



STUDY PROTOCOL

REVISED Determinants of in-hospital death in patients with a thrombus straddling a patent foramen ovale: protocol of a systematic review [version 2; peer review: 2 approved]

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V2 First published: 10 Dec 2020, 9:1437
<https://doi.org/10.12688/f1000research.27622.1>

Latest published: 05 May 2021, 9:1437
<https://doi.org/10.12688/f1000research.27622.2>

Abstract

Background: Thrombi identified on echocardiography at the time of straddling a patent foramen ovale (PFO) constitute a medical emergency with an associated imminent risk of death. Ischemic stroke (IS) and myocardial infarction (MI) occurring in patients with a thrombus straddling a PFO (TSPFO) may be associated with increased risk of in-hospital death. Variables associated with increased risk of death in women and men may be different. We will perform a systematic review of case reports and cases series of patients with a TSPFO to assess if IS and MI are associated with increased risk of in-hospital death and we will further stratify analyses by sex.

Methods: This systematic review will include all case reports and case series of adult patients (18-year-old or older) with echocardiographic or pathological (e.g. at autopsy for older reports) evidence of a TSPFO published between inception and June 30, 2020, in any language. We will search in PubMed and Embase databases. Two reviewers will independently screen titles and abstracts, retrieve full texts, and extract the data in a predesigned form. We will apply a multivariable logistic regression analysis to estimate the association of IS and MI with in-hospital mortality. We will stratify analyses by sex.

Discussion: IS and MI in patients with TSPFO could potentially be associated with worse outcomes if they are not timely identified or left untreated. Both acute IS and MI require specific treatment (e.g. thrombolysis, primary coronary intervention, or mechanical thrombectomy) that may be influenced by the therapy instituted for the TSPFO. Knowing the incidence of acute IS and MI among patients

Open Peer Review

Reviewer Status

Invited Reviewers

	1	2
version 2		
(revision)	report	report
05 May 2021	↑	↑
version 1		
10 Dec 2020	report	report

1. **Paolo Eusebi** , Regional Health Authority of Umbria, Perugia, Italy
2. **Leonardo Varotto** , San Bortolo Hospital, viale Rodolfi, Italy

Any reports and responses or comments on the article can be found at the end of the article.

diagnosed with TSPFO and whether they are associated with an increased risk of death would help to improve the management of this medical emergency.

Protocol registration: CRD42020216118, PROSPERO.

Keywords

Stroke, myocardial infarction, patent foramen ovale, paradoxical embolism, death, mortality, thrombus in transit

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Author roles: **Jiménez-Ruiz A:** Conceptualization, Data Curation, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Shah P:** Conceptualization, Data Curation, Investigation, Methodology, Writing – Review & Editing; **Gibson A:** Conceptualization, Data Curation, Investigation, Methodology, Writing – Review & Editing; **Vargas-González JC:** Conceptualization, Formal Analysis, Methodology, Software, Validation, Writing – Original Draft Preparation; **Sposato LA:** Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: LAS is supported by the Kathleen & Dr. Henry Barnett Research Chair in Stroke Research (Western University, London, Canada); the Edward and Alma Saraydar Neurosciences Fund (London Health Sciences Foundation, London, Canada); and the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO) (Ontario, Canada).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Jiménez-Ruiz A, Shah P, Gibson A *et al.* **Determinants of in-hospital death in patients with a thrombus straddling a patent foramen ovale: protocol of a systematic review [version 2; peer review: 2 approved]** F1000Research 2021, 9:1437 <https://doi.org/10.12688/f1000research.27622.2>

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REVISED Amendments from Version 1

This is part of the methods for data analysis stating we will use AIC (Akaike Information Criterion) to select the best model and improve overall accuracy instead of using a backward stepwise selection until fulfilling a prespecified level of significance of 0.05 for potential covariables.

Any further responses from the reviewers can be found at the end of the article

Introduction

A patent foramen ovale (PFO) is a common finding, present in 25% of individuals on autopsy¹ and frequently reported as an incidental finding on echocardiography studies². Most patients are asymptomatic, and the presence of a PFO is usually considered clinically irrelevant. However, a thrombus can sometimes be found straddling a PFO in the context of acute pulmonary embolism, deep venous thrombosis, acute respiratory insufficiency, acute coronary syndromes, or acute ischemic stroke (IS)³.

A thrombus straddling a PFO (TSPFO) carries a high risk of impending paradoxical embolism and death⁴. Most of the evidence on the diagnosis and treatment of TSPFO comes from anecdotal single case reports or small case series⁴. As such, factors associated with increased risk of death are unknown. Similarly, there is clear guidance on what the best treatment approach is for TSPFO. Paradoxical embolism is a relatively common cause of IS in patients with PFO and could possibly explain the high mortality in patients with a TSPFO⁵. Although less frequently reported, paradoxical embolism has also been identified as a cause of acute myocardial infarction (MI). Both IS and MI are well recognized causes of death among the general population. We hypothesized that IS and MI identified at the time of the diagnosis of a TSPFO are associated with increased risk of in-hospital death. We will therefore systematically review all case reports and case series of patients with TSPFO published in the medical literature to assess whether IS, MI, and different therapeutics (e.g. anticoagulation, thrombolysis or surgical removal of the TSPFO) are associated with the adjusted risk of in-hospital death. We will also stratify these analyses by sex.

Methods/design**Objectives**

The primary objective is to assess whether IS and MI at presentation are independently associated with the adjusted risk of in-hospital death in patients with a TSPFO. The secondary objective is to assess whether the association between IS and MI at presentation and the risk of in-hospital death in patients with a TSPFO varies in women and men.

Study design

This study protocol has been prepared according to the 2015 Preferred Reporting Items for Systematic Reviews, and Meta-Analyses Protocols (PRISMA-P) guidelines. We will use the PRISMA flowchart. We have submitted this systematic review to the International Prospective Register for Systematic

Reviews and Meta-analysis (PROSPERO, registration number: CRD42020216118).

Search strategy

We will search PubMed and Embase databases to identify potentially eligible studies by applying predefined search terms (Table 1 and Table 2), published from inception to June 30, 2020 in any language.

Study selection

Three reviewers will independently screen titles and abstracts and will solve disagreements by consensus (AJR, PS, AG). The same reviewers will thoroughly assess all potentially relevant full texts and will document the reasons for excluding specific publications. We will include studies fulfilling all inclusion criteria and no exclusion criteria. Inclusion criteria will be: (a) case reports or case series; (b) adult patients (≥ 18 years-old); (c) complete data on in-hospital outcomes (e.g. dead or alive); and (d) complete demographic data (e.g. age and sex) and information on comorbidities, risk factors and acute treatment. Exclusion criteria include: (a) editorial or review articles; (b) duplicate reports; and (c) publications in which data at the patient-level is unavailable.

Data extraction

Three independent reviewers will be used for selecting studies through each phase of the review (screening, eligibility, and inclusion meta-analysis). We will create and use a standardized Microsoft Forms data extraction form and Excel spreadsheet, extracting the following data from published reports: study identification (year of publication, first author); study characteristics (number of cases, continent where the study was conducted); patients' characteristics (age, sex), risk factors and comorbidities (obesity, hypertension, diabetes mellitus, hyperlipidemia, known atrial fibrillation, coronary artery disease, obstructive sleep apnea, cancer, chronic kidney disease, deep vein thrombosis, pulmonary embolism, transient ischemic attack, stroke, autoimmune disease); acute diagnoses upon admission (acute MI, acute IS, transient ischemic attack, hemorrhagic stroke, pulmonary embolism, deep vein thrombosis, syncope, peripheral paradoxical embolism, newly diagnosed atrial fibrillation); presenting symptoms (dyspnea, chest pain, palpitations, dizziness, syncope, focal neurological deficit, shock, loss of consciousness or coma, seizures, peripheral embolism); laboratory parameters (D-Dimer value, fibrinogen, brain natriuretic peptide, cardiac troponin); main affected coronary artery in patients with MI; vascular territory involved in patients with cerebrovascular events; organ involved in patients with peripheral embolism; most likely cause of venous thromboembolism (unprovoked, thrombophilia, cancer, trauma, post-operative, immobilization, pregnancy, recent flight, infection, other); cardiac and pulmonary investigations (transthoracic echocardiogram, transesophageal echocardiogram, computed angiography of the lungs, cardiac magnetic resonance imaging, cardiac computed tomography, electrocardiogram); main electrocardiographic findings (SIQ3T3 pattern, sinus tachycardia, other); echocardiographic findings [left ventricular dysfunction, right ventricular dysfunction, right ventricular function not reported, increased pulmonary artery pressure (>20 mmHg), dilated right ventricle,

Table 1. PubMed search terms.

Transit[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Migrat*[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Transit[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Migrat*[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Travel*[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Travel*[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Pending*[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Pending*[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Straddling*[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Straddling*[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Impending*[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Impending*[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Impending*[Title/Abstract] AND paradoxical[Title/Abstract] AND patent [Title/Abstract]
Floating*[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Floating*[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Entrapped[Title/Abstract] AND embol*[Title/Abstract] AND patent[Title/Abstract]
Entrapped[Title/Abstract] AND Thromb*[Title/Abstract] AND patent[Title/Abstract]
Saddl*[Title/Abstract] AND patent[Title/Abstract]
Biatrial[Title/Abstract] AND patent[Title/Abstract]
Impending paradoxical embol*[Title/Abstract]
Transit[Title/Abstract] AND thromb*[Title/Abstract] AND atri*[Title/Abstract]
Crossing[Title/Abstract] AND thromb*[Title/Abstract] AND atri*[Title/Abstract]
Crossing[Title/Abstract] AND embol*[Title/Abstract] AND atri*[Title/Abstract]
Thromb*[Title] AND patent foramen ovale[Title]
Pulmonary[Title/Abstract] AND paradoxical[Title/Abstract]
Riding[Title/Abstract] AND thromb*[Title/Abstract] AND atri*[Title/Abstract]
Riding[Title/Abstract] AND embol*[Title/Abstract] AND atri*[Title/Abstract]
Stuck[Title/Abstract] AND thromb*[Title/Abstract] AND atri*[Title/Abstract]
Stuck[Title/Abstract] AND embol*[Title/Abstract] AND atri*[Title/Abstract]

Table 2. Embase search terms.

Impending paradoxical embolism
Thrombus in transit

dilated right atrium]; acute treatment (intravenous thrombolysis, surgery, anticoagulation); in-hospital outcomes (full recovery, partial recovery, death); secondary prevention treatment (Aspirin or other antiplatelet agent, vitamin K antagonists, non-specified oral anticoagulants, direct oral anticoagulants, low molecular weight heparin, unfractionated heparin, PFO closure, Inferior vena cava filter); and secondary prevention outcome (no events, recurrent venous thromboembolism, incident/recurrent stroke or transient ischemic attack, recurrent/incident peripheral embolism, recurrent/incident MI, death).

Data analysis

We will conduct univariate analyses comparing the patients who died or survived during hospital stay. Variables with a p-value of <0.05 and those known to influence death in patients

with venous thromboembolism, regardless of their level of significance on univariate in the analysis, will be included in a multivariable logistic regression for in-hospital death. We will use a random intercept model to account for the potential clustering effect of the different decades on outcomes. We will initially include all the potential covariates and we will subsequently perform AIC (Akaike Information Criterion) to select the best model and improve overall accuracy. We will keep sex and age in the model because of being recognized confounders for death. We will conduct all analyses with R version 3.6.2.

Risk of bias and quality of reports

We will apply the tool originally proposed by Murad *et al.* for assessing the methodological quality and synthesis of case series and case reports⁶ (domains, selection, ascertainment, causality, and reporting).

Potential amendments

We do not anticipate any amendment to this review protocol. If an amendment is needed, we will document it and report it in a timely manner.

Ethics and dissemination

This systematic review will be based on published data. As such, it is not subject to ethical approval. The results will be published in peer-reviewed journals and presented at scientific conferences. All data underlying the results will be made available upon reasonable request.

Discussion

In the context of more available point of care echocardiography, TSPFO are expected to be increasingly reported among patients seen in the Emergency Department and intensive care unit for acute onset respiratory failure, shock or acute coronary syndromes^{7,8}. The timely diagnosis of a TSPFO could radically influence acute treatment options and could provide critical information on potential patient outcomes. IS and MI can likely impact on the prognosis of patients with TSPFO, and are well-recognized complications of PFO in patients with pulmonary embolism and associated with increased risk of death⁹. Paradoxical embolism to the coronary arteries has been reported less frequently and its incidence remains undetermined³. Data on potential therapeutic interventions for patients with TSPFO are also scarce. A previous systematic review including 174 patients found a 35% lower 30-day mortality among surgically treated patients, although this was non-significant⁴. Knowing the incidence of IS and MI in patients with TSPFO and their association with in-hospital death, as well as outcomes

of different therapeutic interventions would be important for improving awareness about prognostic factors and treatment options in this population.

Study status

Preliminary searches have been carried out in PubMed and Embase databases.

Registration

This review protocol has been submitted to the International Prospective Register for Systematic Reviews and Meta-analysis (PROSPERO, registration number: CRD42020216118).

Data availability

Underlying data

No data is associated with this article.

Reporting guidelines

Figshare: PRISMA-P checklist for 'Determinants of in-hospital death in patients with a thrombus straddling a patent foramen ovale: protocol of a systematic review', <https://doi.org/10.6084/m9.figshare.13281242.v1>¹⁰.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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<http://www.doi.org/10.6084/m9.figshare.13281242.v1>

Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 20 May 2021

<https://doi.org/10.5256/f1000research.56395.r84540>

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Leonardo Varotto 

Department of Cardiology, San Bortolo Hospital, viale Rodolfi, Vicenza, 36100, Italy

I received your reply and understood your choices, even for not using the suggested technique. No need to review further your work, but I believe that its quality is currently not optimal because the a priori information is missing. Some steps you have taken are clear and I have no reason to doubt that it is good exploratory work. It is in fact impossible for me to judge at the moment the quantity and quality of the information you have access to.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical trials, meta-analysis, interventional cardiology, interventional cardiology-neurology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 19 May 2021

<https://doi.org/10.5256/f1000research.56395.r84539>

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Paolo Eusebi 

Regional Health Authority of Umbria, Perugia, Italy

Thanks for this revised version. The study protocol deserves indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical trials; meta-analysis; diagnostics; data visualization

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 29 March 2021

<https://doi.org/10.5256/f1000research.30530.r80694>

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Leonardo Varotto

Department of Cardiology, San Bortolo Hospital, viale Rodolfi, Vicenza, 36100, Italy

- **Is the rationale for, and objectives of, the study clearly described?**

Yes, the importance of the study (the rationale that "promotes" it) is clear.

- **Is the study design appropriate for the research question?**

Partially or, more properly, no!

- **Are sufficient details of the methods provided to allow replication by others?**

Yes, with the limitations mentioned below.

- **Are the datasets clearly presented in a useable and accessible format?**

Yes, but this aspect cannot be currently fully judged.

Thank you for the opportunity to review this manuscript.

From my point of view, the study design should better develop the following points that I would like to resume briefly as below:

- **1st problem:** The patients who will constitute the matrix and the data do not come from randomized studies, but from publications-observational studies and for this reason "pre-selected" in order to "promote a certain point of view" concerning, for example, a therapy, etc...
Patient selection (not the selection made by the authors) constitutes a heavy source of bias. Is it not possible to conduct the study by aggregating multiple therapy centers (hospitals) with which to agree on a therapeutic and screening protocol? (see next point)...
- **2nd problem:** The search for co-morbidities, and in general the patient's health state and risk factors, is truly "refined" and timely. However, the absence of one of the information to be acquired in a specific patient does not mean that it was absent. Unfortunately, given that the patients do not come from the same study cohort with an a priori standardized observation protocol, it does not guarantee that the information collected is homogeneous.

In the meta-analyses conducted by aggregating randomized studies, this problem is addressed with graphic tools (funnel plot), or with in-depth analyses on the heterogeneity of the studies.

In summary, in this research plan (study design) not a word is spent on how to overcome these serious and typical problems of heterogeneity of patients connected to the purposes of the publication and to the different way in which they have been screened at the moment, for example, of hospitalization.

- **3rd problem:** In the data analysis techniques (logistic model) the search for interaction between the factors that could affect the probability of death in hospital of the patient does not appear and, moreover, using the "backward stepwise selection" strategy the first part of the univariate analysis becomes superfluous.

It is not wrong to use a logistic regression model (although for such models it is always difficult to offer an overall picture of the quality of the obtained result) but I would also use an analysis technique such as the "random forest" which could probalimize patients with particular co-morbidities or risk factors.

Of the logistic model, it is necessary to present also quality indicators: wrong classification, pseudo R2, Nagelkerke indicator. These are fundamental indicators to give credibility to the results obtained.

- **4th problem:** It is not clear how many patients could be analyzed. The author described a previous systematic review with 174 patients analysed, a number apparently very limited to contain measurement errors and to offer adequate power to statistical tests. What is the information gathering forecast?

I hope that the authors are encouraged by my remarks made with a constructive aim because it is very important to carry on such typology of studies. For this reason, it would be desirable that authors will accomplish their hard work with even more attention and dedication.

To quote an aphorism: never give up. You would risk doing it an hour before the miracle!

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

No

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical trials, meta-analysis, interventional cardiology, interventional cardiology-neurology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Apr 2021

Amado Jiménez-Ruiz, Western University, London, Canada

Dear Dr. Leonardo Varotto,

First, we want to thank you for considering our manuscript and the time you and the reviewers devoted to reading it. We have received the feedback and suggestions, and we are addressing them. We have modified the manuscript according to the comments below.

Impending paradoxical embolism is an uncommon condition rarely reported in the medical literature. Our pilot exercise for the review concluded that the published information is limited to case reports and small case series and therefore based our data extraction plan and further analysis on these results.

During the process of analysis and selection of potential covariables for the project, we considered different methods. Some of those models were Ridge and LASSO. However, when we thought about our problem, we concluded that some variables should be in the model irrespective of their statistical significance (age and sex). In the case of LASSO and its autonomous nature for covariates for model selection, we could not ensure that the model would include both. Also, we performed multiple imputations through MICE; we cannot find a universal method to combine both techniques. For these two reasons, we selected a traditional stepwise approach.

Instead of targeting significance for the covariates, we targeted overall accuracy in predictions or AIC.

Thanks again for taking the time to review this manuscript.

Sincerely,

The Authors

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 March 2021

<https://doi.org/10.5256/f1000research.30530.r80248>

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Paolo Eusebi 

Regional Health Authority of Umbria, Perugia, Italy

- Why a meta-analysis of case reports and case series? Are other studies not available?
- Please correct covariable with covariate.
- Please consider adding penalized regressions like lasso (R package glmnet) in the methods. It could be a good option in the case of a small number of events per predictor.
- Please, consider cross-validation techniques.
- Instead of targeting significance for the covariates, it would be better to target overall accuracy in predictions or AIC.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical trials; meta-analysis; diagnostics; data visualization

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Mar 2021

Amado Jiménez-Ruiz, Western University, London, Canada

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2. Please correct covariable with covariate.

We have corrected covariable to covariate as stated.

3. Please consider adding penalized regressions like lasso (R package glmnet) in the methods. It could be a good option in the case of a small number of events per predictor.

During the process of analysis and selection of potential covariables for the project, we considered different methods. Some of those models were Ridge and LASSO. However, when we thought about our problem, we conclude that some variables should be in the model irrespective of their statistical significance (age and sex). In the case of LASSO and its autonomous nature for covariates for model selection, we could not ensure that the model would include both. Also, we performed multiple imputations through MICE; we cannot find a universal method to combine both techniques. For these two reasons, we selected a traditional stepwise approach.

4. Please, consider cross-validation techniques.

We appreciate the suggestion to use cross-validation. However, to manage uncertainty, we decided to perform sensitivity analysis using a multilevel model and the scenario of cases with complete data. We decided this because our target audience (cardiologists and neurologists) is more familiar with sensitivity analysis.

5. Instead of targeting significance for the covariates, it would be better to target overall accuracy in predictions or AIC.

We appreciate the suggestion of using the AIC to select the best model. It is explicitly stated in the protocol now.

Thanks again for taking the time to review this manuscript.

Competing Interests: No competing interests.

Author Response 22 Apr 2021

Amado Jiménez-Ruiz, Western University, London, Canada

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We appreciate the suggestion to use cross-validation. However, to manage uncertainty, we decided to perform sensitivity analysis using a multilevel model and the scenario of cases with complete data. We decided this because our target audience (cardiologists and neurologists) is more familiar with sensitivity analysis.

Instead of targeting significance for the covariates, it would be better to target overall accuracy in predictions or AIC.

We appreciate the suggestion of using the AIC to select the best model. It is explicitly stated in the protocol now.

Thanks again for taking the time to review this manuscript.

Sincerely,

The Authors

Competing Interests: No competing interests were disclosed.

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