PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Validation of a Simplified Score for Predicting Latent Rheumatic Heart Disease Progression Utilizing a Prospective Cohort of Brazilian Schoolchildren
AUTHORS	Bechtlufft, Bárbara; Nascimento, Bruno; Sable, Craig; Fraga, Clara; Barbosa, Márcia; Reis, Susana; Diamantino, Adriana; Meira, Zilda Maria; Castilho, Sandra Regina; Arantes, Nayana; Oliveira, Kaciane; Silva, José Luiz; Rezende, Breno; Costa, Waydder Antônio; Mata, Mariana; Pereira, Augusto; Ribeiro, Antonio Luiz; Beaton, Andrea; Pereira Nunes, Maria Carmo

VERSION 1 – REVIEW

REVIEWER	Valirie Ndip Agbor University of Oxford, United Kingdom
REVIEW RETURNED	19-Jan-2020

GENERAL COMMENTS	Dear authors, Thank you for the efforts generating evidence on an area of rheumatic heart disease which is receiving much attention in recent years. I have some comments. ABSTRACT 1. The authors need to make the aim of their study clearer. What is exactly is the question that this study seek to answer? 2. Still in the objective, the authors said they sought to assess the accuracy of " the simplified score...". It is unclear if this is a score which they developed or they are referring to the simplified WHF criteria. Please, clarify. Points 1 and 2 above are clearly defined in the main text. MAIN TEXT 1. The authors should mention the sampling technique used in the parent study. 2. What is the duration of follow up for the present study? 3. Why is the font in Methods/paragraph 5, different? Copy and paste? Can the authors report on the dropout rate? 4. Statistical analysis: How did the authors define "low, intermediate, and high risk categories"? I think it would have been better for the authors to adjusted their prediction model for at least age, gender, area of residence (rural/urban) and socioeconomic

	status. Unfortunately, the power of their analysis might be limited by their sample size. 5. Limitation: Can the authors rewrite the following sentence for clarity? "Second, absent a gold standard, initiation of penicillin prophylaxis was left to the decretion of the treating physician. " 6. Conclusion: Seems the authors have followed up the participants for just 29 months. This is not long enough to make firm conclusion statements on the evolution of RHD. Secondly, with the small sample size, these findings are likely to be due to chance. Other minor comments 1. Discussion P2: I believe the authors meant "Epidemiological characterization..." NOT "Epidemiologicaly characterization...". The authors should also highlight the small sample size of their study.

REVIEWER	Thomas Pilgrim Bern University Hospital, Switzerland
REVIEW RETURNED	29-Jan-2020

GENERAL COMMENTS	Bechtlufft and colleagues report echocardiographic outcomes of children detected to have rheumatic heart disease and validate a simplified score to predict mid-term outcomes. The manuscript presents original data and addresses a topic of interest. The introduction adequately outlines the clinical context of the study, the methods are appropriate to study the hypothesis, the results are original and the discussion is well balanced. This reviewer has minor comments. 1. The low participation in school-based screening and the high attrition rate introduce a selection bias of the reported data. The authors addressed this limitation by presenting a comparison of patients with versus without follow-up. It may be interesting to look into predictors for loss to follow-up. 2. Duration of follow-up is limited; in addition, I suggest to describe the methods used to collect clinical follow-up and provide information about independent adjudication of echocardiographic endpoints. 3. Under “patient and public involvement”, the authors write that “study participants were not involved in the design of this study” and “no patients involvement”. The second statement seems to be redundant. Please delete or specify.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Reports: Reviewer: 1 Thank you for the efforts generating evidence on an area of rheumatic heart disease which is receiving much attention in recent years. I have some comments.
A: Thank you for the review and for your positive and encouraging comments.
ABSTRACT 1. The authors need to make the aim of their study clearer. What is exactly is the question that this study seeks to answer?
A: As suggested, the aim of the study was rephrased to improve understanding, in the first paragraph of the Abstract. 2. Still in the objective, the authors said they sought to assess the accuracy of "

the simplified score...". It is unclear if this is a score which they developed or they are referring to the simplified WHF criteria. Please, clarify.
A: Following your suggestion, the Abstract was rephrased and this was made clearer in its first paragraph (Objectives). Points 1 and 2 above are clearly defined in the main text. MAIN TEXT 1. The authors should mention the sampling technique used in the parent study.
A: Considering this an exploratory study, being the first large-scale RHD screening program in Brazil, we considered the whole sample of schoolchildren enrolled during the 26-month screening phase. Subsequently, all screen-positive children were invited for follow-up appointments, and those who attended the clinical / echo appointments were included in this analysis. This information was added to the Statistical Analysis section. 2. What is the duration of follow up for the present study?
A: The prespecified follow-up interval was 24 months, and this information was added to the 4th paragraph of the Methods section (line 168), as suggested. Considering the logistics of the study, the median follow-up time was 29 months, ranging from 11 – 48. 3. Why is the font in Methods/paragraph 5, different? Copy and paste? Can the authors report on the dropout rate?
A: The different font was probably a problem during the conversion of the proof file, and not a copy-and-paste issue. We have reported the drop-out rate, with slightly more than 36% completing follow-up. Furthermore, we stressed this point in the limitations paragraph of the Discussion section, lines 304 - 305. 4. Statistical analysis: How did the authors define "low, intermediate, and high risk categories"? I think it would have been better for the authors to adjusted their prediction model for at least age, gender, area of residence (rural/urban) and socioeconomic status. Unfortunately, the power of their analysis might be limited by their sample size.
A: Low, intermediate and high-risk categories were defined in the score derived by Nunes et al from Brazilian and Ugandan RHD screening studies, with outcomes validation in a second Ugandan cohort, considering the risk of having unfavorable echo outcome. This information was added to the Methods / Statistical Analysis section, lines 204 - 205. As the model was developed by this group with a specific methodology, without adjustment for clinical and demographic variables (e.g. age, gender, etc.) and intended to apply only echo variables, we used the same methodology. This study was not aimed at model development or recalibration. Furthermore, as you mentioned, this analysis would be limited by sample size at this point.
5. Limitation: Can the authors rewrite the following sentence for clarity? "Second, absent a gold standard, initiation of penicillin prophylaxis was left to the discretion of the treating physician."
A: Following your recommendation, this sentence was changed to: “Second, in the absence of a gold standard, prescription of penicillin for secondary prophylaxis was left to the discretion of the treating physician” for better understanding. 6. Conclusion: Seems the authors have followed up the participants for just 29 months. This is not long enough to make firm conclusion statements on the evolution of RHD. Secondly, with the small sample size, these findings are likely to be due to chance.
A: We totally agree with your comments, and these are considerable major limitations of the study. In accordance with your suggestion, these limitations were stressed in the last paragraph of the Discussion section, lines 304, 305, 313, 314.
Other minor comments 1. Discussion P2: I believe the authors meant "Epidemiological characterization..." NOT "Epidemiologicaly characterization...". The authors should also highlight the small sample size of their study. A: This was a typo and this change was made to the text.
Reviewer: 2
Bechtlufft and colleagues report echocardiographic outcomes of children detected to have rheumatic heart disease and validate a simplified score to predict mid-term outcomes. The manuscript presents original data and addresses a topic of interest. The introduction adequately outlines the clinical context of the study, the methods are appropriate to study the hypothesis, the results are original and the discussion is well balanced.
A: Thank you for the positive and encouraging comments.
This reviewer has minor comments. 1. The low participation in school-based screening and the high attrition rate introduce a selection bias of the reported data. The authors addressed this limitation by

presenting a comparison of patients with versus without follow-up. It may be interesting to look into predictors for loss to follow-up.
A: As you mentioned, we addressed the high attrition in the analysis by showing there were no characteristics that differed between children who did and did not continue follow-up, as demonstrated in lines 220 – 227. Considering this, the only variable which differed statistically between groups was gender, although the proportions were quite similar from the clinical point of view (66% vs. 57%). In addition, the study was not designed nor powered to determine differences in participants who were lost vs. continued in follow-up, and associations may be found by chance.
2. Duration of follow-up is limited; in addition, I suggest to describe the methods used to collect clinical follow-up and provide information about independent adjudication of echocardiographic endpoints.
A: We agree that duration of follow-up time was limited, and this was stressed in the last paragraph of the Discussion as a limitation, lines 304 – 305. Following your recommendation, more detailed information on clinical follow-up – including the systematic reminders of the follow-up visit by phone and mail to improve adherence and the variables collected in the standardized clinical form – were added to the Methods section, lines 167 – 171. The follow-up standard echocardiograms were adjudicated for study echo outcomes by 2 experts, and this information was added to the Methods, line 175.
3. Under “patient and public involvement”, the authors write that “study participants were not involved in the design of this study” and “no patients’ involvement”. The second statement seems to be redundant. Please delete or specify.
A: This was a typo, and the sentence was changed to “Patients and public were not involved in the design and conduct of this research” in accordance with the journal’s requirements.

VERSION 2 – REVIEW

REVIEWER	Valirie Ndip Agbor University of Oxford, United Kingdom
REVIEW RETURNED	24-Feb-2020

GENERAL COMMENTS	The authors have responded satisfactorily to my comments. I have no further comments.