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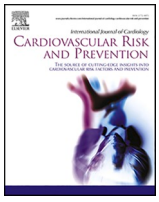

Development and validation of a predictive model for the diagnosis of rheumatic heart disease in low-income countries based on two cross-sectional studies

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ABSTRACT

Objectives: We developed a questionnaire-based risk-scoring system to identify children at risk for rheumatic heart disease (RHD) in rural India. The resulting predictive model was validated in Nepal, in a population with a similar demographic profile to rural India.

Methods: The study involved 8646 students (mean age 13.0 years, 46% boys) from 20 middle and high schools in the West Midnapore district of India. The survey asked questions about the presence of different signs and symptoms of RHD. Students with possible RHD who experienced sore throat and joint pain were offered an echocardiogram to screen for RHD. Their findings were compared with randomly selected students without these symptoms. The data were analyzed to develop a predictive model for identifying RHD.

Results: Based on our univariate analyses, seven variables were used for building a predictive model. A four-variable model (joint pain plus sore throat, female sex, shortness of breath, and palpitations) best predicted the risk of RHD with a C-statistic of 0.854. A six-point scoring system developed from the model was validated among similarly aged children in Nepal.

Conclusions: A simple questionnaire-based predictive instrument could identify children at higher risk for this disease in low-income countries where RHD remains prevalent. Echocardiography could then be used in these high-risk children to detect RHD in its early stages. This may support a strategy for more effective secondary prophylaxis of RHD.

1. Introduction

1.1. Background/rationale

Rheumatic heart disease (RHD) remains common in low-income countries [1,2]. In India, there are more than one million estimated cases of RHD in children [3]. The estimated prevalence of RHD in Nepal is similar to that of children 10–16 years old living in India [4]. Children with RHD experience suboptimal physical growth and significant associated morbidity and mortality, with adverse economic consequences [5–7]. Poor socioeconomic status is one of the major determinants of RHD [8,9].

Using echocardiograms to screen children for RHD is not feasible for many populations with limited resources, which have a dearth of trained

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personnel, echocardiography machines, infrastructural support, and funding. The natural course of this disease involves sore throat due to streptococcal beta hemolyticus infection followed by immune-mediated arthritis and carditis [10]. Identifying those at high risk for RHD is possible with the answers to several questions. A more cost-effective public health strategy may be a questionnaire-based screening tool for children suspected of being at risk for RHD, followed by an echocardiogram for those identified as at increased risk.

1.2. Objectives

The goal of this study was to evaluate the efficacy of a questionnaire-based tool to help diagnose RHD among children 10–16 years old living in West Midnapore, India. The resulting predictive model was then validated among similarly aged children living in the Dhading district of Nepal.

2. Methods

2.1. Study design

The study design was cross-sectional with a questionnaire-based survey of susceptible schoolchildren in resource-limited communities.

2.2. Setting

In the summer of 2017, we conducted a cross-sectional study with a questionnaire-based survey in West Midnapore, a rural district in West Bengal, India. The survey had 20 questions about demographic characteristics and symptoms and signs suggestive of RHD. The children were divided into two groups (symptomatic or asymptomatic) depending on their survey responses. Students with one or more episodes of sore throat and joint pain in the preceding five years were classified as symptomatic. Students who did not report the occurrence of sore throat and joint pain during the past five years were considered asymptomatic.

All students in the symptomatic group and a similar number of randomly selected asymptomatic students were offered screening for RHD using the World Heart Foundation echocardiographic criteria.

A similar cross-sectional study was conducted in the Dhading district of Nepal in the summer of 2018.

2.3. Participants

We visited 20 schools and administered the questionnaire to 8646 middle- and high-school students 10–16 years old who were suspected of being at risk for RHD based on the reported RHD prevalence [1–3]. People in this area belong to low to middle socioeconomic classes, with the majority having their education limited to primary and secondary schools and a small proportion (28%) having a college education or higher. Approximately 38% of students from the symptomatic group (383 out of 1015) and 3% of randomly selected participants from the asymptomatic group (249 out of 7631) were screened for possible RHD by echocardiogram.

The study in Nepal involved 11 schools with a total population of 3000 students 10–16 years old. The predictive model developed from the Indian study was used for validation in Nepal.

The Institutional Review Board of Tufts University, Boston, USA, approved both studies in India and Nepal. The India and Nepal studies were also approved by the Ethics Committee of the Calcutta Medical College and the Ethics Committee of the Government of Nepal, respectively. Informed consent from the parents or legal guardians and assent from the participating students were obtained for the study.

2.4. Variables

Study participants were evaluated for their demographic profile, including age, sex, level of parental education, and the number of people sharing a room to sleep as an indicator of poor socioeconomic status. Each sign and symptom of RHD reported in the survey was measured in terms of its frequency during the past five years.

2.5. Data sources/measurement

Data were collected from each student in a response sheet with pen and paper. Mean values were calculated for the continuous variables, and median values were calculated for the categorical variables. Simple t-statistics were used to compare the numerical variables, and Chi-square statistics were used to compare categorical variables between the symptomatic and asymptomatic groups and also between participants in the Indian study and the Nepal study.

2.6. Bias

The community in the West Midnapore district in West Bengal was selected because of convenience and prior acquaintances with the study team. Similarly, the Dhading district in Nepal was chosen because of prior relationships with the principal investigator from Nepal. The selection of the study sites might have introduced some selection bias. However, the degree of bias was considered small, as no factor other than acquaintances through a previous study unrelated to the current one was the reasoning behind our selection process. Execution of the project was feasible through the local network, which otherwise would have been more difficult.

Another source of potential bias was recall bias because the students responded to the questionnaire from memory. Information provided by the students was verified by the parents/guardians at the time of echocardiography in an effort to reduce the extent of recall bias. For students who did not undergo echocardiography, such verification was not possible, and some degree of recall bias was considered unavoidable in this group of students.

2.7. Study size

The study populations consisted of 8646 schoolchildren in India and 3000 in Nepal. With a prevalence of RHD of approximately 2–3 per thousand in the age group 10–16 years old based on the published literature, 24–36 cases of RHD were expected in the study population. This number of cases of RHD was thought to help build a predictive model by multivariable logistic regression analysis with the inclusion of 4–5 predictor variables.

2.8. Quantitative variables

Categorical variables were created from the numerical variables to represent signs and symptoms of RHD when the frequency of signs and symptoms experienced was twice or more by any student in the preceding five years.

2.9. Statistical methods

In the statistical model, the sociodemographic characteristics, symptoms, and signs of RHD in the study sample were used as explanatory variables; the presence or absence of RHD, as diagnosed by echocardiogram, was used as the dependent variable.

Demographic variables and signs and symptoms of rheumatic fever and heart disease were examined with univariate logistic regression analyses to study their association with RHD. Variables associated with RHD in univariate analyses were used in multivariable logistic regression analysis for purposes of building a predictive model.

A sex-specific subgroup analysis was carried out to investigate possible differences in the risk of RHD for the girls compared with the boys using multivariable logistic regression analysis and adjusting for

other relevant signs and symptoms (joint pain and sore throat, shortness of breath, and palpitations). Odds ratios were calculated to compare the risk of RHD between the girls and the boys.

Interaction terms were introduced in the logistic regression analyses to examine the possibility for any interaction between sex and other signs and symptoms of RHD.

Any missing data were addressed at the time of echocardiography, and any missing element was collected in participants who underwent echocardiography. For those who did not undergo echocardiography, a complete case analysis was used. Baseline characteristics were evaluated based on the available data, and no adjustment was made for the missing information. No obvious change in the principal study results was expected because of the large number of study participants.

All of the students from the symptomatic group and an equal number of randomly selected participants from the asymptomatic group underwent echocardiography. For building the predictive model, data from the Indian study were randomly split into an 80:20 ratio.

A sensitivity analysis was performed to identify the optimum threshold of estimated probability for effective use of the predictive model. With the goal to identify participants with RHD when the risk was higher than one percent, a probability of 0.01 was selected as the clinically meaningful threshold for detecting RHD.

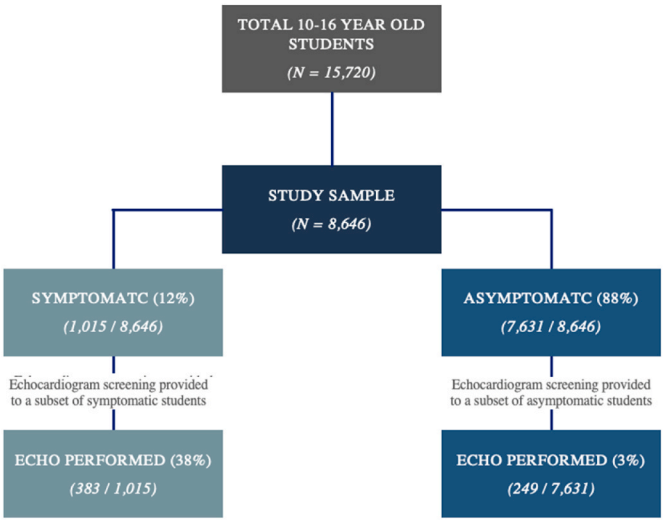
3. Results

3.1. Participants

We visited 20 schools and administered the questionnaire to 8646 middle- and high-school students aged 10–16 years suspected of being at risk for RHD. The total number of 10–16-year-old students in the school registry was 15,720. All the students present in the schools on the day of the study participated in the survey with a response rate of 55% (8646/15,720).

Every student in the symptomatic group and a similar number of randomly selected asymptomatic students were offered screening for RHD using the World Heart Foundation echocardiographic criteria. Approximately 38% of students from the symptomatic group (383 out of 1015) and 3% of randomly selected participants from the asymptomatic group (249 out of 7631) were screened by echocardiogram. The reasons for non-participation were thought to be lack of RHD awareness, difficulty in getting the echocardiography done, and, in some circumstances, social stigma attached to the diagnosis of RHD. Echocardiography was done at the district town in a diagnostic center, and the students were transported back and forth from the schools with the help of research volunteers and an escort from the school. Although offering an echocardiogram at school premises was considered, it could not be done because of government regulations to avoid misuse of echocardiogram machines for fetal screening and female feticide.

Flow diagram: Questionnaire based screening for RHD in India.



3.2. Descriptive data

Table 1 shows the baseline characteristics of the study population. There were no significant differences in the mean age, parental education level, and the number of people sharing a room to sleep when compared between the children having a sore throat and joint pain (the symptomatic group) and those not having these symptoms (the asymptomatic group)

3.3. Outcome data

Thirty students from the symptomatic group and four from the asymptomatic group had evidence of RHD after undergoing echocardiography, per the World Heart Foundation echocardiographic criteria used [11].

Table 1
Baseline characteristics of the study population in India.

	Symptomatic	Asymptomatic
	(n = 383)	(n = 249)
Age (mean, years)	13.2	12.6
Male	59%	54%
Grade (median)	8	7
Mother's Education		
School Education	81% (310)	72% (179)
Higher Education	10% (38)	9% (22)
Missing	9% (35)	19% (48)
Father's Education		
School Education	73% (280)	62% (154)
Higher Education	16% (61)	16% (40)
Missing	11% (42)	22% (55)
Room Sharing		
Signs and Symptoms (Mean frequency; % with≥twice in 5 years (number of participants)		
>=3 Persons/Room	222 (58%)	147 (59%)
Fever	5; 93% (357)	4.3; 90% (223)
Sore Throat	3.3; 68.9% (264)	1.3; 34.9% (87)
Joint Pain	3; 63% (241)	0.3; 4.8% (12)
Chest Pain	1.4; 32.6% (125)	1.3; 16.9% (42)
Shortness of Breath	1.1; 78% (299)	0.6; 13.3% (33)
Dizziness	0.7; 13.3% (51)	0.3; 5.6% (14)
Easy Tiredness	3.0; 49.6% (190)	1.2; 22.9% (57)
Palpitations	1.3; 27% (105)	0.8; 13.7% (34)
Skin Rash	1.3; 15.1% (58)	0.2; 4.8% (12)
Skin Nodule	0.4; 89.8% (344)	0.2; 5.2% (13)
Seizures	0.5; 11.5% (44)	0.2; 4.8% (12)
Leg Swelling	1.6; 19.6% (75)	0.3; 6% (15)

3.4. Main results

Among the 21 variables included in the univariate analyses, seven variables (female sex, fever, chest pain, seizures, shortness of breath, palpitations, and having both symptoms of sore throat and joint pain) were associated with the presence of RHD (Appendix, Table 1). Categorical variables were created for fever, chest pain, seizures, shortness of breath, and palpitations when these symptoms were experienced more than twice in the preceding five years. The occurrence of both sore throat and joint pain one or more times was used to define the symptomatic group.

For model building and cross-validation, the data were randomly split into training and test data in a ratio of 80:20. Training data were used to develop the predictive model. The model's performance was tested in the training data for internal validation and in-sample prediction. Test data were used for cross-validation and out-of-sample prediction. The Nepal dataset was used for further external validation study of the model's robustness.

Multivariable logistic regression analysis was used for statistical modeling with the aforementioned seven categorical variables. A four-variable model (joint pain plus sore throat, female sex, shortness of breath, and palpitations) appeared to perform best with the stepAIC function in R. These four variables performed best when compared using forward, backward, and forward/backward variable selection methods when starting with the seven variables that had predictive value from our univariate logistic regression analyses.

The area under the receiver operating characteristic curve (AUC) for the four-variable model was very similar to that from the full model using seven variables (85.4% vs. 85.6%). (see Table 2) The negative predictive value of the model was 99%. The positive predictive value was 6.8%, with a likelihood ratio (sensitivity/1- specificity) of 1.25 when a threshold of predicted probability for RHD was set at 0.01 based on a sensitivity analysis. The clinical justification for choosing this threshold was to screen children whose susceptibility to RHD, as predicted by the model, was more than one percent. Since the goal of screening is to offer an echocardiogram, a noninvasive and relatively inexpensive process, this threshold was considered a realistic proposition and clinically important.

3.4.1. Development of scoring system

To develop a scoring system based on the above model, the coefficients were rounded to the nearest integer for effective use in resource-limited communities where RHD is more prevalent. Two variables (joint pain and sore throat together, and female sex) each assumed a score of two, while the other variables were assigned a score of one, resulting in a maximum score of six for the predictive model (see Table 3).

3.4.2. Performance of the final model

Table 4 shows the performance metrics of the predictive model. The final model had a C statistic of 0.854 with a 95% confidence interval of 0.780–0.921 using 2000 bootstraps by DeLong's method, indicating good model discrimination. (see Fig. 1) The calibration histogram in different quantiles of prediction showed excellent model performance. There was no significant difference between the predicted and observed mean in the prediction model examined (95% confidence interval: 0.01–0.10). The Hosmer-Lemeshow test for the model calibration with a large p-value of 0.71 and a small Chi-squared value of 1.4 suggested a good logistic regression model fit. (see Fig. 2)

Table 2
Comparison of the final (four-variable) model with the full (seven-variable) model.

Model	Variables	AIC	AUC
Full	Sore throat and joint pain together, sex, fever, chest pain, seizures, shortness of breath, and palpitations	178	0.856 (0.781–0.928)
Final	Sore throat and joint pain together, sex, shortness of breath, and palpitations	173	0.854 (0.780–0.921)

Table 3
Final model with coefficients.

Variables	Coefficient	95% Confidence Interval
(Intercept)	−6.56	−8.62–−5.04
Join pain + Sore Throat	2.17	0.90–4.02
Sex (Female)	2.01	1.06–3.15
Shortness of Breath	1.15	0.28–2.01
Palpitations	1.16	0.30–2.01

3.4.3. Validation of the model in Nepal

The baseline characteristics of the study population in Nepal who participated in the screening echocardiogram were similar to those found in the Indian population. Their mean age was 13.3 years, and 44% were boys. Most of the parents (95%) had only basic school education. In Nepal and India, a similar proportion (57%) of students shared a room to sleep with more than three persons.

From a study sample of 3,000, nearly 14% had symptoms of sore throat and joint pain one or more times in the preceding five years and were considered to be symptomatic. All students in the symptomatic group, and an approximately equal number of randomly selected students from the asymptomatic group, were offered echocardiographic screening for RHD using World Heart Foundation criteria. From the symptomatic group, 66% (n = 269 out of 407) completed the screening, as did 19% of the students from the asymptomatic group (n = 496 out of 2593). Nine students were found to have RHD: seven from the symptomatic group and two from the asymptomatic group.

The six-point scoring system developed from the Indian study was applied to the Nepal study sample to validate our predictive tool. With the application of this scoring system, all positive cases could be identified when the score was three or more. One in five students (20%) in the study population had RHD if they scored six in the scoring system (Table 4). By comparing the results in Table 5 to the performance metrics for the final model in Table 4, the six-point scoring system maintained the statistical accuracy of the final model to a large extent while providing ease of usability in low-resource environments such as schools in rural areas.

3.5. Other analysis

Subgroup analysis based on sex showed that the odds of RHD for the girls were 7.36 compared to the boys when sex was adjusted for among the other variables in the final predictive model. No interaction was noted between the sex and the signs and symptoms of RHD (sore throat and joint pain together, shortness of breath, and palpitations) in the final model. There was no significant collinearity among the model parameters. A sensitivity analysis with different thresholds of estimated probability of RHD was performed. A threshold probability of 0.01 to identify a participant with suspected RHD when the estimated risk was more than one percent was found to be clinically most useful.

4. Discussion

4.1. Key results

Rheumatic heart disease remains a significant public health problem in low-income countries [12,13]. Our study offers a predictive model to identify children at high risk for RHD using a simple questionnaire. In this model, children with sore throat and joint pain were more likely to have RHD if they also had recurrent complaints of shortness of breath and palpitations in the preceding five years. This predicted risk of RHD is

Table 4
Development and evaluation of the predictive model.

Model Development and Cross Validation

Train Data

	RHD	
Predicted	1	0
1	27	369
0	1	110

Test Data

	RHD	
Predicted	1	0
1	6	47
0	0	72

Nepal Data

	RHD	
Predicted	1	0
1	9	576
0	0	180

Model Performance Metrics

	Train Data	Test Data	Nepal Data
Sensitivity	96	100	100
Specificity	23	60	23.8
PPV	6.8	11.3	1.5
NPV	99	100	100
FPR	77	39	76
FNR	0.04	0	0
Precision	7	11	2
Accuracy	27	62	25
Recall	27	39	76
f1 score	13	18	3
AUC (ROC)	85.4%	87.1%	73.5
CI of AUC	77% —92%	81% —100%	62%—86%

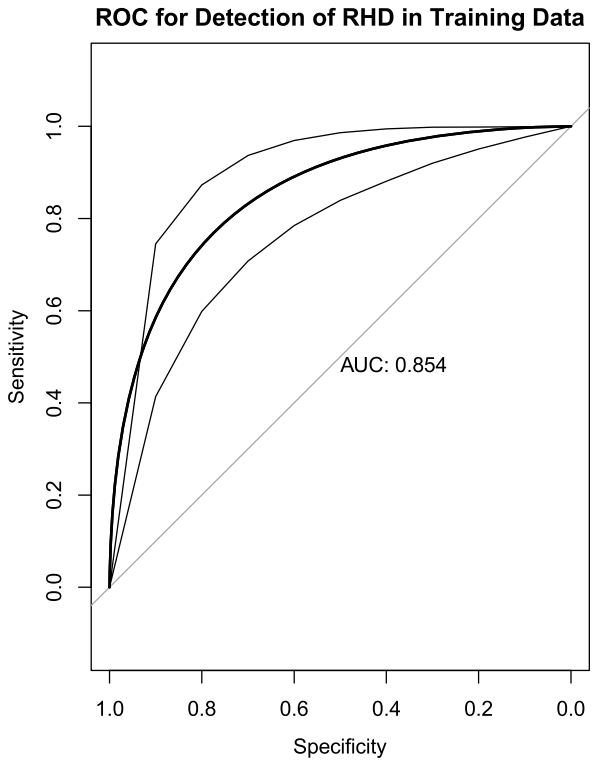


Fig. 1. Receiver operating characteristic curve on the train data.

even higher for girls 10–16 years old. The odds of RHD for the girls were 7.36 compared to the boys when sex was adjusted for among the other variables in the final predictive model.

4.2. Limitations

Our predictive model for the early diagnosis of RHD has very good discrimination, with a ROC of 0.854. The validation study in Nepal showed good performance, with a negative predictive value of 100%. This simple scoring system and the ease of implementation in schools make it a promising tool for screening for RHD.

Nonetheless, the present study has several limitations that need to be considered in interpreting our results. First, some children with RHD may not have the symptoms and signs used in the predictive model. Second, since the initial risk is ascertained based on student responses to the questionnaire with different symptoms and signs, there will be some recall bias in answering the questions. Third, some students, particularly girls, may not have participated in the screening echocardiogram due to social inhibitions, since it involves baring the chest during the examination. Furthermore, in some communities, RHD is viewed as a social stigma, compromising voluntary participation in undergoing screening and subsequent echocardiogram. Lastly, our study was conducted in a rural area in India and validated in an analogous community in Nepal. Application of the screening tool in different populations will be needed to validate the wider use of the model.

4.3. Interpretation

A study conducted in American Samoa using echocardiographic screening found that approximately one in every eight school children had RHD, the highest rate in the published literature [14]. Poor socioeconomic conditions, inadequate access to healthcare, and lack of awareness are among the many factors contributing to the high prevalence of RHD in resource-limited communities. Our previous study on RHD awareness among school children in India demonstrated that student awareness was modest, as reflected by their responses to the survey questionnaire used in the study [15].

Objectives: The objective of the present study was to identify RHD in its early stages to facilitate the effective use of secondary prophylaxis in a resource-limited environment. Progression of RHD is largely preventable if detected early and secondary prophylaxis initiated [16]. In a cluster randomized controlled trial in Nepal, a school-based echocardiographic screening program in conjunction with secondary prophylaxis with antibiotics significantly reduced the burden of RHD in the community (3.8 vs. 10.8 per thousand children) [17]. A delayed diagnosis of RHD leads to disability, premature death, and high societal and

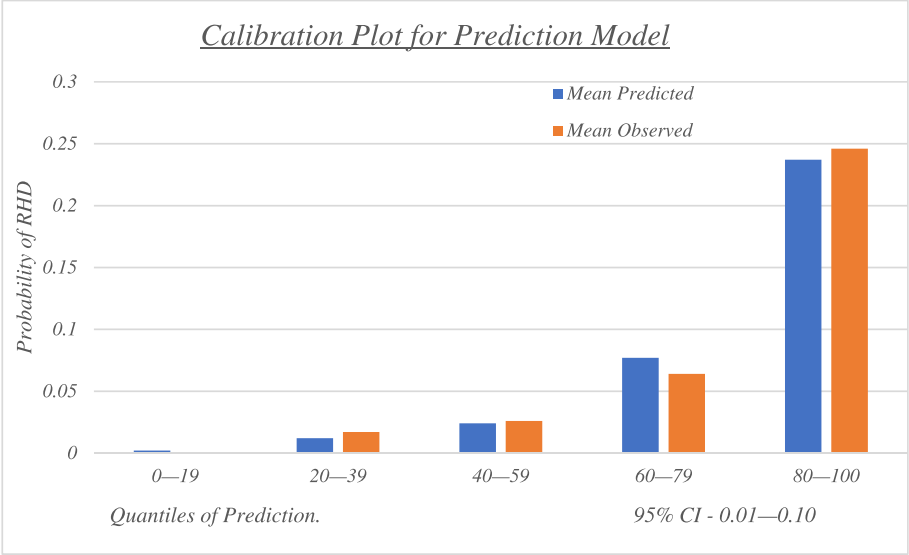


Fig. 2. Calibration histogram in different quantiles of prediction.

Table 5
Validation of the RHD model in Nepal.

Score	RHD Present (n = 9)	RHD Absent (n = 756)	Total (N = 765)	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
6	1	21	22	7.70%	90.00%	100%	42.86%
5	3	48	51	7.14%	90.00%	75%	18.75%
4	4	140	144	2.91%	85.71%	80%	43.1%
3	1	137	138	1.57%	89.66%	100%	1.58%
2	0	217	217				
1	0	35	35				
0	0	158	158				
≥3	9	756	765	2.83%	81.31%	75%	7.76%

economic burdens [18].

4.3.1. Limitations

There are many challenges in the diagnosis of RHD. This disease is currently diagnosed with echocardiography using criteria established by the World Heart Foundation [11] and the simplified criteria derived from it [19,20]. Although the echocardiogram is non-invasive and takes only a few minutes for trained personnel to perform, it is not practical as the primary diagnostic tool for every child. Echocardiograms are not easily accessible to much of the population in low-income countries, are relatively expensive, and the required trained personnel are scarce. In addition, there is currently no easy way to identify children at risk for developing RHD. A simple screening tool to identify children at higher risk could be helpful for the diagnosis of RHD in resource constrained communities.

4.3.2. Multiple analyses

We carried out multiple analyses in developing and validating the predictive model. The inherent problem of any chance association of RHD with the variables tested remains a possibility. However, the variables selected in the predictive model are well aligned with the clinical course of RHD, and any chance association seems to be less likely. Moreover, detailed stepwise model selection with multivariable logistic regression analysis, relatively narrow confidence intervals of the model parameters, and an excellent C statistic with multiple iterations with bootstrapping demonstrate the robustness of the model.

4.3.3. Results from similar studies

Concordance of results from similar studies often provides strength in making inferences from any observational study. Unfortunately, no such screening tool exists in the current literature.

4.4. Generalizability

Rather than scanning every child in the community, we can offer echocardiograms to those suspected of having RHD based on the screening questions used in the present study. Children 10–16 years old with sore throat and joint pain, shortness of breath, and palpitations were more likely to suffer from RHD than those without these symptoms. This risk is higher for girls than boys, even after adjustment for the other variables in the regression model. This approach may offer a strategy for more cost-effective utilization of scarce resources.

5. Conclusions

Our study offers a simple predictive model for identifying RHD in resource-limited communities in developing countries. Once validated in other community-based studies, it has potential as an effective tool for nationwide screening programs for RHD in low-income parts of the world where the disease remains prevalent. In the future, we plan to build a digital application where our volunteers input the covariate data, and the app outputs the risk score, which can be readily used to scale up the screening of vulnerable populations.

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Credit author statement

Madhab Ray: Conceptualization, Methodology, Investigation and Writing-Original Draft. **Santanu Guha:** Supervision. **Ranga Raj Dhungana**: Supervision and Project administration. **Avik Karak:** Project administration. **Basabendra Choudhury:** Project administration. **Bipasha Ray:** software, validation, and formal analysis. **Haroon Zubair:** methodology and funding acquisition. **Meghna Ray:** methodology, data curation, writing-reviewing, and visualization. **Srijan Sengupta:** statistical analysis and review. **Deepak L Bhatt:** methodology, writing-reviewing, and supervision. **Robert J Goldberg:** methodology, writing-reviewing, and supervision. **Harry P Selker:** conceptualization, methodology, writing-reviewing, and supervision

6. Take home message

In low-income countries, children 10–16 years old with sore throat and joint pain are at risk for RHD, especially girls who have shortness of breath and/or palpitations. An echocardiogram should be performed on children determined to be at risk for RHD.

Disclosures

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Appendix

Table 1
Univariate Analyses of Demographic Variables and Different Signs and Symptoms of the Study Participants

Variable	Intercept	Co-efficient	p-value
Age	−5.10	0.17	0.13
Female Sex	**−3.37**	**0.94**	**0.01**
Grade	−4.12	0.16	0.17
Room Sharing	−2.96	0.03	0.78
Mother's Education	−3.19	0.18	0.46
Father's Education	−3.31	0.23	0.32
Fever	**−3.20**	**0.06**	**0.04**
Palpitations	−2.96	0.05	0.16
Leg Swelling	−2.83	−0.07	0.59
Easy Tiredness	−2.96	0.03	0.25
Chest Pain	−3.03	0.11	0.05
Sore Throat	−2.96	0.04	0.48

(*continued on next page*)

Table 1 (*continued*)

Variable	Intercept	Co-efficient	p-value
Dizziness	−2.88	0.03	0.67
Joint Pain	−2.88	0.01	0.83
Seizures	**−3.03**	**0.25**	**0.002**
Shortness of Breath	**−3.02**	**0.12**	**0.02**
Skin Rash	−2.87	0.00	0.97
Skin Nodule	−2.88	0.03	0.84
Joint Pain + Sore Throat	**−4.12**	**1.65**	**0.002**
Sore throat without Joint Pain	−2.81	−0.26	0.57
Joint Pain without Sore Throat	−2.83	−14.74	0.99
No Joint Pain or Sore Throat	−2.79	−0.63	0.31

Table 2
Univariate Analysis with Categorical Variables of Different Signs and Symptoms of RHD

Variable (categorical)	Intercept	Co-efficient	p value
Fever	−2.84	0.38	0.61
Sore Throat	−3.03	0.27	0.45
Joint Pain	−2.92	0.08	0.83
Sore Throat and Joint Pain	**−4.11**	**1.65**	**0.002**
Shortness of Breath	**−3.26**	**1.35**	**<0.001**
Seizures	**−3.05**	**1.26**	**0.003**
Skin Rash	−2.99	0.79	0.08
Chest Pain	−2.47	0.58	0.11
Skin Nodule	−2.91	0.42	0.44
Easy Tiredness	−3.02	0.35	0.33
Dizziness	−2.72	0.16	0.77
Palpitations	**−3.11**	**0.84**	**0.02**
Leg Swelling	−2.83	−0.04	0.94

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