PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

Authors

Zhu, Lei; Xue, Zheng-Kai; Wu, Xue; Zhang, JingKun; Hu, Su-Tao; Zhang, Yu-Kun; Gu, Tian-Shu; Liu, Tong; Rha, Seung-Woon; Chen, Kang-Yin

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Rezende, Paulo**
Affiliation	**Instituto do CoraÃ§Ã£o (InCor), Faculdade de Medicina da Universidade de SÃ£o Paulo (FMUSP)**
Date	**03-Dec-2024**
COI	**None**

I congratulate the authors for the hard work In preparing this manuscript.

Although the study has strengths and is well-written, the methodology has strong limitations. The authors opted to assess combined clinical outcomes of overall death, myocardial infarction, stroke, and revascularization. However, they studied patients with non-obstructive coronary artery disease. In such patients, the study question is the identification of factors that could be associated with myocardial infarction during follow-up. Overall death, stroke and revascularization have many other associated factors, and could be associated with many of the predictors that the authors found, and these associations could have nothing to do with the fact that the patients have non-obstructive CAD. For example, anemia and renal insufficiency are factors that can be associated with overall death by many different non-cardiological mechanisms. However the authors are studying and focusing on non-obstructive CAD patients. Using this same reasoning, how stroke could also be interpreted in such patients? Thus, this reviewer thinks that the authors choose endpoints that do not answer the study question, and this, unfortunately, is a very strong limitation of this study.

Another point of discussion that was quickly commented by the authors in the Limitations section is that they included patients with no evidence of CAD and patients with non-obstructive CAD (patients that had lesions < 50% of obstruction) in the same group of patients. Although they state that these patients are quite similar, they are not. Their evolution is not similar, their treatments are different. The inclusion of both group of patients turn the population too heterogeneous, and this complicates the interpretation of the results.

Another point that deserves to be commented is that the authors performed a retrospective analysis, with the limitations inherent to this type of study. The methodology has many issues, in the selection of the population as discussed previously, in the clinical treatment of these patients that was not standardized or controlled by the authors, the adjudication of the clinical events, choosing clinical events that are not related to the coronary artery disease... thus, all of these major limitations compromise the realiability of the prognostic score proposed by the authors.

Reviewer	**2**
Name	**Golubovic, Mladjan**
Affiliation	**Klinicki centar Nis, Clinic for Anesthesiology and Intensive care**
Date	**26-Jan-2025**
COI	**None**

Very good job and very interestig manuscript,

Reviewer	**3**
Name	**Chen, Zhenfei**
Affiliation	**The Second People 's Hospital of Hefei, Cardiology**
Date	**12-Feb-2025**
COI	**None**

Need to answer or modify something.

1.Study Design: This study employs a retrospective cohort design. Could you elaborate on the reasons for choosing this design and its potential impact on the results?

2.Patient Selection Criteria: In the inclusion and exclusion criteria, how do you define "no significant stenosis" in coronary arteries? Is this standard consistent with existing clinical guidelines?

3.Data Collection Methods: You mentioned using electronic medical records to collect patient data. Could you detail the specific process of data collection and its reliability?

4.Variable Selection: In the LASSO regression, how did you determine the selected variables (such as age, hemoglobin, serum urea, etc.) impact the primary endpoint? Was multicollinearity testing performed?

5.Model Validation: You mentioned that the model underwent internal validation. Could you elaborate on the specific methods and results of this validation? Was external validation considered?

6.Survival Analysis Methods: In the Kaplan-Meier survival analysis, how did you handle missing data? Did you use appropriate statistical methods to ensure the validity of the results?

7.Statistical Analysis: What hypothesis tests did you use in the statistical analysis? How did you ensure the applicability and validity of these tests?

8.Clinical Significance: What is the potential application of the predictive model in clinical practice? How do you ensure its applicability across different populations?

9.Results Interpretation: How do the event rates (such as all-cause mortality, myocardial infarction, etc.) you mentioned in the results compare with data from existing literature? How do you explain these differences?

10.Discussion of Limitations: The limitations you mentioned in the discussion (such as being a single-center study) specifically affect the results in what ways? How can these limitations be addressed in future research?

11.Selection of Biomarkers: When selecting blood biomarkers (such as NT-proBNP, serum urea, etc.), how did you assess their independence and effectiveness in predicting adverse outcomes?

12.Risk Stratification: How was the risk stratification method you mentioned developed? In clinical applications, how do you ensure that high-risk patients receive timely interventions?

13.Ethical Considerations: Was this study approved by an ethics committee? How did you ensure patient privacy and data security during the data collection process?

14.Future Research Directions: Based on the findings of this study, what areas do you believe future research should focus on to further validate and expand your results?

VERSION 1 - AUTHOR RESPONSE

Response to Reviewer 2

Comment:

"Very good job and very interesting manuscript."

Response:
We sincerely appreciate your positive feedback and are grateful for your recognition of our work. Your encouragement reinforces the clinical relevance of developing risk stratification tools for patients with angina and non-obstructive coronary artery disease.

Response to Reviewer 1:

Comment 1:

"The composite endpoint (overall death, myocardial infarction, stroke, and revascularization) may not directly answer the study question, as some outcomes (e.g., stroke, non-cardiac death) could be influenced by factors unrelated to non-obstructive CAD."

Response:

We sincerely appreciate the reviewer's insightful comment regarding endpoint selection. While we acknowledge that the composite endpoint incorporates events that may involve non-coronary mechanisms, our choice was guided by the clinical imperative to comprehensively capture adverse outcomes in this unique population. ANOCA represents a clinically distinct patient population characterized by substantial heterogeneity and increased risks of all-cause mortality and major cardiovascular events including stroke, as demonstrated in recent registry studies [1-3]. This prognostic pattern has led numerous contemporary investigations to adopt composite endpoints encompassing both cardiac and cerebrovascular events when evaluating ANOCA outcomes [4-6]. This approach ensures comparability with previous investigations.

To address this valid concern, we have implemented the following enhancements:

1. Supplementary Sensitivity Analysis:

We conducted additional analyses using a refined MACE definition (cardiac-related death, nonfatal MI, nonfatal stroke, repeat revascularization) to specifically evaluate coronary-related outcomes. Our analysis demonstrated that the risk-stratification tool maintained strong prognostic performance for this more targeted endpoint (**Supplementary Figure 2**).

2. Endpoint Rationale Clarification:

We have revised the Methods **Follow-Up and Endpoints** section to explicitly state that the composite endpoint aligns with previous studies for prognostic studies in ANOCA populations.

Revision in manuscript (**Methods: Follow-Up and Endpoints**):

"The composite endpoint was selected based on its established utility in prognostic studies of ANOCA."

[1] Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. Arch Intern Med. 2009;169(9):843-850. doi:10.1001/archinternmed.2009.50
[2] Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012;33(6):734-744. doi:10.1093/eurheartj/ehr331
[3] Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. Eur Heart J. 2006;27(12):1408-1415. doi:10.1093/eurheartj/ehl040
[4] Al-Badri A, Tahhan AS, Sabbak N, et al. Soluble Urokinase-Type Plasminogen Activator Receptor and High-Sensitivity Troponin Levels Predict Outcomes in Nonobstructive Coronary Artery Disease. J Am Heart Assoc. 2020;9(8):e015515. doi:10.1161/JAHA.119.015515
[5] Mansour M, Radaideh Q, Alaiwah MN, et al. Major adverse cardiac events in symptomatic women with non-obstructive CAD on coronary CTA: pooled analysis from PROMISE and SCOT-HEART. Int J Cardiovasc Imaging. 2022;38(3):683-693. doi:10.1007/s10554-021-02429-3
[6] Sedlak T, Herscovici R, Cook-Wiens G, et al. Predicted Versus Observed Major Adverse Cardiac Event Risk in Women With Evidence of Ischemia and No Obstructive Coronary Artery Disease: A Report From WISE (Women's Ischemia Syndrome Evaluation). J Am Heart Assoc. 2020;9(7):e013234. doi:10.1161/JAHA.119.013234

Comment 2:

"Heterogeneity in the study population due to combining patients with no CAD and non-obstructive CAD (<50% stenosis)."

Response:

We sincerely appreciate this insightful critique. We acknowledge the pathophysiological distinction between patients with normal coronary arteries (no atherosclerosis) and non-obstructive CAD (stenosis <50%). However, our approach was guided by 2 key considerations:

1. Contemporary ANOCA Definitions: Current diagnostic frameworks, including the 2023 JACC State-of-the-Art Review [7], operationalize ANOCA as angina pectoris occurring in patients with non-obstructive epicardial coronary arteries (stenosis <50%), irrespective of atherosclerotic burden. Notably, comprehensive invasive assessments reveal that

ANOCA patients frequently demonstrate heterogeneous mechanisms including coronary microvascular dysfunction, vasospastic disorders, and endothelial dysfunction - a pathophysiological spectrum that extends beyond atherosclerotic manifestations. Our inclusion criteria were thus intentionally aligned with this broad phenotypic definition to fully capture the ANOCA population as currently conceptualized.

2. Clinical Real-World Applicability: In real-world practice, invasive imaging (e.g., IVUS/OCT) to confirm atherosclerotic presence is performed in a minority of ANOCA cases. Retrospective differentiation was therefore infeasible.

We have strengthened the **Limitations** section to state:

"The inability to subclassify ANOCA patients into those with versus without atherosclerosis represents an important limitation, as pathophysiological differences between these cohorts may contribute to population heterogeneity. However, this aligns with current guideline definitions, and Future studies incorporating intracoronary imaging could refine risk stratification."

[7] Samuels BA, Shah SM, Widmer RJ, et al. Comprehensive Management of ANOCA, Part 1-Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;82:1245–63. doi: 10.1016/j.jacc.2023.06.043

Comment 3:

"Retrospective design limitations (selection bias, unstandardized treatments, event adjudication)."

Response:
We sincerely appreciate these methodologically important observations. Our endpoint assessment process incorporated standard quality control system:

Data Sources:

Structured EHR extraction: Comprehensive review of diagnosis, treatment records, and imaging reports.

Mortality validation: regional death registry database, supplemented by telephone/email confirmation with next-of-kin.

Independent dual review: Two board-certified cardiologists (L.Z. and ZK.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria:

Myocardial infarction (MI): Based on the Fourth Universal Definition of MI (ESC/ACCF/AHA/WHF 2018)[8]

Stroke: Classified according to AHA/ASA 2019 Guidelines[9]

Revascularization: Documented ischemia-driven procedures with supporting angiographic evidence

For discordant cases, joint reviewed by two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience).

We have restructured the "**Methods Follow-up"** section as follows:

"A dedicated follow-up team conducted systematic post-discharge surveillance through a standardized protocol, with scheduled assessments at 30 days, 3 months, 6 months, and annually thereafter. Data collection employed a multimodal approach: (1) comprehensive electronic health record review, (2) cross-referencing with regional death registries, (3) and telephone or email interviews. The observational window for this analysis was finalized on August 1, 2023. Two board-certified cardiologists (L.Z. and ZK.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria. For discrepancies in event classification, an adjudication committee comprising two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience) conducted final arbitration through consensus review."

2. We fully acknowledge these inherent limitations of retrospective studies. As noted in our **Limitations section**:

"The retrospective design precludes control of treatment strategies and introduces potential selection bias."

[8] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-2264. doi:10.1016/j.jacc.2018.08.1038
[9] Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2019 Dec;50(12):e440-e441. doi: 10.1161/STR.0000000000000215.]. Stroke. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211

Response to Reviewer 3:

Thank you very much for your detailed and professional comments, we will reply as follows:

Comment 1: Study Design Rationale

Q: *"Why choose a retrospective cohort design? Explain its potential impact."*

Response:
We selected a retrospective cohort design for two key reasons:

1. **Feasibility**: ANOCA is a relatively low-prevalence condition; prospective recruitment would require prohibitively long timelines to achieve our sample size (n=5,934).
2. **Data availability**: Electronic health records provided comprehensive longitudinal data on both exposures (e.g., biomarkers) and outcomes.

Addressed in Limitations:

"First, the retrospective design precludes control of treatment strategies and introduces potential selection bias"

Comment 2: Definition of "No Significant Stenosis"

Q: *"Is the definition aligned with guidelines?"*

Response:
Yes. We adopted the 2023 JACC State-of-the-Art Review [10], operationalize ANOCA as angina pectoris occurring in patients with non-obstructive epicardial coronary arteries (stenosis <50%).

Add in Methods- Study Population:

"'ANOCA patients were defined as angina with nonobstructive epicardial coronary arteries (stenosis <50%), adhering to current expert consensus "

[10] Samuels BA, Shah SM, Widmer RJ, et al. Comprehensive Management of ANOCA, Part 1-Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;82:1245–63. doi: 10.1016/j.jacc.2023.06.043

Comment 3: Data Collection Process

Q: *"Detail data collection methods and reliability."*

Response:
Data were extracted through a 3-step process:

1. Data extraction: Data Sources: Structured EHR extraction: Comprehensive review of diagnosis, treatment records, and imaging reports. Mortality validation: regional death registry database, supplemented by telephone/email confirmation with next-of-kin.
2. Independent dual review: Two board-certified cardiologists (L.Z. and ZK.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria: Myocardial infarction (MI): Based on the Fourth Universal Definition of MI (ESC/ACCF/AHA/WHF 2018)[8]; Stroke: Classified according to AHA/ASA 2019 Guidelines[9]; Revascularization: Documented ischemia-driven procedures with supporting angiographic evidence.
3. For discordant cases, joint reviewed by two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience).

We have restructured the "**Methods Follow-up"** section as follows:

"A dedicated follow-up team conducted systematic post-discharge surveillance through a standardized protocol, with scheduled assessments at 30 days, 3 months, 6 months, and annually thereafter. Data collection employed a multimodal approach: (1) comprehensive electronic health record review, (2) cross-referencing with regional death registries, (3) and telephone or email interviews. The observational window for this analysis was finalized on August 1, 2023. Two board-certified cardiologists (L.Z. and ZK.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria [25,26]. For discrepancies in event classification, an adjudication committee comprising two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience) conducted final arbitration through consensus review."

Comment 4: LASSO Variable Selection

Q: *"How were variables selected? Multicollinearity testing?"*

Response:

- **LASSO tuning**: λ selected via 10-fold cross-validation (minimum MSE criterion).
- **Multicollinearity**: Variance Inflation Factor (VIF) <5 for all retained variables.
  Added to Statistical Analysis:

"Variables with VIF ⩾5 were excluded prior to LASSO regression to mitigate multicollinearity."

Comment 5: Internal Validation Details

Q: *"Specify validation methods and external validation plans."*

Response:

- **Internal validation**: The total cohort was randomly partitioned into a training set and an internal validation set. The prediction model developed from the training cohort demonstrated robust performance in the validation cohort, including strong discrimination, adequate calibration, and effective risk stratification.

Addressed in Results section: Discrimination and calibration of the nomogram, Decision Curve, Risk stratification.

- **External validation**: While no independent external validation dataset is currently available, we are actively pursuing collaborative opportunities with multicenter cohorts to validate the generalizability of our model in diverse clinical settings.

Comment 6: Handling Missing Data

Q: *"How were missing data addressed in survival analysis?"*

Response:

- Participants with missing outcome data during follow-up were excluded from the primary analysis using a complete-case approach. Among aprroximately 6000 patients cohort, patients missing outcome data were only 9 (0.15%),therefore, this methodology is appropriate. This methodology aligns with recommendations from the STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative for handling missing-at-random data in time-to-event analyses.
  Addressed in methods section:
  " (5) patients lost to follow-up"
  and Results section:
  " An additional 131 individuals were excluded due to missing baseline or follow-up data "

Comment 7: Hypothesis Testing Methods

Q: *"Specify statistical tests and validity checks."*

Response:

- **Primary analysis**: Cox proportional hazards (PH) models
- **PH assumption**: Tested via Schoenfeld residuals (p>0.05 for all covariates). **Added to Results-Nomogram built based on LASSO-COX regression section:** *"All models satisfied proportional hazards assumptions (global test p=0.057)."*

Comment 8: Clinical Application Strategy

Q: *"How to ensure cross-population applicability?"*

Response:

- **Step 1**: Nomograms enable clinicians to easily assess the risk of adverse prognosis in ANOCA patients using readily available indicators, thereby optimizing clinical management.
- **Step 2**: Recommend validation in local cohorts before implementation. **Added in Results-Nomogram built based on LASSO-COX regression section:** *"For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively."*
  and limitation section：
  "Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations."

Comment 9: Comparison with Existing Literature

Q: *"How do event rates compare to prior studies?"*

Response:

During a median follow-up period of 2 years, the rates of all-cause death, and MI were 1.79%, and 0.56%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3%[11].

Addressed in Discussion section:
'During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous

study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3%[11]."

[11] Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. JAMA. 2014;312:1754–63. doi: 10.1001/jama.2014.14681

Comment 10: Limitations and Mitigation

Q: *"How do single-center limitations affect results?"*

Response:

- **Impact**: Potential overestimation of model performance due to homogeneous practices.
- **Mitigation**: Provided full nomogram prediction model (figure 3) for external adjustment.

  Revised in Limitations section:

  "Finally, while the predictive model developed from single-center data has not yet undergone external validation, internal validation confirmed its robust discrimination and calibration, indicating strong performance within the original cohort."

Comment 11: Biomarker Selection Rationale

Q: *"How were biomarkers validated as independent predictors?"*

Response:

To mitigate overfitting and prioritize robust predictors, we applied LASSO regression (10-fold cross-validation). selected biomarkers retained non-zero coefficients, underscoring their independent contributions. Variables with VIF ⩾5 were excluded prior to LASSO regression to mitigate multicollinearity.and Selected biomarkers were entered into a multivariable Cox proportional hazards model alongside clinical covariates, and all models satisfied proportional hazards assumptions (global test p=0.057).

Addressed in Methods-Statistical Analysis section:

"Variables with VIF ⩾5 were excluded prior to LASSO regression to mitigate multicollinearity. The variables selected through LASSO regression were incorporated into the Cox proportional hazards regression model, and a nomogram was generated based on the Cox regression analysis model."

and Results-Nomogram built based on LASSO-COX regression section:

"LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (Figure 2A). We used a tenfold cross-validation approach to identify the optimal model."

Comment 12: Risk Stratification Implementation

- **Q:** *"How to operationalize risk stratification clinically?"*
  Response:

The total score for each patient was calculated based on the nomogram, and the study population was stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability.
Clinicians calculate a patient's death and adverse cardiovascular event risk score using the nomogram, which can empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

Addressed in Methods-Statistical Analysis section:
"The total score for each patient was calculated based on the nomogram, and the study population was stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability. "
and Discussion section:
"The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes."

Comment 13: Ethical Approval Details

Q: *"Ethics approval and data security measures?"*

Response:

This study was approved by the Institutional Review Board of the Second Hospital of Tianjin Medical University, with a waiver for written informed consent granted for the retrospective use of fully anonymized clinical data. To ensure compliance with personal information protection law, all patient identifiers (e.g., name, ID number, contact details) were irreversibly removed prior to analysis. The Ethics Committee confirmed that no individual privacy could be compromised given these safeguards.

- **Revised in Methods-Study Population section:**

"This study received approval from the Ethics Committee of the Second Hospital of Tianjin Medical University, and the requirement for written informed consent from patients was waived."

Comment 14: Future Research Directions

Q: *"What are the next steps?"*

Response:

We appreciate the reviewer's thoughtful inquiry into potential extensions of our work. Based on our findings, we propose the following prioritized research directions to validate and expand the clinical utility of our risk stratification model for ANOCA patients:

1. Multicenter External Validation
2. Integration of Novel Biomarkers
3. Mechanistic Investigations
4. Longitudinal Outcome Expansion
5. Prospective evaluation of model-guided therapy.

VERSION 2 - REVIEW

Reviewer **1**

Name **Rezende, Paulo**

Affiliation **Instituto do CoraÃ§Ã£o (InCor), Faculdade de Medicina da Universidade de SÃ£o Paulo (FMUSP)**

Date **20-Apr-2025**

COI

The authors have responded adequately to all my questions. No further review is necessary.

Reviewer **3**

Name **Chen, Zhenfei**

Affiliation **The Second People 's Hospital of Hefei, Cardiology**

Date **12-Mar-2025**

COI

Accept