 (18.5%) regressed to borderline, 5 (18.5%) regressed to normal and 4
49
50 52 (14.8%) were reclassified as other heart disease. The simplified echo score was a
51
52 53 significant predictor of RHD unfavorable outcome (hazard ratio [HR] 1.197, 95%
53
54 54 confidence interval 1.098-1.305, $p<0.001$).
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58 55 **Conclusion:** The simple risk score provided an accurate prediction of RHD status at 2-
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3 56 year follow-up, showing a good performance in Brazilian schoolchildren, with a potential
4
5 57 value for risk stratification and monitoring of echocardiography-detected RHD.
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7

8 **Trial registration:** N/A.
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10 59
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12 **Key-words:** Rheumatic heart disease; screening; echocardiography; follow-up;
13
14 61 prognosis.
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16

17 **Word count:** 2,456
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19 63

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21
22 64 **Strengths and limitations of this study:**
23

- 24 65 • This study utilized the PROVAR+ cohort, the first large prospective cohort of
25
26 66 schoolchildren with latent RHD in Brazil.
27
28 67 • This is the first validation study of a previously published (2019) scoring system
29
30 68 to discriminate children found to have early echocardiography evidence of RHD
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32 69 into those who are likely to have favorable vs. unfavorable outcome.
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34 70 • Echocardiograms were interpreted by the consensus of two experts with high
35
36 71 familiarity in the World Heart Federation Criteria.
37
38 72 • As this was an established cohort, no predefined sample size was calculated for
39
40 73 this study and all screen-positive patients were invited for follow-up.
41
42 74 • A passive recruitment strategy meant that there was low overall participation; only
43
44 75 36% of screen-positive children were enrolled in the follow-up program, reducing
45
46 76 the size of the potential cohort.
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106 **Introduction**

107 Rheumatic heart disease (RHD) is the major cause of acquired cardiovascular
108 disease in children and young adults worldwide. Its global burden is noteworthy, affecting
109 39 million people and causing 319,400 deaths annually^{1 2}. The disease is more prevalent
110 in low and middle-income countries, where it is typically diagnosed only once advanced
111 valve disease is present and symptoms develop¹. However, there is a latent period, often
112 up to decade, between the first episode of acute rheumatic fever (ARF) and advanced
113 RHD, when early identification can improve outcomes.

114 In this context, echocardiographic screening in endemic areas has emerged as an
115 effective approach to identify patients who are in this latent, subclinical stage of RHD³⁻⁶.
116 Diagnostic criteria for subclinical RHD– asymptomatic patients with echocardiographic
117 findings suggestive of RHD without history of ARF – have been standardized by the
118 World Heart Federation (WHF) consensus in 2012. Three categories are defined: definite,
119 borderline and normal⁷. The morphological findings of RHD and the criteria for
120 pathologic valve regurgitation are also established. This standardization has allowed for
121 comparison between studies carried out in different populations.

122 Although criteria are standardized, prognosis and natural history of latent RHD,
123 and the impact of clinical interventions – such as secondary prophylaxis – still require
124 further evaluation. The first studies that evaluated the follow-up of patients with
125 subclinical RHD have several limitations, including relatively short follow-up times,
126 small sample size and lack of standardized criteria for echocardiographic and clinical
127 progression⁸. However, data suggests that RHD progression in children with latent RHD
128 is not negligible⁹. Therefore, we aimed to assess the mid-term evolution of Brazilian
129 schoolchildren (5-18 years) with subclinical RHD findings observed in
130 echocardiographic screening^{4 5 10} and to assess the performance of a simplified score

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3 131 developed by Nunes *et al*⁹, consisting of 5 components of the WHF criteria, as a predictor
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5 132 of unfavorable echocardiographic outcomes.
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10 134 **Methods:**

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12 135 This is a prospective cohort study with systematic clinical and echocardiographic
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14 136 follow-up of children with subclinical RHD. It was derived from a RHD screening
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16 137 program, established in Brazil in 2014 - the PROVAR+ (*Programa de Rastreamento da*
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18 138 *Valvopatia Reumática*) study - a collaboration between the Children's National Health
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20 139 System, Washington – DC, US, the Universidade Federal de Minas Gerais and the
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22 140 Telehealth Network of Minas Gerais¹¹, Belo Horizonte, Minas Gerais, Brazil. This
23
24 141 screening program has already screened more than 12,000 children and adolescents from
25
26 142 21 schools in Minas Gerais, Brazil, between October 2014 and December 2016^{4 5 10}. The
27
28 143 study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and
29
30 144 ethics approval was obtained from the institutional review boards of the participant
31
32 145 institutions (Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais and
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34 146 Children's National Health System Institutional Review Board) as well as from the local
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36 147 Boards of Health and Education.
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42 148 In brief, public schools and primary care centers from low income areas of
43
44 149 metropolitan Belo Horizonte, Brazil, were selected to participate in the screening
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46 150 program, based on socioeconomic data (Human Development Index (HDI)) and priorities
47
48 151 of the health authorities. Selected private schools (2) were also invited in order to
49
50 152 characterize RHD in high-income youth. All asymptomatic students, without history of
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52 153 ARF or RHD, were eligible for screening^{4 5}. All participants were informed about the
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54 154 study and had informed consent signed by their parents or by themselves, if of legal age.
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3 155 The echocardiographic screening was performed from 2014 to 2016 by
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5 156 previously trained non-physicians (nurses and imaging technicians) and images were
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7 157 uploaded to a dedicated cloud storage system and interpreted through telemedicine by
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9 158 cardiologists in Brazil and the US¹², applying the WHF criteria. Detailed screening
10
11 159 methodology has been previously published^{4 5}.

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14 160 Participants with abnormal screening were invited for the UFMG Pediatric
15
16 161 Cardiology outpatient clinics, and were prospectively enrolled. All patients included in
17
18 162 the follow-up from Belo Horizonte had the baseline screening diagnosis confirmed by
19
20 163 standard echocardiography, scheduled in the University Hospital. The ones from Montes
21
22 164 Claros had the diagnosis based on consensus reads of VSCAN studies. Specific care of
23
24 165 these patients was left to the discretion of the caring cardiologist with experience in RHD.
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26 166 Families received phone reminders of the follow-up visits and, when necessary, study
27
28 167 correspondence by mail. The prespecified 24-month follow-up consisted of a clinical
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30 168 appointment by a pediatrician (BB, AD), with standardized clinical history
31
32 169 (demographics, comorbidities, cardiovascular symptoms, recurrence of pharyngitis,
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34 170 medications and adherence to prophylaxis – when indicated) and detailed physical
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36 171 examination forms, and standard echocardiogram by an experienced pediatric
37
38 172 cardiologist (SR) (Vivid IQ®, GE Healthcare, Milwaukee, WI, USA), blinded to the
39
40 173 findings of the previous exam, and based on the WHF criteria. A standardized imaging
41
42 174 protocol was applied. Patients were then reclassified by consensus with adjudication by
43
44 175 2 experts (MCN and ZM) in the 4 pre-established categories. Specific care of these
45
46 176 patients and indication for secondary prophylaxis – not mandatory for any category – was
47
48 177 left to the discretion of the caring cardiologist (ZM, SRC and MCN). All echo and clinical
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50 178 variables were systematically collected in a dedicated online database.
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3 179 The simplified echocardiographic score proposed by Nunes *et al*, consisting of 5
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5 180 variables (mitral valve anterior leaflet thickening, excessive leaflet tip motion, and
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7
8 181 regurgitation jet length ≥ 2 cm, and aortic valve focal thickening and any regurgitation)⁹
9
10 182 was applied to this population. An unfavorable outcome was defined as
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13 183 worsening in diagnostic category (borderline to definite),
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15 184 remaining with mild definite RHD or worsening in the grade of mitral
16
17 185 or aortic valve regurgitation or development/worsening grade
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19
20 186 of mitral stenosis. A favorable outcome was defined as disease regression –
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22 187 considered when an improvement in diagnostic category was observed or in case of
23
24 188 reduction of regurgitation severity – or remaining with stable borderline RHD.
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26 189 ***Patient and public involvement***

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29 190 Patients and public were not involved in the design and conduct of this research.
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31 191 ***Data analysis and statistics***

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34 192 Data were systematically entered to the RedCap® online database¹³. Statistical
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36 193 analysis was performed using SPSS® software version 23.0 for Mac OSX (SPSS Inc.,
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38 194 Chicago, Illinois). As we utilized a pre-existing cohort, no pre-specified sample size
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40 195 calculation was performed, and we considered the total sample of asymptomatic
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42 196 schoolchildren enrolled in the 26-month screening. All screen-positive children who
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44 197 attended the follow-up visit were included in this analysis. Continuous variables were
45
46 198 expressed as mean \pm standard deviation (SD) or as median and interquartile range (IQR,
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48 199 [Q1/Q3]) when appropriate. Categorical variables were expressed as absolute values and
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50 200 percentages. The between-group comparison (progression vs regression/stable) was
51
52 201 performed using the Fisher's Exact Test for categorical variables.
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56 202 The simplified echo score⁹ was applied to this population of schoolchildren to
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58 203 assess its discrimination and calibration in predicting unfavorable outcome using logistic
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3 204 regression. The predictive value of the score was assessed as a time-dependent variable
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5 205 in the Cox proportional hazards model. RHD favorable outcome rates of the 3 risk
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7 206 categories (low/intermediate/high), based on the hazard of evolving with unfavorable
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9 207 echo outcome, were estimated by the Kaplan–Meier method and compared by the log-
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11
12 208 rank test. A two-tailed significance level of 0.05 was considered statistically significant.
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17 210 **Results:**

19 211 Total 197 patients were included, being 114 (36%) out of 317 children with
20
21 212 positive screening echos in Belo Horizonte and 83 (37%) of 224 in Montes Claros, with
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23 213 a mean 29±9 (range 11 to 48) months follow-up, considering the latest clinical visit. At
24
25 214 baseline, 170 (86.3%) had borderline and 27 (13.7%) definite RHD. Median age was 14.1
26
27 215 (IQR 12.0 – 16.2) years, and 130 (66%) were female. Belo Horizonte and Montes Claros
28
29 216 had similar rates of borderline (85.1% vs. 88.0%) and definite (14.9% vs. 12.0%) RHD
30
31 217 at baseline (p=0.56). Only 13 (6.6%) patients, 4 of whom originally classified as definite
32
33 218 RHD, were regularly receiving Penicillin (7 with <80% adherence). Detailed baseline
34
35 219 demographic and echocardiographic characteristics are depicted in **Table 1**. Compared to
36
37 220 the 344 patients without follow-up, the study sample had similar baseline distribution of
38
39 221 borderline/definite diagnoses (86.3%/13.7% vs. 89.5%/10.5%, p=0.26) as well as WHF
40
41 222 subgroups for borderline (p=0.27) and definite (p=0.10) RHD, human development index
42
43 223 (0.77 [IQR 0.76 – 0.80] vs. 0.77 [IQR 0.76 – 0.80], p=0.22, household (4 [IQR 4 – 5] vs.
44
45 224 4 [IQR 4 – 6] inhabitants, p=0.25) and age (14.2 [IQR 12.0 – 16.2] vs. 14.1 [IQR 11.8 –
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47 225 15.8] years, p=0.46), but a slightly higher proportion of females (66.3% vs. 57.0%,
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49 226 p=0.03) was observed.
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56 227 Cardiovascular symptoms were reported by 69 (35%) patients in the follow-up
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58 228 visits, including dyspnea (15.2%) and palpitations (14.2%). However, clinical evaluation,
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3 229 physical examination, and echocardiograms did not support a cardiac etiology of these
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5 230 symptoms. During follow-up, at least 1 episode of pharyngitis was reported by 92
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7 231 patients, with 62 (67%) adequately treated in primary care, as informed by patients or
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9 232 parents.

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12 233 Among patients with borderline RHD, 29 (17.1%) progressed to definite RHD, 49
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14 234 (28.8%) remained stable, 86 (50.6%) regressed to normal and 6 (3.5%) were reclassified
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16 235 as other heart diseases. Among those with definite RHD, 13 (48.1%) remained in the
17
18 236 category, while 5 (18.5%) regressed to borderline, 5 (18.5%) regressed to normal and 4
19
20 237 (14.8%) were reclassified as other heart disease (**Figure 1**). No patients had worsening
21
22 238 grade of mitral or aortic regurgitation or
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24 239 development/worsening grade of mitral stenosis.

25
26 240 Among borderline patients who progressed, 26 (89.7%) had mitral regurgitation
27
28 241 (MR), 2 had aortic regurgitation and 14 (48.3%) had at least 1 morphological abnormality
29
30 242 of the mitral valve as the initial criteria. At follow-up, 12 patients developed
31
32 243 morphological abnormalities of the mitral (N=10) and aortic (N=4) valves. No patients
33
34 244 developed ventricular dysfunction or enlargement (**Table 2**).

35 245 **Predictive Performance of the simplified echocardiographic score**

36
37 246 The simplified score, based on components of the WHF criteria, was a significant
38
39 247 predictor of RHD unfavorable outcome (hazard ratio [HR] 1.197, 95% confidence
40
41 248 interval [CI] 1.098 - 1.305, $p < 0.001$). The discrimination of the score was good (C-
42
43 249 statistic=0.714, 95% CI 0.627 - 0.801) and the model was well calibrated (**Appendix**
44
45 250 **Figure 1**). A Hosmer-Lemeshow $p = 0.589$ confirmed no significant difference between
46
47 251 observed and predicted unfavorable outcome (**Appendix Figure 2, A and B**).

48
49 252 The score classified 121 children in low risk, 48 in the intermediate risk, and 28
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51 253 in the high-risk groups. Additionally, the score model was able to separate low-,
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3 254 intermediate- and high-risk categories for unfavorable disease outcome (**Figure 2**).
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5 255 Favorable RHD outcome risk rate in the low-risk children at 1-, and 2-years follow-up
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7 256 was 99%, and 97% respectively, compared to 76%, and 47% in the high-risk group.
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12 258 **Discussion:**

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14 259 In agreement with growing international data⁸, subclinical RHD in Brazil has a
15
16 260 variable outcome. Approximately 1 in 5 children with borderline RHD progressed to
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18 261 definite RHD and more than 1 in 3 children with definite RHD remained in this category.
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20 262 A recently developed risk stratification score⁹ was a modest, but significant, predictor of
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22 263 unfavorable echocardiographic outcome in our population.
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26 264 Since its inception, the PROVAR+ research program has been studying the use of
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28 265 echocardiography to improve the early detection of RHD¹² in Brazil. Epidemiological
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30 266 characterization of RHD prevalence, and study of portable and handheld devices, task-
31
32 267 shifting, and telemedicine have been undertaken to understand how to improve diagnostic
33
34 268 access in low-resource populations^{4 10 12 14}. Determining outcomes for children with
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36 269 subclinical RHD is a critical next step to inform program evaluation, as for other screening
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38 270 programs worldwide. These data, with a mean follow-up of 29-months, show that both
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40 271 borderline and definite RHD are dynamic phenotypes, with borderline RHD showing
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42 272 more favorable outcomes^{6 8 15}.
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45
46 273 Nearly half (46%) of the youth in this program improved echocardiographically
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48 274 to normal, similar to global rates ranging from 47-67%^{8 16}. Yet borderline RHD was not
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50 275 a benign finding, with one in five (17%) of children progressing to definite RHD, in line
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52 276 with global data which has reported 17-23% progression at 2.5-7.5 years of follow-up^{8 17}
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54 277 ¹⁸. Children with definite RHD at diagnosis had more unfavorable outcomes with 40%
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56 278 remaining definite, though no child progressed to moderate or severe RHD, reflecting a
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3 279 mildly phenotype in screen-detected RHD in Brazilian youth compared to global data^{8 15}
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5 280^{17 19 20}. This milder phenotype may reflect the relatively stronger public health system in
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7 281 Brazil, compared to many other RHD-endemic areas, facilitating higher rates of sore
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9 282 throat and rheumatic fever diagnoses, but more data are needed. The impact of secondary
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11 283 prophylaxis in this cohort cannot be determined, as few were prescribed prophylaxis and
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13 284 adherence was not well captured, and we await the results of a large randomized clinical
14
15 285 trial on the impact of penicillin prophylaxis in screen-detected youth, currently ongoing
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17 286 in Uganda (*Gwoko Adunu pa Lutino*; clinicaltrials.gov No. NCT03346525).

21 287 The most novel aspect of this follow-up study was the application of a newly
22
23 288 developed score to predict unfavorable outcome among children with screen-detected
24
25 289 RHD⁹. Addressing the need to simplify the WHF criteria and improve the applicability
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27 290 for use with handheld echocardiography (lacking spectral Doppler), Nunes et al
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29 291 developed a five-component point-based score that showed considerable accuracy for
30
31 292 predicting disease progression in two large African cohorts⁹. The score showed modest
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33 293 discrimination for unfavorable outcome in our population, potentially related to the less
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35 294 aggressive RHD phenotype in Brazil as compared to African cohorts^{8 19}, suggesting wider
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37 295 external validation and recalibration may be necessary for global application. However,
38
39 296 still in a population with a relatively low risk of progression – especially to clinically
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41 297 significant disease – its discrimination of subgroups at higher risk of unfavorable
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43 298 echocardiographic outcome points towards an useful public health tool, and urges further
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45 299 investigations.

51 300 The PROVAR+ program has encountered several context-specific limitations and
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53 301 lessons learned. First, the program has struggled with low-participation and high attrition
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55 302 compared to other global populations: only 40% of students have consented to school-
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57 303 based screening⁵ and only 36% of screen-positive children from the schools were enrolled
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3 304 in follow-up. Consequently, the sample size was limited – although comparable with
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5 305 other RHD follow-up studies – and may preclude more definite conclusions. Much higher
6
7 306 participation rates were seen in primary healthcare screening (84.4%⁵), suggesting this
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9 307 location is more appropriate in our context. Second, in the absence of a gold standard,
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11 308 prescription of penicillin for secondary prophylaxis was left to the discretion of the
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13 309 treating physician. Low rates of prescription were seen compared to those reported
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15 310 globally, suggesting the need for widespread provider education based on the results from
16
17 311 the GOAL study (*Gwoko Adunu pa Lutino*; clinicaltrials.gov No. NCT03346525).
18
19 312 Finally, no child progressed to clinically significant RHD, suggesting the timeline of
20
21 313 progression may be longer in the Brazilian context and not adequately captured by the
22
23 314 relatively short follow-up interval. This may have important implications on when to
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25 315 screen and cost-effectiveness evaluations. Despite these limitations, the PROVAR+
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27 316 program is the only longitudinal program evaluating the impact of echocardiographic
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29 317 screening in Latin America.
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319 **Conclusion:**

40 320 These data suggest that screen-detected RHD in Brazil is not benign; patients with
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42 321 definite RHD are likely to remain in this category, and progression rates of borderline
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44 322 RHD are not negligible. The simplified echocardiography score⁹ assessed in an
45
46 323 independent population with predominantly low-risk for RHD progression was accurate
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48 324 to predict early unfavorable outcome. Additional investigations are needed to establish
49
50 325 the long-term prognosis of subclinical RHD, and the effects of prophylaxis in high-risk
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52 326 subgroups.
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58 328 **Conflicts of interest:**

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3 329 The authors have no conflicts of interest to declare regarding this manuscript.
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7
8 331 **Author contributions:**
9

10 332 Conception and design of the research: Bechtluft, BMF, Nascimento, BR, Sable,
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15
16
17 335 Diamantino, AC, Rezende, BDF, Costa, WAA, Mata, MDO, Pereira, AFC; Analysis and
18
19 336 interpretation of data: Nascimento, BR, Nunes, MCP, Sable, C, Beaton, AZ, Reis, SDP,
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21 337 Meira, ZMA, Castilho, SRT, Arantes, NF; Statistical analysis: Silva, JLP, Nascimento,
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24 338 BR, Ribeiro, AL, Sable, C; Obtaining financing: Beaton, AZ, Sable, C, Nascimento, BR;
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28 340 Critical revision of the manuscript for intellectual content: All authors; Authors
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30 341 responsible for the overall content as guarantors: Bechtluft, BMF, Nascimento, BR,
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32 342 Beaton, AZ, Ribeiro, AL, Sable, C, Nunes, MCP.
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17 360 **Data sharing statement:**

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19 361 Data analytic methods and study materials will be made available to other
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21 362 researchers for purposes of reproducing the results or replicating the procedure, from the
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23 363 corresponding author upon reasonable request.
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28 365 **References:**

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453 **Tables:**

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455 **Table 1:** Baseline characteristics of patients with borderline and definite rheumatic heart
 456 disease.

Variable:	Result:
Borderline RHD (N=170)	
Age (years), median (IQR)	14 (11 – 16)
Female gender, N (%)	111 (65.7)
Follow-up period (months), mean \pm SD	28.9 \pm 9.0
1. At least two morphological features of RHD of the MV without pathological MR or MS	1. 5 (2.9)
2. Pathological MR	2. 135 (79.4)
3. Pathological AR	3. 30 (17.6)
Definite RHD (N=27)	
Age (years), median (IQR)	14.0 (12 – 16)
Female gender, N (%)	19 (70.4)
Follow-up period (months), mean \pm SD	29.5 \pm 9.2
1. Pathological MR and at least two morphological features of RHD of the MV	1. 24 (88.9)
2. MS mean gradient \geq 4 mmHg	2. 0
3. Pathological AR and at least two morphological features of RHD of the AV	3. 0
4. Borderline disease of both the AV and MV	4. 3 (11.1)

457 **Abbreviations:** AV: aortic valve; AR: aortic regurgitation; IQR: interquartile range (Q1
 458 – Q3); MR: mitral regurgitation; MS: mitral stenosis; MV: mitral valve; RHD: rheumatic
 459 heart disease; SD: standard deviation.

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462 **Table 2:** Baseline echocardiographic variables of patients with progression, stabilization

463 and regression of rheumatic heart disease at 2-year follow-up.

Valve:	Variable:	Progressed: Borderline Definite (N=29)	to Remained Definite (N=11)	Regressed / stable (borderline) / other (N=156)
Mitral valve, N (%):	Anterior leaflet thickening	18 (62.1)	10 (90.9)	103 (65.6)
	Chordal thickening	0	2 (18.2)	0
	Restricted leaflet motion	1 (3.4)	4 (36.4)	4 (2.5)
	Excessive leaflet tip motion	2 (6.9)	6 (54.5)	20 (12.7)
	Mitral stenosis	0	0	0
	Any regurgitation	28 (96.6)	11 (100)	141 (90.4)
	Regurgitation seen in 2 views	26 (89.7)	10 (90.9)	141 (90.4)
	Jet length ≥ 2 cm \ddagger	25 (86.2)	9 (81.8)	116 (74.4)
	Velocity ≥ 3 m/s for 1 envelope \S	9 (31.0)	4 (36.4)	32 (20.5)
Aortic valve, N (%):	Pansystolic jet (color Doppler)	15 (51.7)	8 (72.7)	99 (63.5)
	Irregular or focal thickening	0	2 (18.2)	1 (0.6)
	Coaptation defect	0	1 (9.1)	2 (1.3)
	Restricted leaflet motion	0	0	0
	Leaflet Prolapse	0	0	0
	Any regurgitation	2 (6.9)	3 (27.3)	32 (20.5)
	Regurgitation seen in 2 views	2 (6.9)	2 (18.2)	28 (17.9)
	Jet length ≥ 1 cm \ddagger	1 (3.5)	3 (27.3)	29 (18.6)
	Velocity ≥ 3 m/s in early diastole \S	0	1 (9.1)	6 (3.9)
Pandiatolic jet (color Doppler)	0	2 (18.2)	20 (12.8)	

464 **Abbreviations:** *Congenital mitral valve or aortic valve abnormalities were465 excluded. \ddagger Abnormal thickening of the anterior mitral valve leaflet ≥ 3 or >4 mm using

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3 466 harmonic imaging. ‡In at least 1 view. §Measurements available with the Vivid-Q
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8 468 **Figures legends:**

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10 469 **Figure 1:** RHD progression during the follow-up according to diagnosis at baseline.

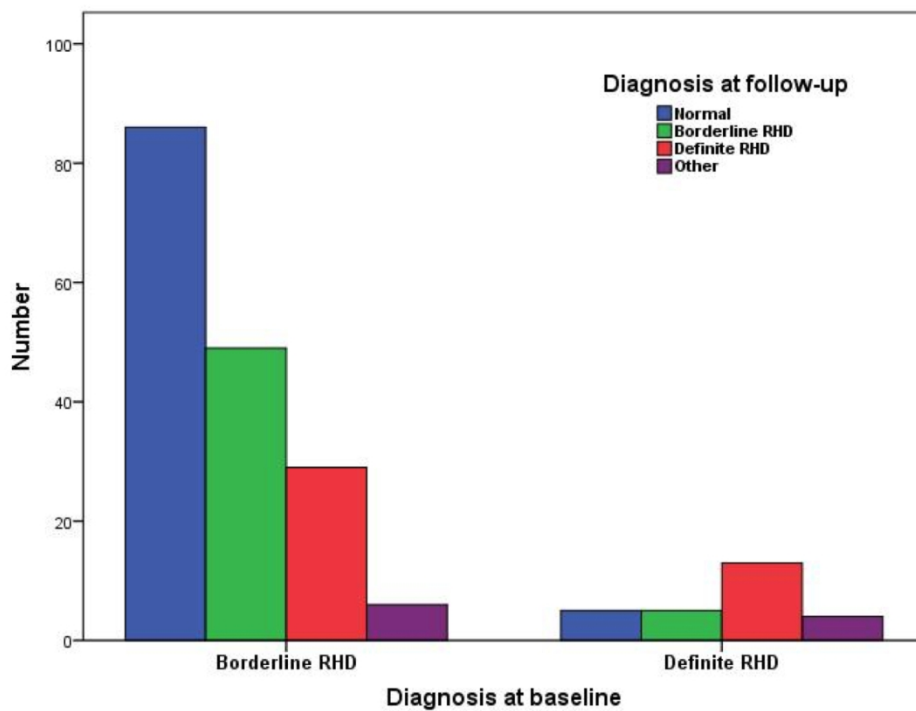
11
12 470 **Figure 2:** Cumulative incidence of disease unfavorable outcome in children with
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14 471 echocardiography-detected RHD according to according to risk categories of the
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17 472 simplified score.

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21
22 474 **Appendix Figure 1:** Receiver operator characteristic curve for echocardiography score
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24 475 showing predicted probability from the model (C-statistic of 0.71).

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26 476 **Appendix Figure 2:** (A) Calibration plots by quintiles for RHD progression risk
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28 477 prediction model in the validation cohort. (B) Calibration plots by quintiles for favorable
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30 478 outcome RHD risk prediction model in the validation cohort.

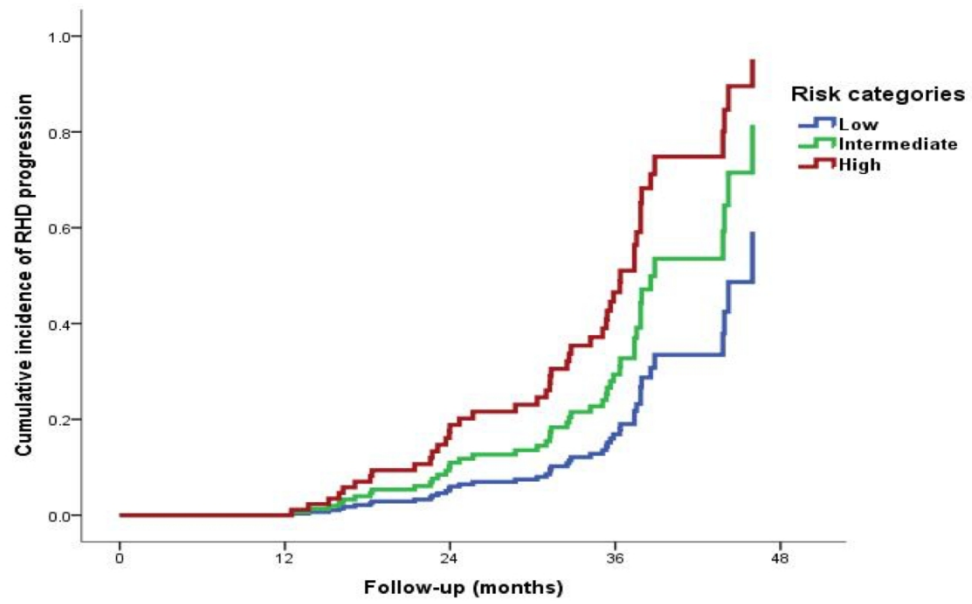
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RHD progression during the follow-up according to diagnosis at baseline.

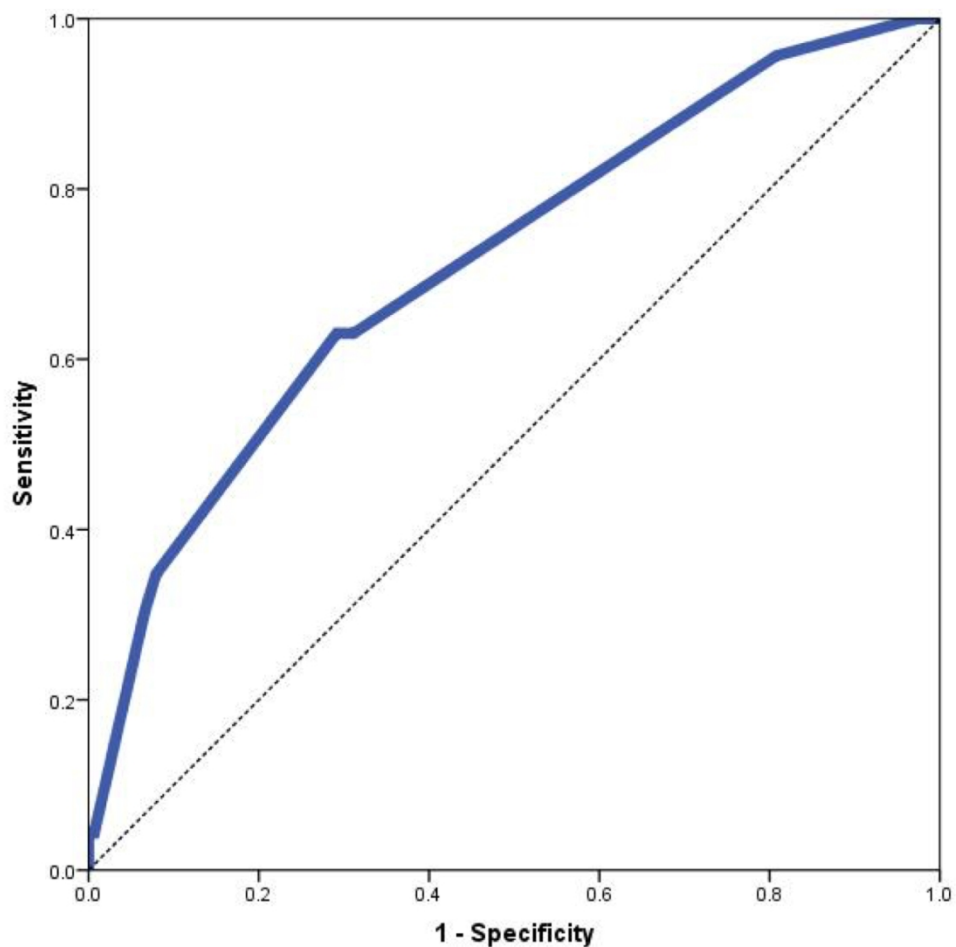
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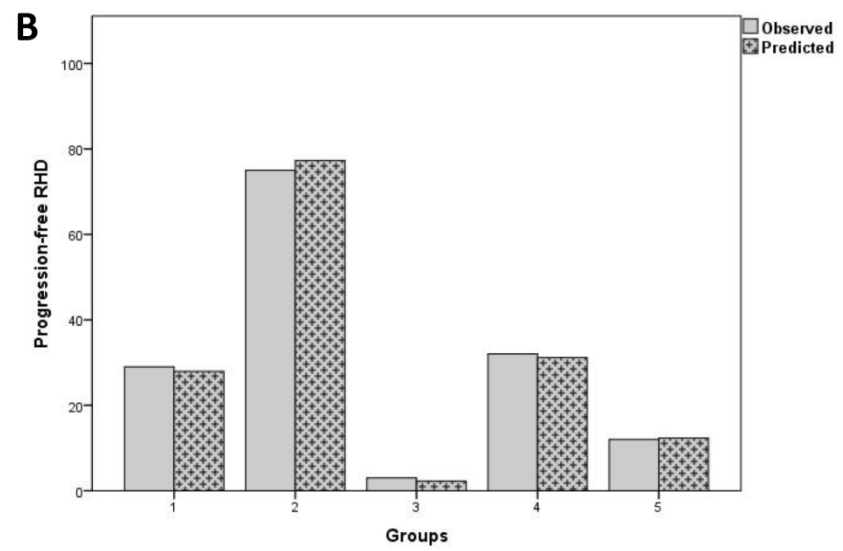
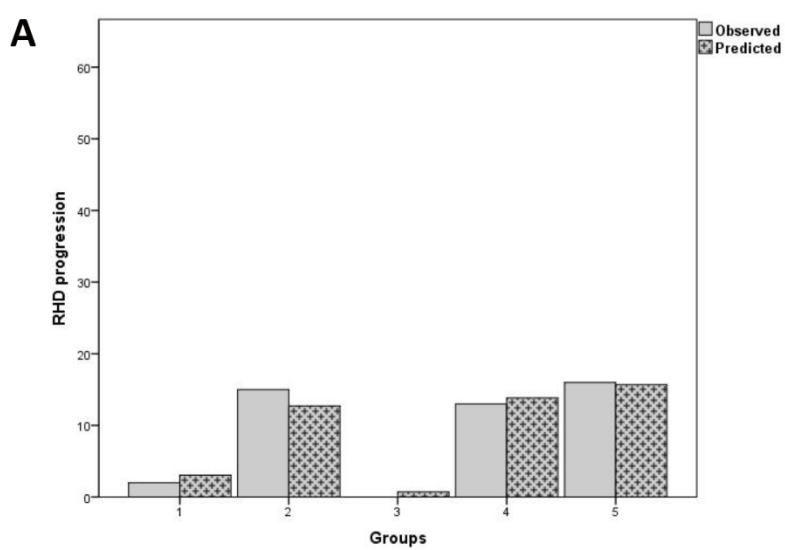
Cumulative incidence of disease unfavorable outcome in children with echocardiography-detected RHD according to according to risk categories of the simplified score.

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Reporting checklist for prediction model development and validation study.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPOD reporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

	Reporting Item	Page Number
Title		
	#1 Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract		
	#2 Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction		
	#3a Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	1, 2
	#3b Specify the objectives, including whether the study describes the	2

development or validation of the model or both.

Methods

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3	Methods		
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5	Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.
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10	Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.
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14	Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.
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18	Participants	#5b	Describe eligibility criteria for participants.
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20	Participants	#5c	Give details of treatments received, if relevant
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23	Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.
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26	Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.
27			N/A
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29	Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured
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34	Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.
35			N/A
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38	Sample size	#8	Explain how the study size was arrived at.
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40	Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.
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45	Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.
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49	Statistical analysis methods	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.
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54	Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.
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58	Statistical analysis	#10d	Specify all measures used to assess model performance and, if relevant,
59			N/A

1	methods	to compare multiple models.	
2	Statistical analysis	#10e If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	N/A
3	methods		
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6	Risk groups	#11 Provide details on how risk groups were created, if done.	N/A
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8	Development vs.	#12 For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	8
9	validation		
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12	Results		
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15	Participants	#13a Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9,10
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20	Participants	#13b Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9
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25	Participants	#13c For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	9, 10
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31	Model	#14a If developing a model, specify the number of participants and outcome events in each analysis.	10
32	development		
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34	Model	#14b If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	N/A
35	development		
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38	Model	#15a If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9, 10
39	specification		
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43	Model	#15b If developing a prediction model, explain how to use it.	10
44	specification		
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47	Model	#16 Report performance measures (with CIs) for the prediction model.	10
48	performance		
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51	Model-updating	#17 If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	N/A
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55	Discussion		
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57	Limitations	#18 Discuss any limitations of the study (such as nonrepresentative sample,	12, 13
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few events per predictor, missing data).

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3	Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data 12
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6	Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. 11 - 13
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10	Implications	#20	Discuss the potential clinical use of the model and implications for future research 12
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14	Other		
15	information		
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18	Supplementary	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. 20
19	information		
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21	Funding	#22	Give the source of funding and the role of the funders for the present study. 14
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 26 This checklist was completed on 03. January 2020 using <https://www.goodreports.org/>, a tool made by the
 27 EQUATOR Network in collaboration with [Penelope.ai](http://penelope.ai)
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