Impact of Incorporating Echocardiographic Screening into a Clinical Prediction Model to Optimize Utilization of Echocardiography in Primary Care

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Abstract

Introduction: Access to public healthcare is limited in Brazilian underserved areas, and long waiting lists remain for echocardiography (echo). We aimed to develop a tool to optimize indications and shorten waiting lists for standard echo in primary care. Methods: Patients in waiting list for standard echo were enrolled. For derivation, patients underwent a clinical questionnaire, simplified 7-view echo screening by non-physicians with handheld devices (GE-VSCAN), and standard echo (Vivid-Q) by experts. Two models were adjusted, one including clinical variables and other adding screen-detected major heart disease (HD). For validation, patients were risk-classified according to the clinical score. High-risk patients and a sample of low-risk underwent standard echo. Intermediate-risk patients first had screening echo, with a complete study if HD was suspected. Discrimination and calibration of the 2 models were assessed to predict HD in standard echo. Results: In derivation (N=603), clinical variables associated with HD were female gender, body mass index, Chagas disease, prior cardiac surgery, coronary disease, valve disease, hypertension, and heart failure, and this model was well calibrated with C-statistic=0.781. Performance was improved with the addition of echo screening, with C-statistic=0.871 after cross-validation. For validation (N=1,526), 227 (14.9%) patients were classified as low-risk, 1082 (70.9%) as intermediate-risk, and 217 (14.2%) as high-risk by the clinical model. The final model with 2 categories had high sensitivity (99%) and negative predictive value (97%) for HD in standard echo. Model performance was good with C-statistic=0.720. Conclusion: The addition of screening echo to clinical variables significantly improves the performance of a score to predict major HD.

INTRODUCTION:

Echocardiography (echo) remains one of the most used imaging modalities in clinical practice, providing incremental information with low risk to the patient by employing ultrasound technology[1,2]. The availability of portable and affordable machines has allowed echocardiography to go beyond the frontiers of specialized centers, and its indications have progressively increased, being frequently ordered by primary-care physicians[3,4]. In response to marked increases in utilization of echocardiography, the delay in its access is inevitable. The first consideration of healthcare providers is that the waiting list is a direct measure of the need for medicals services, and that the size of the list is directly related to the need. However, in a setting of low likelihood of cardiovascular disease, echocardiography does not substantially change cardiovascular therapeutics, even if appropriately ordered[4].

There are growing efforts to improve value-based approaches to diagnostic tests, especially echocardiography, primary targets of ongoing reforms in healthcare delivery and reimbursement[5,6]. In a context of limited-resource settings, such as the Brazilian public health system, the increasing demand for echocardiography yields a critical burden, both for patient management and the health system budget[7]. Therefore, strategies aimed at limiting the costs of health services and shortening waiting lists are essential to efficiently incorporate this imaging modality into daily clinical care[7].

Despite the increasing interest of healthcare managers, limited data are available to enhance physician awareness and education about optimal utilization of imaging, especially when indications were given by non-cardiologists[2]. Several implications for practice point towards the importance of adequately defining the likelihood of disease rather than appropriateness of testing and impact on outcome for management of diagnostic flowcharts[4,8].

Implementation of echo screening into the Brazilian primary care has preliminary proven to be feasible as a tool for risk stratification and prioritization of referrals[9]. However, its impact on the population's likelihood of cardiac disease in addition to clinical evaluation is yet to be defined. Therefore, the present study was designed to develop a tool to optimize indications and shorten the waiting lists of patients who have a standard echo ordered by primary-care physicians through a community-based approach in resource-limited settings.

METHODS:

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. The PROVAR+ study is a continuation of the rheumatic heart disease screening program, as a collaboration between the Universidade Federal de Minas Gerais, Telehealth Network of Minas Gerais[10] and the Children's National Health System, Washington, DC, USA. Details about the study's methodology and results have been published elsewhere[9]. In this sub-study, Primary Health Centers (PHCs) from the city of Montes Claros (north Minas Gerais, 361,900 inhabitants), areas with poor socioeconomic conditions in the state, were selected to participate of the study, based on priorities of health authorities. Patients in the waiting list for an echocardiogram were selected. Ethics approval was obtained from the institutional review boards and local Boards of Health, and eligible patients signed the informed consent prior to enrollment.

A previous survey carried out in 2017 found a waiting list of 6,330 patients in Montes Claros public health system, with an average availability of around 130 exams/month, distributed in 2 echocardiographic centers. In an exploratory sample of 200 exams performed in these centers in January 2017, only 15% had some degree of heart disease, suggesting an inadequate use of this scarce resource.

This study was conducted in 2 phases with derivation and validation models (**Figure 1**). In the first phase, 603 patients underwent a clinical questionnaire, echo screening, and standard echocardiography. A standardized clinical questionnaire with sociodemographic data, comorbidities, preexistent heart disease, cardiovascular symptoms, and prior cardiac surgery was applied by the research team, in order to identify predictors of cardiac disease. The research team consisted of a nurse and a biomedical professional, both of whom undertook systematic training for research procedures and image acquisition.

Subsequently, echo screening was performed by the non-physician from the research team, with a simplified 7-view echocardiographic protocol, focusing on major cardiologic findings, including ventricular dysfunction and hypertrophy, cardiomyopathies, valvular and congenital heart diseases. Screening echocardiography was performed utilizing standard portable (Vivid-Q®; GE Healthcare, Milwaukee, WI) or handheld (VSCAN®, GE Healthcare) machines and images were uploaded to cloud servers and analyzed via telemedicine by cardiologists in Brazil and the United States. Screening was considered abnormal in the presence of the major following abnormalities: any degree of left ventricular systolic dysfunction, segmental wall-motion abnormalities, moderate or severe left ventricular hypertrophy, any degree of right ventricular dysfunction, moderate or severe valve dysfunction (stenosis or regurgitation), presence of prosthetic valve, dilation of ascending aorta; congenital heart disease, cardiomyopathies, presence of implantable devices – especially

pacemaker and ICD – moderate or severe pericardial effusion; arrhythmias (atrial fibrillation).

After echo screening, a standard full echocardiogram (Vivid-Q®; GE Healthcare) was performed in all patients by an experienced cardiologist, unaware of the results of screening. The echocardiographic findings considered relevant were the same as in screening, for the purpose of further comparisons.

A model that predicted major abnormalities in standard echocardiography, defined as the outcome variable, was assessed by logistic regression and also by Classification and Regression Tree (CART) analysis. Initially, 2 models were adjusted, one including only the clinical questionnaire and the other adding the result of echo screening (binary presence of major abnormalities) to clinical data. Both models were internally validated by cross-validation to prevent overfitting, splitting the derivation population into training (70%) and test (30%) samples, and discrimination and calibration were evaluated in the test group[11]. Among the two models mentioned, we highlight the logistic regression analysis for presenting the calculation of the individual risk of each patient. For the predicted risk of each patient of having abnormal full echocardiography, the following risk categories were defined: low risk (<12%), intermediate risk (13% to 70%) and high risk ([?]71%). The cutoff point of 12% for low risk was chosen to maximize sensibility (>85%) and prevent false negatives, as the individuals classified in low risk did not perform any additional procedures. (**Appendix Figure 1**).

In the second phase, a task-force for the validation of the prediction tool derived in phase 1 was carried out. A research team consisting of medical students and other health professionals (nurses, biomedical, psychologists, pharmacists, biologists) organized the patients in stations, optimized flow during each stage and provided any necessary clarifications. In addition, echo screening (GE, VSCAN(r)) was performed by 2 groups of scanners with different backgrounds: 3 non-medical health professionals (1 nurse, 1 biomedical and 1 psychologist) and another group formed by 2 cardiologists and 1 cardiac sonographer from the US team. The standard full echocardiogram (GE Vivid Q(r), Vivid IQ(r)) was performed by 6 experienced Brazilian cardiologists.

For the validation step, 1,526 patients in the waiting list for standard echocardiography in other PHCs in Montes Claros were included (**Figure 1**). The initial approach was classifying the patients according to their risk of having major echocardiographic abnormalities based only on the clinical score. After entering the questionnaire data into the online RedCap(r) database[12] the patient's risk was automatically calculated. Patients classified as low risk did not perform any additional procedures and were discharged to their homes with a letter to the attending physician stating the initial low risk for significant cardiac abnormalities after clinical assessment. However, to test the performance of the model with only clinical variables, a validation subset randomly underwent standard echo.

Patients classified as high risk were immediately referred for standard echocardiography; and the preliminary report was released shortly after the exam. Patients classified as intermediate risk underwent screening echo, and were re-classified according to the findings as screen negative or positive. The screening results were then inserted into the RedCap(r) online system, generating a new risk estimation for these patients. If the numerical value re-classified them as low risk, they were discharged home without any additional exams, and only a subset was randomly selected to perform the standard echo. However, if they were re-classified as high risk, they were directly referred for standard echo. Therefore, each patient followed a different pathway within the workstations depending on their risk classification.

Patient involvement

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

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, Illinois) and R for Statistical Computing version 3.4.0 (R Foundation, Vienna, Austria). Categorical variables were expressed as numbers and percentages, whereas continuous data were expressed as mean +- standard deviation.

Logistic regression and Classification and Regression Tree (CART) analyses were assessed to predict an abnormal standard echocardiogram as the outcome of interest. Two models were adjusted, one including: 1) only the clinical questionnaire and 2) adding echocardiographic screening (normal or abnormal) to clinical data. The performance of the prediction models was assessed using a variety of different methods[13]. Calibration was based on the Hosmer and Lemeshow test and discrimination on the ROC curve and C-statistic. The models were internally validated by cross-validation to prevent overfitting, splitting into training (70%) and test (30%) samples, and discrimination and calibration were evaluated in the test group.

External validation of both models was performed by applying them to an independent population to assess their discrimination and calibration in predicting abnormal standard echocardiography. A bicaudal p-value <0.05 was considered significant.

RESULTS:

Derivation population

Mean age was 58.7+-15.3 years (range 16 – 101), 370 patients (61%) were women. In a preliminary analysis, the overall prevalence of major abnormalities in standard echo was 25.8%. Clinical variables associated with abnormal standard echocardiography are shown in **Table 1** : female gender, body mass index, Chagas disease, prior cardiac surgery, coronary artery disease, valve disease, hypertension, and history of heart failure were predictors of major echocardiographic abnormalities. Other cardiovascular conditions, including symptoms, did not remain in the model. The first model including only the clinical questionnaire showed a C-statistic of 0.761 and was well calibrated. Cross validation with replication showed optimal discrimination of the model with an average C-statistic of 0.781 and calibration with an average of Hosmer-Lemeshow p-value of 0.21.

The multivariate model after adding the echo screening to the clinical model is provided in **Table 2** . The model's performance improved significantly with a C-statistic of 0.863, and cross validation showed an average C-statistic of 0.871. The head-to-head comparison of the models is displayed in **Table 3** . Illustration of observed versus predicted abnormal echocardiography by decile of predicted risk for the test sample of the models with and without echo screening is shown in**Appendix Figure 2** . Based on the first classification of risk categories, using only the clinical variables, with the addition of screening echo to the model 248 participants (41%) were reclassified as intermediate risk. Abnormal standard echocardiogram was observed in 147 individuals, of whom 21 were classified as low risk.

Validation population

The mean age of the 1,526 patients included in the validation population was 57.9+-15.9 (range 16 – 102), 1,007 (66%) were women. The characteristics of the validation population compared to those of the derivation population are shown in **Table 4** . Although age was similar, there was a higher prevalence of comorbidities in the validation compared with derivation population, especially coronary artery disease, heart valve disease, and heart failure. The 3 risk categories predicted by the model with questionnaire, and 2 risk categories predicted by the model with questionnaire and screening echocardiographic are shown in **Appendix Figure 2** .

Applying the model including only the clinical questionnaire developed in derivation, 227 (14.9%) patients were classified in the low risk, 1082 (70.9%) in the intermediate risk, and 217 (14.2%) in the high-risk groups for having an abnormal standard echo (**Figure 2**). Of those in low-risk randomly selected for standard echo (N=50), only 3 presented major abnormalities (1 interatrial septal defect and 2 left ventricle hypertrophy). In the intermediate risk group, after the screening echo, 450 were reclassified as low risk and the standard echo was normal in the random sample of 62 patients. Of the 619 reclassified as high-risk, 372 had a normal, whereas 242 had an abnormal standard echo. Finally, all patients in the high-risk group directly underwent standard echo, which was normal in 66 and abnormal in 151.

In the overall population, after the screening echo, 372 patients classified in the high-risk category had normal standard echo (false positive), whereas there were no patients in the low-risk group with abnormal standard

echo (false negative). Of the 372, screening echo was positive in 254 patients and negative in 118 patients. The model had a high sensitivity to predict an abnormal standard echo in the validation population (99%) as well as negative predictive value (97%). Overall model performance in this new population of 1,526 patients was good with C-statistic of 0.720. Calibration was on average correct (calibration-in-the-large coefficient close to 0), but the Hosmer-Lemeshow test was significant (**Figure 3**).

DISCUSSION:

In this study, adding screening echo to a clinical score improved the accuracy of the model to predict the presence of major heart disease in primary care patients in waiting lists for standard echo. The final score had optimal sensitivity (99%) and negative predictive value (95%) for risk stratification, and may be a promising tool for prioritization of tests and referrals, and rationalization of health resources in underserved regions.

There has been growing interest in the development of screening echocardiography in the past decade. Different applications have been evaluated, from early detection of acquired heart disease[14] to point-of-care diagnosis of cardiac manifestations in systemic conditions[15,16], and the utilization of handheld devices may expand its utility to other ultrasound modalities, such as prenatal care. Strategies as task-shifting to non-physicians, telemedicine and simplified protocols potentially boost availability of screening – especially to low-resourced areas. While this approach may improve practicality, it leads to limitations associated with quality and detailing of image acquisition, and the technical aspects of the low-cost ultraportable devices pose additional challenges for final diagnoses in the field. Thus, the evaluation of screening echo as an additional categorical variable, flagged as "normal" or "abnormal", rather than focusing on specific diagnostic aspects, may add extra value to existing models to predict cardiovascular risk.

The broad utilization of echo screening for the overall population remains controversial. In 6,861 patients from a population-based nationwide Norwegian cohort, echocardiographic screening did not reduce mortality in 15 years, nor were observed benefits on secondary outcomes (sudden death, mortality from any heart disease, or incidence of fatal and nonfatal myocardial infarction and stroke)[17]. Conversely, for 410 asymptomatic individuals >=65 years-old with at least 1 risk factor for heart failure, comprehensive echo screening with global longitudinal strain added incremental information to clinical parameters to predict incidence of stage-B heart failure[18]. In the UK, among 100 patients >70 years-old without known valve disease undergoing point-of-care echo with the VSCAN, 5% required specialized care or surgery, at a reasonable cost per scan ($182/patient)[19]. Also with an acceptable cost of PS43/scan and PS460 per finding, focused echo screening of 100 young athletes in the UK (6 – 18 years) unveiled 12% with indication of further testing[20]. The later studies support our data regarding the impact of focused echo on the odds of having heart disease, although our population had a much higher baseline cardiovascular risk, and, consequently, higher pre-test probability in a cross-sectional evaluation. This, along with the cost-saving features of our strategy (integration into existing primary care, task-shifting and remote diagnosis), may improve utility and cost-effectiveness.

The Brazilian primary care has a particular flowchart for prescribing specialized tests, aimed at rationalizing resource allocation[21]. Those of higher complexity – e.g. magnetic resonance, computed tomography, colonoscopy – can only be ordered by specialists, after formal referral by the primary care physician, whereas simpler tests – as echo – can be directly prescribed by the primary care clinician or general practitioner. Considering the training and clinical backgrounds, data from over 2,800 echo prescriptions in Italy showed better guideline-driven appropriateness in prescriptions made by experts (cardiologists), resulting in more frequent derivation of useful information (63.1% cardiologist vs. 46% non-cardiologist) and consequently more abnormal findings (74.3% vs. 55%)[22]. In another analysis including 2,110 patients with mean 60.4 years-old, to whom echo was mainly prescribed due to hypertension (22%) and screening (16.8%), cardiology training was also associated with higher rates of class I indication, usefulness and pathological features[23]. Thus, it is anticipated that standard echocardiograms ordered by the primary care staff in Brazil – with heterogeneous training background – will likely have suboptimal pre-test evaluation, limiting their utility. This, in addition to the uneven distribution of health resources and test availability in the Brazilian territory (even inside the same state) and to financial crisis, contribute to the current growing waiting lists. Thus, targeting individuals waiting for echo may be more effective than random population screening, as preliminary data

suggest[9].\

In this context, the application of prediction models may help prioritize patients in waiting lists based on the likelihood of having significant heart disease. This implies that the test's sensitivity – its ability to rule out disease – is the most important accuracy measure, as denoted by our validation data for the model including echo screening, with 2 categories. In addition, integration of ultrasound performed by non-physicians with limited training is favored by the Brazilian primary care strategy and facilitated by telemedicine, as previously demonstrated[9,24]. However, whilst point-of-care diagnosis of specific conditions such as rheumatic heart disease may be possible for healthcare staff with basic training[25,26], a more detailed evaluation of echo variables poses additional challenges, even for remote readers. Thus, modeling echo screening as a single component may broaden its practicality. Furthermore, the clinical components included in the final model (**Table 2**) can be easily assessed by technicians or even community health agents, for baseline risk estimation prior to the medical appointment.

While our strategy seems promising, several steps must precede the implementation of the risk stratification tool. Physicians must be in agreement with a certain degree of interference with their clinical reasoning, especially for low-risk cases. Additionally, medical regulations need to incorporate task-shifting of echo acquisition - a debatable topic in Brazil. Also in this context, embedded apps for optimal probe positioning[27] and to flag abnormalities[28]must be warranted for future handheld devices, to minimize practical limitations. Finally, this novel approach for rationalization of heath resources for cardiology tests deserves further exploration, with validation in different settings and cost-effectiveness assessment.

LIMITATIONS:

Our study has several limitations. First, the derivation and validation samples included all-comers from waiting lists for standard echo, and no stratified sampling procedures were performed. While this limits generalization of the findings, it reflects the characteristics of this specific sub-population, with a particular risk profile. Second, there were remarkable differences between derivation and validation populations, which may bias the weight of relevant variables, such as previous heart failure and surgery. Third, the population in North Minas Gerais has specific characteristics, such as high prevalence of Chagas disease and delayed diagnosis of conditions as heart failure due to limited access to secondary care, markedly in smaller towns. As these variables remained in the model, this may also limit generalization. In addition, even after recalibration of intercept and slope, final Hosmer-Lemeshow test was significant, indicating that fine tuning of test variables will be required for different epidemiological contexts. Forth, only 2 well-defined risk categories (instead of the original 3) remained in validation, with moderate discrimination. While risk stratification is less refined, a simpler output may improve practicality, especially with the optimal sensitivity observed. Finally, as a cross-sectional design was applied, the model is not powered to predict outcomes, and additional investigations must be warranted. Despite these limitations, to the best of our knowledge this is a novel large-scale approach to evaluate the incremental value of echo screening on top of clinical evaluation to predict heart disease, and may result in useful tools for healthcare systems, especially where resources are scarce.

CONCLUSION:

In conclusion, the addition of screening echo to clinical variables significantly improves the performance of a score to predict major cardiac abnormalities. The strategy may be a useful tool to prioritize waiting lists for tests and referrals in primary care, especially in resource-limited settings.

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CONTRIBUTORSHIP STATEMENT:

Conception and design of the research: Nascimento, BR, Ribeiro, AL, Sable, CA; Acquisition of data: Diamantino, AC, Nunes, MCP, Oliveira, KKB, Rabelo, LC, Franco, J, Barbosa, MM, Reese, AT, Olivieri, L, Diamantino, LC; Analysis and interpretation of data: Nascimento, BR, Beaton, AZ, Sable, CA, Diamantino, AC, Diamantino, LC; Statistical analysis: Nascimento BR, Lima, EM, Martins, LNA, Colosimo, EA; Obtaining financing: Beaton, AZ, Sable, CA, Nascimento, BR, Ribeiro, AL; Writing of the manuscript: Nascimento,

BR, Diamantino, AC, Nunes, MC; Critical revision of the manuscript for intellectual content: All authors; Authors responsible for the overall content as guarantors: Nascimento, BR, Ribeiro, AL, Beaton, AZ.

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FIGURES:

Figure 1: Study flow chart**.**

Figure 2: Overall risk classification of the validation population. *13 patients did not perform the screening echocardiography.

Figure 3: Assessing discrimination and calibration of the predictive models with clinical questionnaire (A and B) and clinical questionnaire plus echocardiography screening (C and D).

SUPPLEMENTARY MATERIALS:

Appendix Figure 1: Risk categories according to the best combination of sensibility and specificity of the predictive model.

Appendix Figure 2: Predicted risks based on the prediction model built only with the questionnaire (on the left) in low ([?]12%), indeterminate (>12% to [?]70%), and high (>070%), and on the questionnaire plus screening echocardiography that classify into 2 risk categories (low [?]12% and high >12%).

TABLES:

Table 1 . Multivariable logistic regression model for predicting abnormal standard echocardiogram in the derivation population (model including only the clinical questionnaire).

Variables*	Estimate	OR	95 % CI	P value
Female gender	-0.73	0.48	0.32 - 0.73	0.00
Body mass index (Kg/m^2)	-0.08	0.93	0.89 - 0.97	0.00
Hypertension	0.52	1.68	1.02 - 2.75	0.04
Chagas disease	1.26	3.52	2.09 - 5.91	0.00
Coronary artery disease	1.16	3.19	1.62 - 6.29	0.00
Heart failure	1.27	3.57	1.84 - 6.90	0.00
Heart valve disease	0.99	2.68	1.09 - 6.61	0.03
Prior cardiac surgery	1.28	3.59	1.43 - 9.02	0.01

Table 2 . Multivariable logistic regression model for predicting abnormal standard echocardiogram in the derivation population (model with questionnaire and screening echocardiography)

Variables*	Estimate	OR	95 % CI	P value
Screening echo positive	2.69	14.73	8.44 - 25.72	0.00
Female gender	-0.73	0.48	0.30 - 0.78	0.00
Body mass index (Kg/m^2)	-0.06	0.94	0.90 - 0.99	0.03
Chagas disease	1.25	3.47	1.81 - 6.66	0.00
Hypertension	0.12	1.12	0.61 - 2.07	0.71
Coronary artery disease	0.79	2.20	1.01 - 4.79	0.05
Heart failure	1.08	2.96	1.32 - 6.63	0.01
Heart valve disease	1.46	4.29	1.45 - 12.71	0.01
Prior cardiac surgery	0.36	1.44	0.48 - 4.34	0.52

Table 3 . Head-to-head comparison of the models performance in prediction abnormal standard echocardiogram in the derivation and validation population.

	Derivation	**Derivation**	**Validation**
	Questionnaire	Questionnaire plus screening echocardiography	Questionnaire plus screening echocardiograp
C-statistic	0.761	0.863	0.720
Accuracy	0.782	0.814	0.732
Sensitivity	0.748	0.631	0.992
Specificity	0.558	0.944	0.199
PPV	0.908	0.761	0.473
NPV	0.822	0.782	0.973

Abbreviations

NPV = Negative predictive value; PPV = Positive predictive value

Table 4 . Overall characteristics of the derivation compared with the validation population

Variables*	Derivation cohort (n=603)	Validation cohort (n=1526)	P value
Age (years)	58.7 ± 15.3	57.9 ± 15.9	0.341
Female gender	370 (61)	1007 (66)	0.044
Body mass index (Kg/m^2)	27.9 ± 5.6	27.4 ± 6.1	0.072
Hypertension	432 (72)	1078 (71)	0.647
Chagas disease	98 (16)	296 (19)	0.092
Coronary artery disease	56 (9)	293 (19)	<0.001
Heart failure	55 (9)	433 (28)	<0.001
Heart valve disease	29 (5)	206 (14)	<0.001
Prior cardiac surgery	30 (5)	122 (8)	0.015

*Variables were self-reported by the patients

REFERENCES:

1. INDICARD-out T. Indications, utility and appropriateness of echocardiography in outpatient cardiology. *Journal of cardiovascular echography.* 2013;23(1):24.

2. Frye RL. Does it really make a difference? *J Am Coll Cardiol.* 1992;19(2):468-470.

3. Pearlman AS, Ryan T, Picard MH, Douglas PS. Evolving trends in the use of echocardiography: a study of Medicare beneficiaries. *J Am Coll Cardiol.* 2007;49(23):2283-2291.

4. Bethge A, Penciu O, Baksh S, Parve S, Lobraico J, Keller AM. Appropriateness vs value: Echocardiography in primary care. *Clinical cardiology.* 2017;40(12):1212-1217.

5. Kerley RN, Thornton KP, Kelly RM, O'Flynn S. Appropriate use criteria for transthoracic echocardiography: Are they relevant to European centers? *Echocardiography.*2018;35(1):17-23.

6. American College of Cardiology Foundation Appropriate Use Criteria Task F, American Society of E, American Heart A, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* 2011;24(3):229-267.

7. Paim J, Travassos C, Almeida C, Bahia L, Macinko J. The Brazilian health system: history, advances, and challenges. *Lancet.* 2011;377(9779):1778-1797.

8. McCauley JL. Guidelines and Value-Based Decision Making: An Evolving Role for Payers. *North Carolina medical journal.* 2015;76(4):243-246.

9. Nascimento BR, Beaton AZ, Nunes MCP, et al. Integration of echocardiographic screening by non-physicians with remote reading in primary care. *Heart.* 2018.

10. Alkmim MB, Figueira RM, Marcolino MS, et al. Improving patient access to specialized health care: the Telehealth Network of Minas Gerais, Brazil. *Bulletin of the World Health Organization.* 2012;90(5):373-378.

11. Diamantino AC, Nunes MCP, Sable C, et al. Use of Screening Echocardiography to Improve Healthcare in Underserved Areas of Brazil: Data From the PROVAR+ Study.*Circulation.* 2018;138(118):A16989-A16989.

12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.

13. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. *Epidemiology (Cambridge, Mass).* 2010;21(1):128.

14. Nascimento BR, Sable C, Nunes MCP, et al. Comparison Between Different Strategies of Rheumatic Heart Disease Echocardiographic Screening in Brazil: Data From the PROVAR (Rheumatic Valve Disease Screening Program) Study. *Journal of the American Heart Association.* 2018;7(4).

15. Paixao GMM, Nunes MCP, Beato B, et al. Cardiac Involvement by Yellow Fever(from the PROVAR+ Study).*Am J Cardiol.* 2019;123(5):833-838.

16. Nunes MCP, Badano LP, Marin-Neto JA, et al. Multimodality imaging evaluation of Chagas disease: an expert consensus of Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI). *European heart journal cardiovascular Imaging.* 2018;19(4):459-460n.

17. Lindekleiv H, Lochen ML, Mathiesen EB, Njolstad I, Wilsgaard T, Schirmer H. Echocardiographic screening of the general population and long-term survival: a randomized clinical study. *JAMA Intern Med.* 2013;173(17):1592-1598.

18. Yang H, Negishi K, Wang Y, Nolan M, Saito M, Marwick TH. Echocardiographic screening for non-ischaemic stage B heart failure in the community. *Eur J Heart Fail.*2016;18(11):1331-1339.

19. Williams C, Mateescu A, Rees E, et al. Point-of-care echocardiographic screening for left-sided valve heart disease: high yield and affordable cost in an elderly cohort recruited in primary practice. *Echo Res Pract.* 2019;6(3):71-79.

20. Mitchell AR, Hurry R, Le Page P, MacLachlan H. Pre-participation cardiovascular screening: is community screening using hand-held cardiac ultrasound feasible? *Echo Res Pract.* 2015;2(2):49-55.

21. Macinko J, Harris MJ. Brazil's family health strategy–delivering community-based primary care in a universal health system. *N Engl J Med.* 2015;372(23):2177-2181.

22. Lattanzi F, Magnani M, Cortigiani L, et al. [Evaluation of the appropriateness of prescribing echocardiography]. *Italian heart journal Supplement : official journal of the Italian Federation of Cardiology.* 2002;3(6):613-618.

23. study IN-opAARCAim, Orsini E, Antoncecchi E, et al. Indications, Utility and Appropriateness of Echocardiography in Outpatient Cardiology. *J Cardiovasc Echogr.*2013;23(1):24-32.

24. Lopes EL, Beaton AZ, Nascimento BR, et al. Telehealth solutions to enable global collaboration in rheumatic heart disease screening. *J Telemed Telecare.*2018;24(2):101-109.

25. Beaton A, Nascimento BR, Diamantino AC, et al. Efficacy of a Standardized Computer-Based Training Curriculum to Teach Echocardiographic Identification of Rheumatic Heart Disease to Nonexpert Users. *Am J Cardiol.* 2016.

26. Engelman D, Okello E, Beaton A, et al. Evaluation of Computer-Based Training for Health Workers in Echocardiography for Rheumatic Heart Disease. *Global heart.* 2016.

27. Voelker R. Cardiac Ultrasound Uses Artificial Intelligence to Produce Images. *JAMA.*2020;323(11):1034.

28. Ghorbani A, Ouyang D, Abid A, et al. Deep learning interpretation of echocardiograms. *NPJ Digit Med.* 2020;3:10.