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

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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

value for risk stratification and monitoring of echocardiography-detected RHD.

Trial registration: N/A.

Key-words: Rheumatic heart disease; screening; echocardiography; follow-up; prognosis.

Word count: 2,341

Strenghts and limitations of this study:

- PROVAR is the first longitudinal program evaluating the impact of echocardiographic screening in Latin America and the mid-term prognosis of subclinical RHD in the Brazilian context.
- Unprecedented follow-up data from Latin America data suggest that screen-detected RHD in Brazil is not benign: patients with definite RHD are likely to remain in this category (48.1%), while progression rates of borderline disease are considerable (17.1%).
- A newly developed five-component point-based echo score showed considerable accuracy in this population for discriminating children at risk for unfavorable echo outcome at 2 years.
- The program had low-participation and high attrition: 40% of students consented to school-based screening and only 36% of screen-positive children were enrolled in follow-up.
- No child progressed to clinically significant RHD, suggesting the progression timeline may be longer in the Brazilian context and limiting further conclusions on the long-time prognosis of subclinical RHD.

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 patients[1]. 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 RHD[3-6]. 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 normal[7]. 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 progression[8]. However, data suggests that RHD progression in children with latent RHD is not negligible[9]. 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

developed by Nunes *et al*[9], consisting of 5 components of the WHF criteria, as a predictor of unfavorable echocardiographic outcomes.

Methods:

This is a prospective cohort study with systematic clinical and echocardiographic follow-up of children with subclinical RHD. It was derived from a RHD screening program, stablished in Brazil in 2014 - the PROVAR+ (*Programa de RastreamentO da VAlvopatia Reumática*) study - a collaboration between the Children`s National Health System, Washington – DC, US, the Universidade Federal de Minas Gerais and the Telehealth Network of Minas Gerais[11], Belo Horizonte, Minas Gerais, Brazil. This screening program has already screened more than 12,000 children and adolescents from 21 schools in Minas Gerais, Brazil, between October 2014 and December 2016[4 5 10]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and ethics approval was obtained from the institutional review boards of the participant institutions as well as from the local Boards of Health and Education.

In brief, public schools and primary care centers from low income areas of metropolitan Belo Horizonte, Brazil, were selected to participate in the screening program, based on socioeconomic data (Human Development Index (HDI)) and priorities of the health authorities. Selected private schools (2) were also invited in order to characterize RHD in high-income youth. All asymptomatic students, without history of ARF or RHD, were eligible for screening[4 5]. All participants were informed about the study and had the informed consent signed by their parents or by themselves, if in legal age.

The echocardiographic screening was performed from 2014 to 2016 by previously trained non-physicians (nurses and imaging technicians) and later uploaded to

dedicated cloud storage systems and interpreted through telemedicine by cardiologists in Brazil and the US[12], applying the WHF criteria. Detailed screening methodology has been previously published[4 5].

Participants with abnormal screening were invited for the UFMG Pediatric Cardiology outpatient clinics, and were prospectively enrolled. All patients included in the follow-up from Belo Horizonte had the baseline screening diagnosis confirmed by standard echocardiography, scheduled in the University Hospital. The ones from Montes Claros had the diagnosis based on consensus reads of VSCAN studies. Specific care of these patients was left to the discretion of the caring cardiologist with experience in RHD. Follow-up consisted of clinical examination by a pediatrician (BB, AD), with standardized clinical history and physical examination, and standard echocardiogram by an experienced pediatric cardiologist (SR) (Vivid IQ®, GE Healthcare, Milwaukee, WI, USA), blinded to the findings of the previous exam, and based on the WHF criteria. A standardized imaging protocol was applied. Patients were then reclassified by consensus in the 4 pre-established categories. Specific care of these patients and indication of secondary prophylaxis – not mandatory for any category – was left to the discretion of the caring cardiologist (ZM, FA and MCN). All echo variables were systematically collected in a dedicated online database.

The simplified echocardiographic score proposed by Nunes *et al*, consisting of 5 variables (mitral valve anterior leaflet thickening, excessive leaflet tip motion, and regurgitation jet length ≥2 cm, and aortic valve focal thickening and any regurgitation)[9] was applied to this population. Disease unfavorable outcome assessed by echocardiogram was defined as worsening in diagnostic category (borderline to definite), remaining with mild definite RHD or worsening in the grade of mitral or aortic valve

regurgitation or development/worsening grade of mitral stenosis. Favorable outcome was defined as disease regression – considered when an improvement in diagnostic category was observed or in case of reduction of regurgitation severity – or remaining with stable borderline disease.

Patient and public involvement

The study participants were not involved in the design of this study. No patient involvement.

Data analysis and statistics

Data were systematically entered to the RedCap® online database[13]. Statistical analysis was performed using SPSS® software version 23.0 for Mac OSX (SPSS Inc., Chicago, Illinois). Continuous variables were expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR, [Q1/Q3]) when appropriate. Categorical variables were expressed as absolute values and percentages. The between-group comparison (progression vs regression/stable) was performed using the Fisher's Exact Test for categorical variables.

The simplified echo score[9] was applied to this population of schoolchildren to assess its discrimination and calibration in predicting disease unfavorable outcome using logistic regression. The predictive value of the score was assessed as a time-dependent variable in the Cox proportional hazards model. RHD favorable outcome rates of the 3 risk categories (low/intermediate/high) were estimated by the Kaplan–Meier method and compared by the log-rank test. A two-tailed significance level of 0.05 was considered statistically significant.

Results:

Total 197 patients were included, being 114 (36%) out of 317 children with

positive screening echos in Belo Horizonte and 83 (37%) of 224 in Montes Claros, with a mean 29±9 (range 11 to 48) months follow-up, considering the latest clinical visit. At baseline, 170 (86.3%) had borderline and 27 (13.7%) definite RHD. Median age was 14.1 (IQR 12.0 – 16.2) years, and 130 (66%) were female. Belo Horizonte and Montes Claros had similar rates of borderline (85.1% vs. 88.0%) and definite (14.9% vs. 12.0%) RHD at baseline (p=0.56). Only 13 (6.6%) patients were regularly receiving Penicillin (7 with <80% adherence), 4 in the definite RHD group. Detailed baseline demographic and echocardiographic characteristics are depicted in **Table 1**. Compared to the 344 patients without follow-up, the study sample had similar baseline distribution of borderline/definite diagnoses (86.3%/13.7% vs. 89.5%/10.5%, p=0.26) as well as WHF subgroups for borderline (p=0.27) and definite (p=0.10) RHD, human development index (0.77 [IQR 0.76 – 0.80] vs. 0.77 [IQR 0.76 – 0.80], p=0.22, household (4 [IQR 4 – 5] vs. 4 [IQR 4 – 6] inhabitants, p=0.25) and age (14.2 [IQR 12.0 – 16.2] vs. 14.1 [IQR 11.8 – 15.8] years, p=0.46), but a slightly higher proportion of females (66.3% vs. 57.0%, p=0.03) was observed.

Cardiovascular symptoms were reported by 69 (35%) patients in the follow-up visits, including dyspnea (15.2%) and palpitations (14.2%). However, clinical evaluation, physical examination, and echocardiograms did not support a cardiac etiology of these symptoms. During follow-up, at least 1 episode of pharyngitis was reported by 92 patients, being 62 (67%) adequately treated in primary care, as informed by patients or parents.

Among patients with borderline RHD, 29 (17.1%) progressed to definite RHD, 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 (**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 data[8], subclincal 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.

A recently developed risk stratification score[9] was a modest, but significant, predictor of unfavorable echocardiographic outcome in our population.

Since its inception, the PROVAR research program has been studying the use of echocardiography to improve the early detection of RHD[12] in Brazil. Epidemiologicaly characterization of RHD prevalence, and study of portable and handheld devices, task-shifting, and telemedicine have been undertaken to understand how to improve diagnostic access in low-resource populations in Brazil[4 10 12 14]. Determining outcomes for children with subclincal RHD is a critical next step to inform program evaluation, as for other screening programs worldwide. These data, with a mean follow-up of 29-months, show that both borderline and definite RHD are dynamic phenotypes, with borderline RHD showing more favorable outcomes[6 8 15].

Nearly half (46%) of the youth in this program improved echocardiographically to normal, similar to global rates ranging from 47-67%[8 16]. Yet borderline RHD was not a benign finding, with one in five (17%) of children progressing to definite RHD, in line with global data which has reported 17-23% progression at 2.5-7.5 years of follow-up[8 17 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 relactively 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).

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

The PROVAR program has encountered several context-specific limitations and lessons learned. First, the program has strugged with low-participation and high attrition compared to other global populations: only 40% of students have consented to school-based screening[5] and only 36% of screen-positive children from the schools were enrolled in follow-up. Much higher rates of follow-up were seen in primary healthcare screening (84.4% [5]), suggesting this location is more appropriate in our context. Second, absent a gold standard, initiation of penicillin prophylaxis was left to the decretion of the treating physician. Low rates of prescription were seen compared to those reported globally, suggesting the need for widespread provider education based on the results from the GOAL study (*Gwoko Adunu pa Lutino*; clinicaltrials.gov No. NCT03346525). Finally, no child progressed to clinically significant RHD, suggesting the timeline of progression may be longer in the Brazilian context. This may have important implications on when to

screen and cost-effectivenss evaluations. Despite these limitations, the PROVAR program is the only longitudinal program evaluating the impact of echocardiographic screening in Latin America.

Conclusion:

These data suggest that screen-detected RHD in Brazil is not benign; patients with definite RHD are likely to remain in this category, and progression rates of borderline RHD are not negligible. The simplified echocardiography score[9] assessed in an independent population with predominantly low-risk for RHD progression was accurate to predict early disease unfavorable outcome. Additional investigations are needed to establish the long-term prognosis of subclinical RHD, and the effects of prophylaxis in high-risk subgroups.

Conflicts of interest:

The authors have no conflicts of interest to declare regarding this manuscript.

Author contributions:

Conception and design of the research: Bechtlufft, BMF, Nascimento, BR, Sable, C, Beaton, AZ, Nunes, MCP, Ribeiro, AL; Acquisition of data: Bechtluft, BMF, Fraga, CL, Barbosa, MM, Reis, SDP, Meira, ZMA, Castilho, SRT, Arantes, NF, Oliveira, KKB, Castro, L, Rezende, BDF, Costa, WAA, Mata, MDO, Pereira, AFC; Analysis and interpretation of data: Nascimento, BR, Nunes, MCP, Sable, C, Beaton, AZ, Reis, SDP, Meira, ZMA, Castilho, SRT, Arantes, NF; Statistical analysis: Nascimento, BR, Ribeiro, AL, Sable, C; Obtaining financing: Beaton, AZ, Sable, C, Nascimento, BR; Writing of the manuscript: Bechtlufft, BMF, Nascimento, BR, Sable, C, Nunes, MCP; Critical

revision of the manuscript for intellectual content: All authors; Authors responsible for the overall content as guarantors: Bechtlufft, 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 ± SD	28.9 ± 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 ± SD	29.5 ± 9.2
1. Pathological MR and at least two morphological features of RHD of the MV	1. 24 (88.9)
2. MS mean gradient ≥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 to Definite (N=29)	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‡	25 (86.2)	9 (81.8)	116 (74.4)
	Velocity ≥3 m/s for 1 envelope§	9 (31.0)	4 (36.4)	32 (20.5)
	Pansystolic jet (color Doppler)	15 (51.7)	8 (72.7)	99 (63.5)
Aortic valve, N (%):	**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‡	1 (3.5)	3 (27.3)	29 (18.6)
	Velocity ≥3 m/s in early diastole§	0	1 (9.1)	6 (3.9)
	Pandiastolic jet (color Doppler)	0	2 (18.2)	20 (12.8)

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

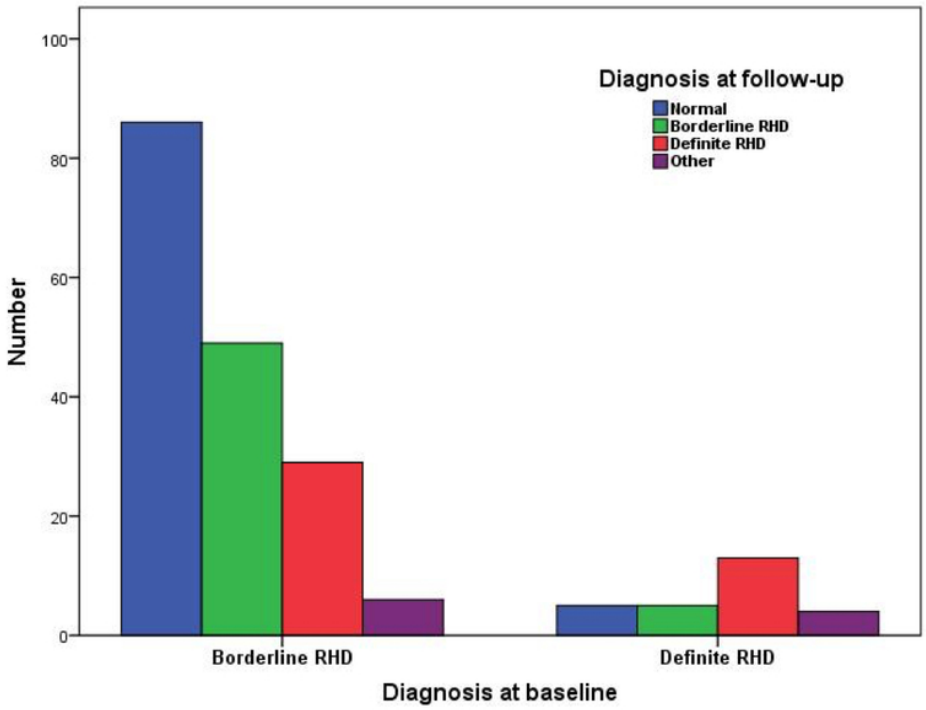
Figures legends:

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

Figure 2: Cumulative incidence of disease unfavorable outcome in children with echocardiography-detected RHD according to according to risk categories of the simplified score.

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

Appendix Figure 2: (A) Calibration plots by quintiles for RHD progression risk prediction model in the validation cohort. (B) Calibration plots by quintiles for favorable outcome RHD risk prediction model in the validation cohort.



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

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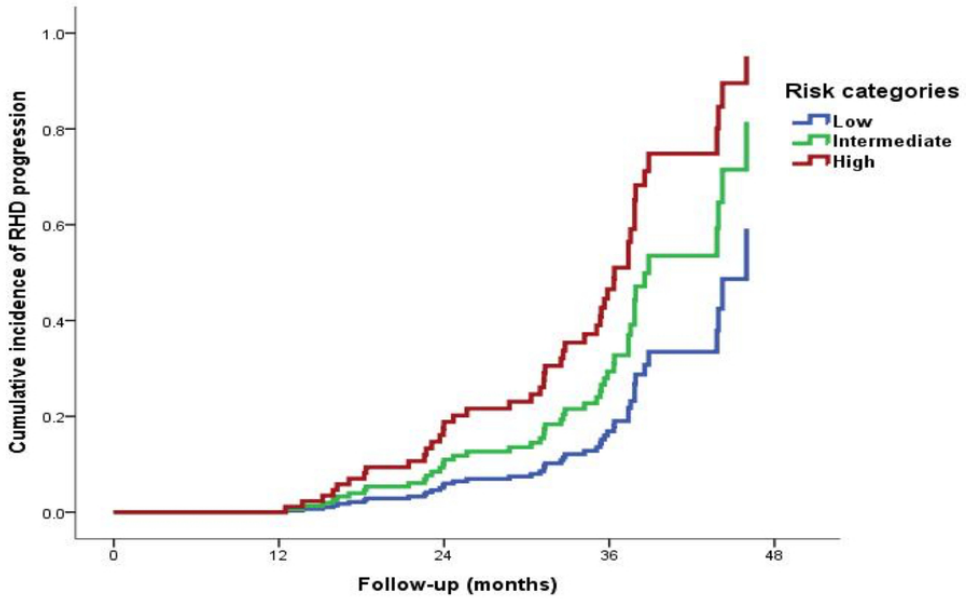

Cumulative incidence of disease unfavorable outcome in children with echocardiography-detected RHD according to according to risk categories of the simplified score.

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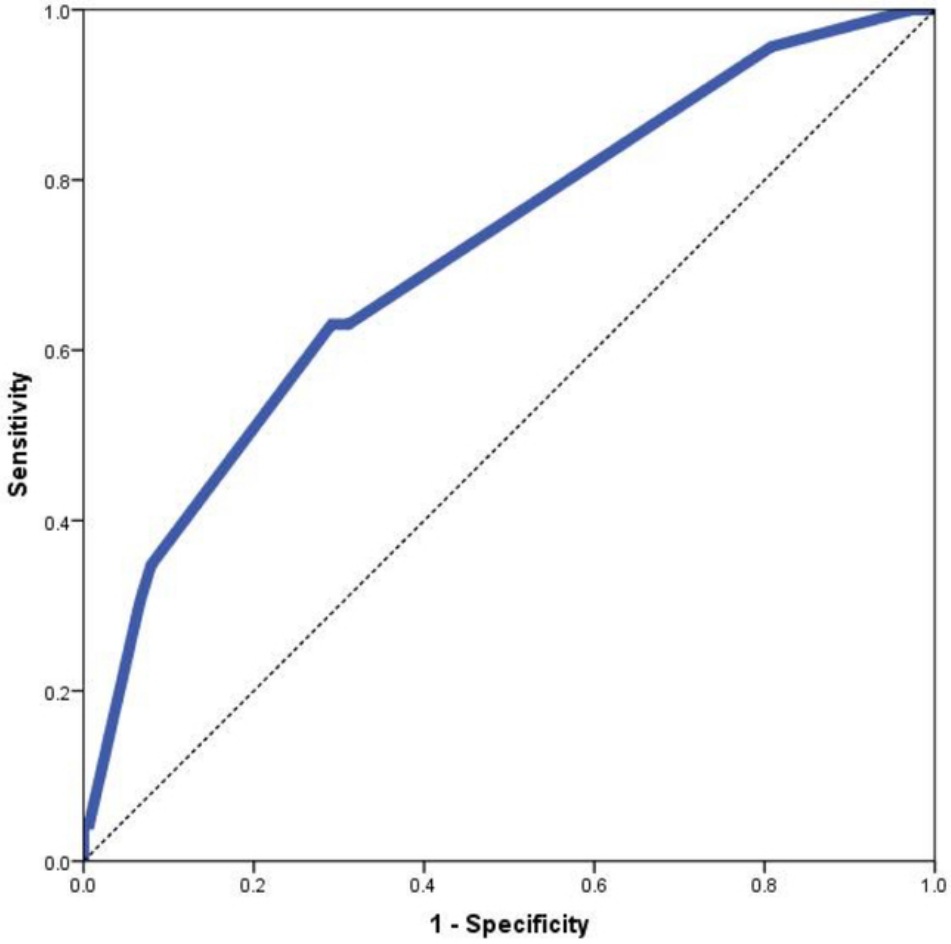

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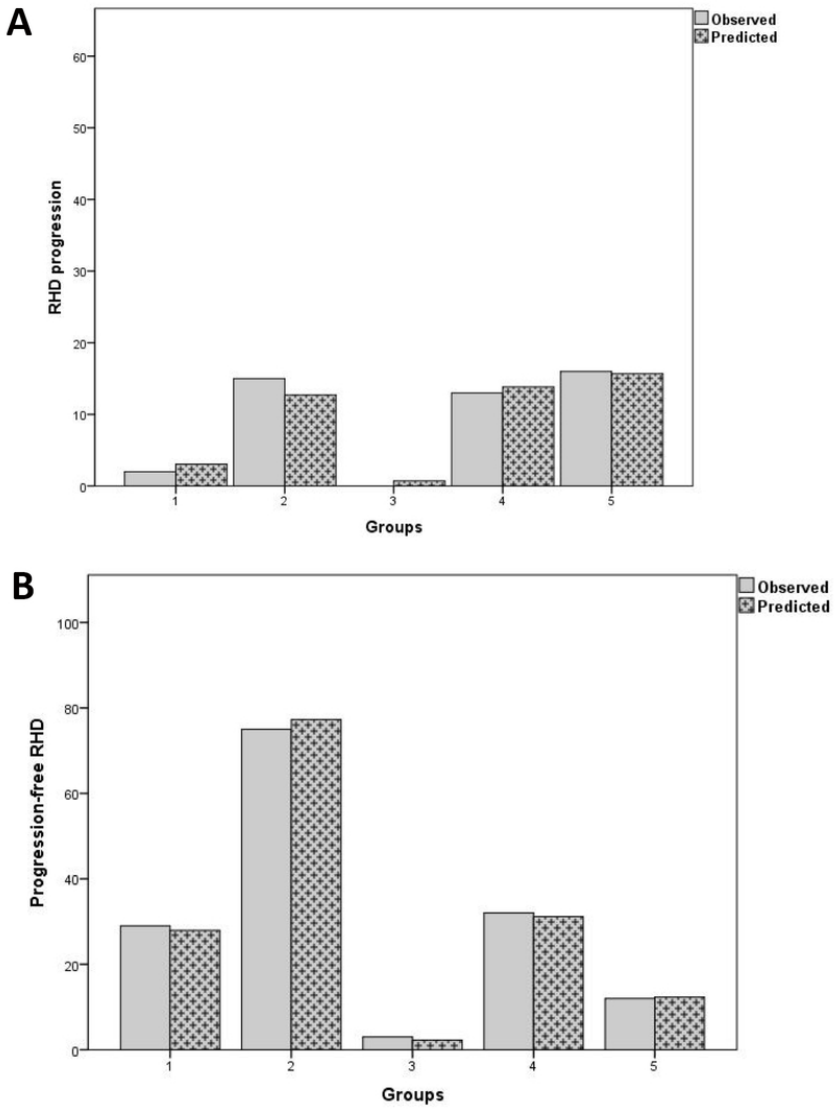

69x97mm (300 x 300 DPI)

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.

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

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		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			
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, 7
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7,8
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6, 7
Participants	#5b	Describe eligibility criteria for participants.	6
Participants	#5c	Give details of treatments received, if relevant	7
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	7, 8
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	#8	Explain how the study size was arrived at.	9
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	8
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.	8
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	8
Statistical analysis	#10d	Specify all measures used to assess model performance and, if relevant,	N/A

methods		to compare multiple models.	
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	N/A
Risk groups	#11	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	8
Results			
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
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
Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	9, 10
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	10
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	N/A
Model specification	#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
Model specification	#15b	If developing a prediction model, explain how to the use it.	10
Model performance	#16	Report performance measures (with CIs) for the prediction model.	10
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	N/A
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample,	12, 13

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

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

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

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Validation of a Simplified Score for Predicting Latent Rheumatic Heart Disease Progression Utilizing a Prospective Cohort of 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 PROVAR+ study, which uses non-experts, telemedicine and portable echo, pioneered RHD screening in Brazil. We aimed to assess the mid-term evolution of Brazilian schoolchildren (5-18 years) with echocardiography-detected subclinical RHD and to assess the performance of a simplified score consisting of 5 components of the WHF criteria, as a predictor of unfavorable echocardiographic outcomes.

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 value for risk stratification and monitoring of echocardiography-detected RHD.

Trial registration: N/A.

Key-words: Rheumatic heart disease; screening; echocardiography; follow-up; prognosis.

Word count: 2,456

Strenghts and limitations of this study:

- This study utilized the PROVAR+ cohort, the first large prospective cohort of schoolchildren with latent RHD in Brazil.
- This is the first validation study of a previously published (2019) scoring system to discriminate children found to have early echocardiography evidence of RHD into those who are likely to have favorable vs. unfavorable outcome.
- Echocardiograms were interpreted by the consensus of two experts with high familiarity in the World Heart Federation Criteria.
- As this was an established cohort, no predefined sample size was calculated for this study and all screen-positive patients were invited for follow-up.
- A passive recruitment strategy meant that there was low overall participation; only 36% of screen-positive children were enrolled in the follow-up program, reducing the size of the potential cohort.

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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, where it is typically diagnosed only once advanced valve disease is present and symptoms develop[1]. However, there is a latent period, often up to decade, between the first episode of acute rheumatic fever (ARF) and advanced RHD, when early identification can improve outcomes.

In this context, echocardiographic screening in endemic areas has emerged as an effective approach to identify patients who are in this latent, subclinical stage of RHD[3-6]. 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 normal[7]. The morphological findings of RHD and the criteria for pathologic valve regurgitation are also established. This standardization has 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 progression[8]. However, data suggests that RHD progression in children with latent RHD is not negligible[9]. 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

developed by Nunes *et al*[9], consisting of 5 components of the WHF criteria, as a predictor of unfavorable echocardiographic outcomes.

Methods:

This is a prospective cohort study with systematic clinical and echocardiographic follow-up of children with subclinical RHD. It was derived from a RHD screening program, stablished in Brazil in 2014 - the PROVAR+ (*Programa de RastreamentO da VAlvopatia Reumática*) study - a collaboration between the Children`s National Health System, Washington – DC, US, the Universidade Federal de Minas Gerais and the Telehealth Network of Minas Gerais[11], Belo Horizonte, Minas Gerais, Brazil. This screening program has already screened more than 12,000 children and adolescents from 21 schools in Minas Gerais, Brazil, between October 2014 and December 2016[4 5 10]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and ethics approval was obtained from the institutional review boards of the participant institutions (Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais and Children's National Health System Institutional Review Board) as well as from the local Boards of Health and Education.

In brief, public schools and primary care centers from low income areas of metropolitan Belo Horizonte, Brazil, were selected to participate in the screening program, based on socioeconomic data (Human Development Index (HDI)) and priorities of the health authorities. Selected private schools (2) were also invited in order to characterize RHD in high-income youth. All asymptomatic students, without history of ARF or RHD, were eligible for screening[4 5]. All participants were informed about the study and had informed consent signed by their parents or by themselves, if of legal age.

The echocardiographic screening was performed from 2014 to 2016 by previously trained non-physicians (nurses and imaging technicians) and images were uploaded to a dedicated cloud storage system and interpreted through telemedicine by cardiologists in Brazil and the US[12], applying the WHF criteria. Detailed screening methodology has been previously published[4 5].

Participants with abnormal screening were invited for the UFMG Pediatric Cardiology outpatient clinics, and were prospectively enrolled. All patients included in the follow-up from Belo Horizonte had the baseline screening diagnosis confirmed by standard echocardiography, scheduled in the University Hospital. The ones from Montes Claros had the diagnosis based on consensus reads of VSCAN studies. Specific care of these patients was left to the discretion of the caring cardiologist with experience in RHD. Families received phone reminders of the follow-up visits and, when necessary, study correspondence by mail. The prespecified 24-month follow-up consisted of a clinical appointment by a pediatrician (BB, AD), with standardized clinical history (demographics, comorbidities, cardiovascular symptoms, recurrence of pharyngitis, medications and adherence to prophylaxis – when indicated) and detailed physical examination forms, and standard echocardiogram by an experienced pediatric cardiologist (SR) (Vivid IQ®, GE Healthcare, Milwaukee, WI, USA), blinded to the findings of the previous exam, and based on the WHF criteria. A standardized imaging protocol was applied. Patients were then reclassified by consensus with adjudication by 2 experts (MCN and ZM) in the 4 pre-established categories. Specific care of these patients and indication for secondary prophylaxis – not mandatory for any category – was left to the discretion of the caring cardiologist (ZM, SRC and MCN). All echo and clinical variables were systematically collected in a dedicated online database.

The simplified echocardiographic score proposed by Nunes *et al*, consisting of 5 variables (mitral valve anterior leaflet thickening, excessive leaflet tip motion, and regurgitation jet length ≥2 cm, and aortic valve focal thickening and any regurgitation)[9] was applied to this population. An unfavorable outcome was defined as worsening in diagnostic category (borderline to definite), remaining with mild definite RHD or worsening in the grade of mitral or aortic valve regurgitation or development/worsening grade of mitral stenosis. A favorable outcome was defined as disease regression – considered when an improvement in diagnostic category was observed or in case of reduction of regurgitation severity – or remaining with stable borderline RHD.

Patient and public involvement

Patients and public were not involved in the design and conduct of this research.

Data analysis and statistics

Data were systematically entered to the RedCap® online database[13]. Statistical analysis was performed using SPSS® software version 23.0 for Mac OSX (SPSS Inc., Chicago, Illinois). As we utilized a pre-existing cohort, no pre-specified sample size calculation was performed, and we considered the total sample of asymptomatic schoolchildren enrolled in the 26-month screening. All screen-positive children who attended the follow-up visit were included in this analysis. Continuous variables were expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR, [Q1/Q3]) when appropriate. Categorical variables were expressed as absolute values and percentages. The between-group comparison (progression vs regression/stable) was performed using the Fisher's Exact Test for categorical variables.

The simplified echo score[9] was applied to this population of schoolchildren to assess its discrimination and calibration in predicting unfavorable outcome using logistic

regression. The predictive value of the score was assessed as a time-dependent variable in the Cox proportional hazards model. RHD favorable outcome rates of the 3 risk categories (low/intermediate/high), based on the hazard of evolving with unfavorable echo outcome, were estimated by the Kaplan–Meier method and compared by the log-rank test. A two-tailed significance level of 0.05 was considered statistically significant.

Results:

Total 197 patients were included, being 114 (36%) out of 317 children with positive screening echos in Belo Horizonte and 83 (37%) of 224 in Montes Claros, with a mean 29±9 (range 11 to 48) months follow-up, considering the latest clinical visit. At baseline, 170 (86.3%) had borderline and 27 (13.7%) definite RHD. Median age was 14.1 (IQR 12.0 – 16.2) years, and 130 (66%) were female. Belo Horizonte and Montes Claros had similar rates of borderline (85.1% vs. 88.0%) and definite (14.9% vs. 12.0%) RHD at baseline (p=0.56). Only 13 (6.6%) patients, 4 of whom originally classified as definite RHD, were regularly receiving Penicillin (7 with <80% adherence). Detailed baseline demographic and echocardiographic characteristics are depicted in **Table 1**. Compared to the 344 patients without follow-up, the study sample had similar baseline distribution of borderline/definite diagnoses (86.3%/13.7% vs. 89.5%/10.5%, p=0.26) as well as WHF subgroups for borderline (p=0.27) and definite (p=0.10) RHD, human development index (0.77 [IQR 0.76 – 0.80] vs. 0.77 [IQR 0.76 – 0.80], p=0.22, household (4 [IQR 4 – 5] vs. 4 [IQR 4 – 6] inhabitants, p=0.25) and age (14.2 [IQR 12.0 – 16.2] vs. 14.1 [IQR 11.8 – 15.8] years, p=0.46), but a slightly higher proportion of females (66.3% vs. 57.0%, p=0.03) was observed.

Cardiovascular symptoms were reported by 69 (35%) patients in the follow-up visits, including dyspnea (15.2%) and palpitations (14.2%). However, clinical evaluation,

physical examination, and echocardiograms did not support a cardiac etiology of these symptoms. During follow-up, at least 1 episode of pharyngitis was reported by 92 patients, with 62 (67%) adequately treated in primary care, as informed by patients or parents.

Among patients with borderline RHD, 29 (17.1%) progressed to definite RHD, 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 (**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 unfavorable disease outcome (**Figure 2**). Favorable RHD outcome 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 data[8], subclincal 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. A recently developed risk stratification score[9] was a modest, but significant, predictor of unfavorable echocardiographic outcome in our population.

Since its inception, the PROVAR+ research program has been studying the use of echocardiography to improve the early detection of RHD[12] in Brazil. Epidemiological characterization of RHD prevalence, and study of portable and handheld devices, task-shifting, and telemedicine have been undertaken to understand how to improve diagnostic access in low-resource populations[4 10 12 14]. Determining outcomes for children with subclincal RHD is a critical next step to inform program evaluation, as for other screening programs worldwide. These data, with a mean follow-up of 29-months, show that both borderline and definite RHD are dynamic phenotypes, with borderline RHD showing more favorable outcomes[6 8 15].

Nearly half (46%) of the youth in this program improved echocardiographically to normal, similar to global rates ranging from 47-67%[8 16]. Yet borderline RHD was not a benign finding, with one in five (17%) of children progressing to definite RHD, in line with global data which has reported 17-23% progression at 2.5-7.5 years of follow-up[8 17 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 relactively 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).

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

The PROVAR+ program has encountered several context-specific limitations and lessons learned. First, the program has strugged with low-participation and high attrition compared to other global populations: only 40% of students have consented to school-based screening[5] and only 36% of screen-positive children from the schools were enrolled

in follow-up. Consequently, the sample size was limited – although comparable with other RHD follow-up studies – and may preclude more definite conclusions. Much higher participation rates were seen in primary healthcare screening (84.4%[5]), suggesting this location is more appropriate in our context. Second, in the absence of a gold standard, prescription of penicillin for secondary prophylaxis was left to the discretion of the treating physician. Low rates of prescription were seen compared to those reported globally, suggesting the need for widespread provider education based on the results from the GOAL study (*Gwoko Adunu pa Lutino*; clinicaltrials.gov No. NCT03346525). Finally, no child progressed to clinically significant RHD, suggesting the timeline of progression may be longer in the Brazilian context and not adequately captured by the relatively short follow-up interval. This may have important implications on when to screen and cost-effectiveness evaluations. Despite these limitations, the PROVAR+ program is the only longitudinal program evaluating the impact of echocardiographic screening in Latin America.

Conclusion:

These data suggest that screen-detected RHD in Brazil is not benign; patients with definite RHD are likely to remain in this category, and progression rates of borderline RHD are not negligible. The simplified echocardiography score[9] assessed in an independent population with predominantly low-risk for RHD progression was accurate to predict early unfavorable outcome. Additional investigations are needed to establish the long-term prognosis of subclinical RHD, and the effects of prophylaxis in high-risk subgroups.

Conflicts of interest:

The authors have no conflicts of interest to declare regarding this manuscript.

Author contributions:

Conception and design of the research: Bechtlufft, BMF, Nascimento, BR, Sable, C, Beaton, AZ, Nunes, MCP, Ribeiro, AL; Acquisition of data: Bechtluft, BMF, Fraga, CL, Barbosa, MM, Reis, SDP, Meira, ZMA, Castilho, SRT, Arantes, NF, Oliveira, KKB, Diamantino, AC, Rezende, BDF, Costa, WAA, Mata, MDO, Pereira, AFC; Analysis and interpretation of data: Nascimento, BR, Nunes, MCP, Sable, C, Beaton, AZ, Reis, SDP, Meira, ZMA, Castilho, SRT, Arantes, NF; Statistical analysis: Silva, JLP, Nascimento, BR, Ribeiro, AL, Sable, C; Obtaining financing: Beaton, AZ, Sable, C, Nascimento, BR; Writing of the manuscript: Bechtlufft, BMF, Nascimento, BR, Sable, C, Nunes, MCP; Critical revision of the manuscript for intellectual content: All authors; Authors responsible for the overall content as guarantors: Bechtlufft, BMF, Nascimento, BR, Beaton, AZ, Ribeiro, AL, Sable, C, Nunes, MCP.

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de Desenvolvimento Científico e Tecnológico) e FINEP (Financiadora de Estudos e Projetos). Dr. Ribeiro was supported in part by CNPq (Bolsa de produtividade em pesquisa, 310679/2016-8) and by FAPEMIG (Programa Pesquisador Mineiro, PPM-00428-17). Medical students received scholarships from the National Institute of Science and Technology for Health Technology Assessment (IATS, project: 465518/2014-1).

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 ± SD	28.9 ± 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 ± SD	29.5 ± 9.2
1. Pathological MR and at least two morphological features of RHD of the MV	1. 24 (88.9)
2. MS mean gradient ≥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 to Definite (N=29)	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‡	25 (86.2)	9 (81.8)	116 (74.4)
	Velocity ≥3 m/s for 1 envelope§	9 (31.0)	4 (36.4)	32 (20.5)
	Pansystolic jet (color Doppler)	15 (51.7)	8 (72.7)	99 (63.5)
Aortic valve, N (%):	**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‡	1 (3.5)	3 (27.3)	29 (18.6)
	Velocity ≥3 m/s in early diastole§	0	1 (9.1)	6 (3.9)
	Pandiastolic jet (color Doppler)	0	2 (18.2)	20 (12.8)

Abbreviations: *Congenital mitral valve or aortic valve abnormalities were excluded. †Abnormal thickening of the anterior mitral valve leaflet ≥3 or >4 mm using

harmonic imaging. ‡In at least 1 view. §Measurements available with the Vivid-Q exams.

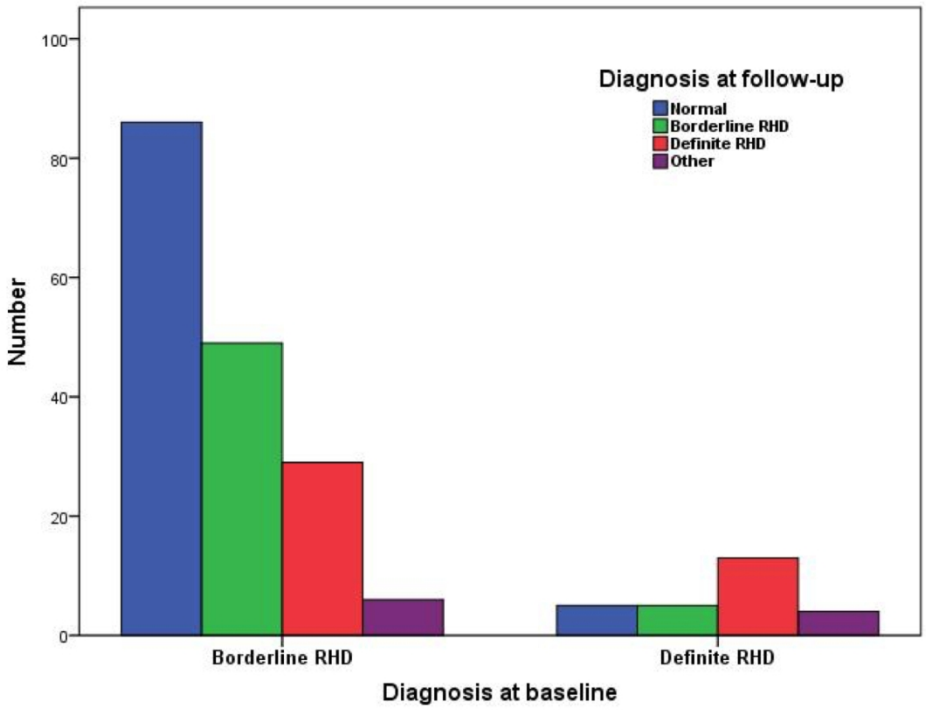
Figures legends:

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

Figure 2: Cumulative incidence of disease unfavorable outcome in children with echocardiography-detected RHD according to according to risk categories of the simplified score.

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

Appendix Figure 2: (A) Calibration plots by quintiles for RHD progression risk prediction model in the validation cohort. (B) Calibration plots by quintiles for favorable outcome RHD risk prediction model in the validation cohort.



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

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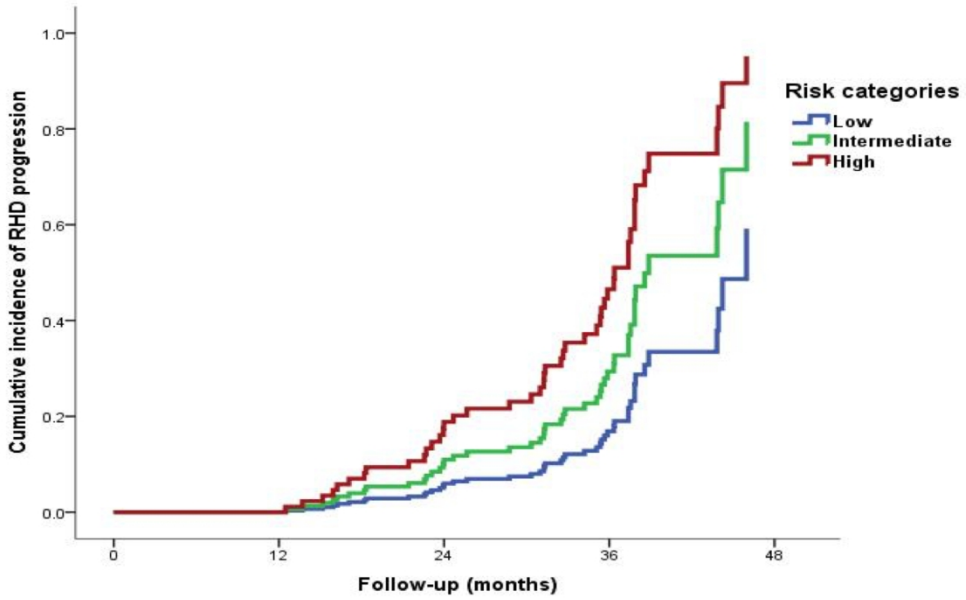

Cumulative incidence of disease unfavorable outcome in children with echocardiography-detected RHD according to according to risk categories of the simplified score.

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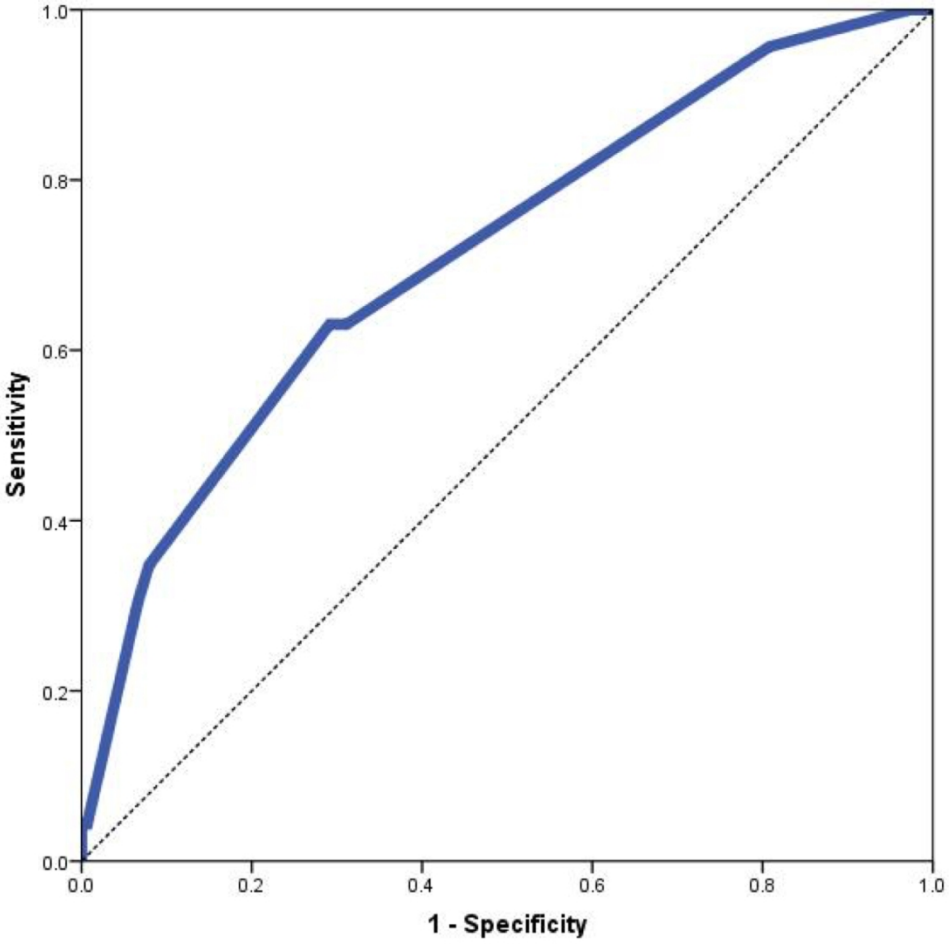

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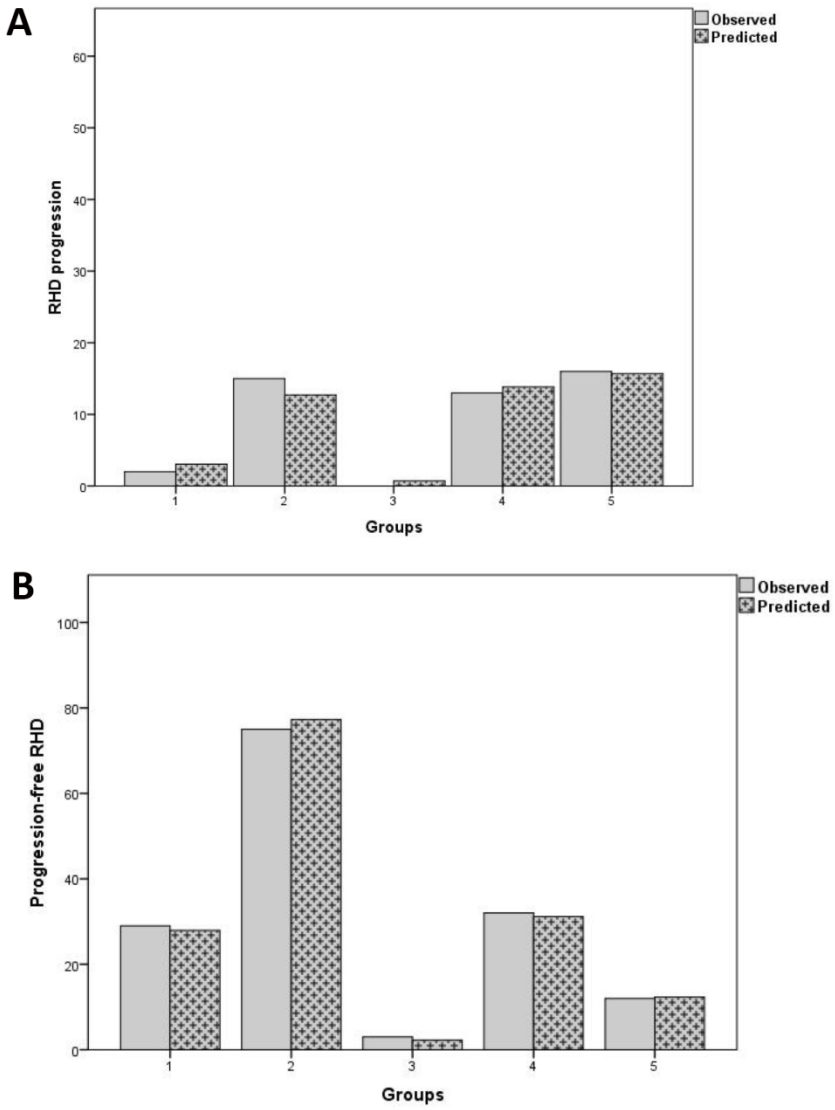

69x97mm (600 x 600 DPI)

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 TRIPODreporting 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			
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, 7
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7,8
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6, 7
Participants	#5b	Describe eligibility criteria for participants.	6
Participants	#5c	Give details of treatments received, if relevant	7
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	7, 8
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	#8	Explain how the study size was arrived at.	9
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	8
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.	8
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	8
Statistical analysis	#10d	Specify all measures used to assess model performance and, if relevant,	N/A

methods		to compare multiple models.	
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	N/A
Risk groups	#11	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	8
Results			
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
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
Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	9, 10
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	10
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	N/A
Model specification	#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
Model specification	#15b	If developing a prediction model, explain how to the use it.	10
Model performance	#16	Report performance measures (with CIs) for the prediction model.	10
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	N/A
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample,	12, 13

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

This checklist was completed on 03. January 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai