PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between cardiovascular risk factors and coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population
AUTHORS	Popa, Loredana; Petresc, Bianca; Cătană, Cristina; Moldovanu, Claudia; Feier, Diana; Lebovici, Andrei; Schiau, Călin; Rancea, Raluca; Molnar, Adrian; Buruian, Mircea

VERSION 1 – REVIEW

REVIEWER	Dr Louise Marston University College London
REVIEW RETURNED	03-Jun-2019

GENERAL COMMENTS	This is a statistical review. General: change the word subjects to patients throughout. Page 2, design and page 3, strengths and limitations: A cohort study cannot be cross sectional and vice versa. Abstract, page 6 line 12, page 7 line 36: change multivariate to multivariable. Page 6, line 44: 5 subjects... this disagrees with Table 1 which says 8 patients. Please refer to Table 2 in the text. 0.05/9 is 0.006 to 3dp (this makes no difference to the results presented). Say somewhere in the methods section that you used logistic regression in the multivariable analysis. It does not make much sense to do statistical tests using six categories for Table 2, but reducing it to two categories in Table 3, but basing the included variables in Table 3 on those that were statistically significant in Table 2 (and then appear to ignore this anyway as obesity is included in the model in Table 3, but is not significant in Table 2). Age could be included in the logistic regression modelling as a continuous variable as it is in Table 2. For results in Table 3, assume you have dichotomised clinical presentation to typical angina versus other?

	Page 7, line 45: Hypertension was not correlated. It was associated. Correlation and association are different. If the prediction model stays in the paper (and I think you should take it out), you need to say more about it both in the methods and results. There is certainly not enough information present for someone to be able to use it. There is established methodology for doing a good risk prediction model. Page 8, lines 9-11: reference some studies that use CAD-RADS Page 8, line 29: do you mean correlation or association? Page 9, line 54: I think you mean associated not correlated.

REVIEWER	Ghayour Mobarhan, Majid Faculty of Medicine, Biochemistry&Nutrition
REVIEW RETURNED	23-Jun-2019

GENERAL COMMENTS	Which guideline did you use for definition of blood pressure and dyslipidemia? it would be better mention specificity and sensitivity in ROC curve In table 3, did you did you adjust OR for confounder factors? This article seems novel and has collected some results in this field, it can be useful for the researchers want to know about the CAD-RADS for monitoring cardiovascular disease. This article reviewed by Dr. Susan Darroudi behalf in Prof. Ghayour Mobarhan et al. So, we recommend this article for publication in the Journal of BMJ open after revision including mentioned comments.

REVIEWER	Jonathon Leipsic University of British Columbia
REVIEW RETURNED	01-Oct-2019

GENERAL COMMENTS	Thank you for the opportunity to review your work. I commend the authors for their efforts Major concerns 1) Lack of novelty. There are countless manuscripts that have looked at risk factors and disease extent. The authors suggest that the relationship between risk and CADRAD is novel. Given that CADRADS is simply a modified stenosis grade I see nothing new about these data 2) This question was recently answered by Leslee Shaw and colleagues which also included outcomes 3) The cohort is quite small for 2019 4) The discussion is far too long.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

1. General: change the word subjects to patients throughout.

We thank the reviewer for this comment. We replaced the word “subjects” with the word “patients” throughout the entire document.

2. Page 2, design and page 3, strengths and limitations: A cohort study cannot be cross sectional and vice versa.

We thank the reviewer for this observation. We changed the classification of the study into a cross-sectional one. For instance, we corrected the sentence in the abstract section: page 2, line 12 as following: “Design: A cross-sectional observational, patient-based study”. In the “Strenghts and limitations” section, the last phrase remained unmodified (page 3, line 16): “Another limitation is the design of the study: a cross-sectional, retrospective one.”

3. Abstract, page 6 line 12, page 7 line 36: change multivariate to multivariable.

As recommended by the reviewer, we changed to word “multivariate” with “multivariable” in abstract (page 2 lines 29 and 35), page 6 line 12, and page 8 line 3 (former page 7 line 36).

4. Page 6, line 44: 5 subjects... this disagrees with Table 1 which says 8 patients.

We thank the reviewer for spotting this error. We made a mistake when writing the manuscript body, the correct number is 8, as it is written in Table 1. We have now changed the number in the manuscript, replacing number “5” with “8” (page 6, line 52).

5. Please refer to Table 2 in the text.

We thank the reviewer for this comment. We referred Table 2 in text on page 7, line 11. Furthermore, we added references to Table 2 in page 7 line 23, page 7 line 28, page 7, line 37, page 7 line 47.

6. 0.05/9 is 0.006 to 3dp (this makes no difference to the results presented).

We thank the reviewer for this observation. As the Bonferonni correction didn’t change the results, we eliminated the sentence regarding the Bonferonni correction and we considered statistically significant result for a p value<0.05.

7. Say somewhere in the methods section that you used logistic regression in the multivariable analysis.

We thank the reviewer for this suggestion. We replaced the paragraph on page 6 lines 11-14 as following: “Cardiovascular risk factors that showed a significant association with CAD-RADS score were included in the multivariable logistic regression analysis in order to evaluate their simultaneous influence. Through logistic regression analysis, independent predictors for obstructive CAD (CAD-RADS ≥ 3) were identified”.

8. It does not make much sense to do statistical tests using six categories for Table 2, but reducing it to two categories in Table 3, but basing the included variables in Table 3 on those that were

statistically significant in Table 2 (and then appear to ignore this anyway as obesity is included in the model in Table 3, but is not significant in Table 2).

We thank the reviewer for this comment and we agree with her. For instance, we have made some changes regarding the way that we report our result in tables. We have replaced the initial table 1 ("Clinical and CCTA characteristics of the study population") with the initial table 2. We made this replacement since table 2 offers details of both the distribution of cardiovascular risk factors and the CAD-RADS categories of our study population. The new table 1 is named: "Baseline clinical and CCTA characteristics of our study population".

Afterwards, we divided our study population into 2 groups according to CAD-RADS score: group 1- CAD-RADS score of 0-2 (coronary stenosis < 50%) and group 2 – CAD-RADS score ≥3 (coronary stenosis ≥ 50%). We did this division into only 2 categories, since the therapeutical approach changes from CAD-RADS score of 3. According to the CAD-RADS score, patients who receive a CAD-RADS score of at least 3 need further investigation. However, patients with lower CAD-RADS scores between 0 and 2 do not need supplementary investigation.

We performed the univariate analysis between risk factors and CAD-RADS score on these new groups and this is included in the new table 2: "Univariate analysis for the association between cardiovascular risk factors and obstructive CAD classified using CAD-RADS categories". We removed the clinical presentation (typical/atypical angina or nonanginous chest pain) from the list of cardiovascular risk factors since this is rather a symptom and not a risk factor. Finally, we made a new multivariable analysis (Table 3), using logistic regression modeling, in which we included only the risk factors that were statistically significant in Table 2. We have rewritten the Results section according to the new statistical results.

9. Age could be included in the logistic regression modelling as a continuous variable as it is in Table 2.

We thank the reviewer for this comment. In the new multivariable analysis, we have included age as a continuous variable.

10. For results in Table 3, assume you have dichotomised clinical presentation to typical angina versus other?

Yes, we have dichotomized clinical presentation to typical angina versus other. However, as we excluded clinical presentation from the new multivariable analysis, there is no need to make this dichotomization anyomore.

11. Page 7, line 45: Hypertension was not correlated. It was associated. Correlation and association are different.

We thank the reviewer for this comment. In the new version of the manuscript, we have rewritten this sentence as follows: "The odds ratio for coronary stenosis ≥ 50% was approximately 3.5-fold greater in hypertensive individuals" (page 8, lines 11-12).

12. If the prediction model stays in the paper (and I think you should take it out), you need to say more about it both in the methods and results. There is certainly not enough information present for someone to be able to use it. There is established methodology for doing a good risk prediction model.

We thank the reviewer for this comment and we take into consideration her suggestion, therefore we have removed the prediction model from our study.

13. Page 8, lines 9-11: reference some studies that use CAD-RADS

We thank the reviewer for this comment. We added references of the studies that have used CAD-RADS classification (page 9 line 17)

14. Page 8, line 29: do you mean correlation or association?

We have replaced “correlation” with “association”.

15. Page 9, line 54: I think you mean associated not correlated.

Yes, we agree with the reviewer’s comment. However, we have removed this paragraph from the newest version of the manuscript, so there was no need to make this replacement.

REVIEWER 2

1. Which guideline did you use for definition of blood pressure and dyslipidemia?

We thank the reviewer for this question. For the definition of blood pressure we used the ESC/ESH guidelines for the management of arterial hypertension from 2018. Regarding dyslipidemia, we have revised the criteria applied for defining dyslipidemia. We redefined dyslipidemia as total cholesterol > than 5mmol/L according to the HEART score for high risk countries (Romania is considered a high-risk country in the HEART score). Therefore, we have reclassified the patients included in this study according to this new criterion. We performed all the statistics again and in the new version of the manuscript we report the new results.

We have mentioned the references for the guidelines of blood pressure and dyslipidemia in the Methods section (page 5, lines 39-40)

2. It would be better mention specificity and sensitivity in ROC curve.

We thank the reviewer for this comment. However, as suggested by Reviewer 1, we have removed the prediction model from the paper.

3. Did you adjust OR for confounder factors?

Yes, we have adjusted OR for confounders in the logistic regression analysis.

REVIEWER 3

1. Lack of novelty. There are countless manuscripts that have looked at risk factors and disease extent. The authors suggest that the relationship between risk and CADRAD is novel. Given that CADRADS is simply a modified stenosis grade I see nothing new about these data.

We thank the reviewer for this comment and we are honoured to have our manuscript reviewed by one of the developers of the CAD-RADS reporting system. We agree that there are many studies which investigated the association between risk factors and the degree of coronary stenosis. However, in the Romanian population, to our knowledge, this is the first study to evaluate the relationship between coronary stenosis assessed using CCTA and cardiovascular risk factors. In Europe, Romania records one of the greatest incidences of cardiovascular diseases, according to the latest statistics offered by EuroStat in 2018. Our country occupies the second place in Europe regarding the percent of total deaths caused by diseases of the circulatory system. Concerning the standardized death rates caused by ischemic heart disease, Romania is also one of the leading countries, being on the 6th and 5th place in deaths of men and women respectively. Regarding the radiological approach, since the development of CAD-RADS system, in our institution we have introduced this classification into our radiology reports, in order to facilitate the communication between radiologists and clinicians. We believe that using a common lexicon is very important for improving the management of the patients. Taking these arguments into consideration, we think that our study brings valuable information for Romanian

radiologists and cardiologists, offering a comprehensive view both in terms of clinical and imaging characteristics of coronary artery disease in the Romanian population.

2. This question was recently answered by Leslee Shaw and colleagues which also included Outcomes

We acknowledge the recent research made by Leslee Shaw and colleagues, which included a bigger number of patients and performed a prospective study, including also outcomes. We are aware that one of the greatest limitations of our study is the retrospective design. However, the purpose of this study was a different one; we did not aim to assess the outcome of patients with CAD. For this current study, we chose to assess the association between CAD-RADS system and cardiovascular risk factors in the Romanian population, since there is no data in our country regarding the relationship of coronary stenosis evaluated using CCTA and cardiovascular risk factors.

3. The cohort is quite small for 2019

We thank the reviewer for this comment and we agree that the small population sample is another limitation of our study. Unfortunately, in our country, coronary CT angiography is a limited imaging investigation and only selected patients are examined using this modality. This happens mainly because of the limited number of imaging centers that perform this type of investigation in Romania, our center being one of the few centers in Transylvania where CCTA is available. Another reason for the small study population is represented by the fact that this is a single-institution study. Also, our research was conducted over a period of 1 year and 8 months and during this time the number of patients which performed CCTA was relatively small.

4. The discussion is far too long.

We thank the reviewer for this comment. We have revised the discussion and shortened this section.

VERSION 2 – REVIEW

REVIEWER	Dr Louise Marston University College London, UK
REVIEW RETURNED	08-Nov-2019

GENERAL COMMENTS	Thank you for updating this manuscript. In general, the English needs correcting and some sentences could be removed because they are redundant. It is not clear whether ethical approval was sought and obtained from each patient. Now that the prognostic modelling has been removed, the introduction does not fit with the paper. In the tables, there is no need to put stars to indicate statistical significance. Tables 1 and 2 are essentially showing the same thing. Consider removing one of them (or if you find it necessary to keep both, then move one t the appendix).

	P7, line 12 - The interpretation with respect to age is wrong. The correct interpretation is that the mean (SD) ago of those with a CAD-RADS score of 3+ is 6.3 (SD).

REVIEWER	Dr Susan Darroudi behalf in Prof. Majid Ghayour-Mobarhan Mashhad University of Medical Sciences, Iran
REVIEW RETURNED	03-Dec-2019

GENERAL COMMENTS	The authors have studied the association between cardiovascular risk factors and the CAD-RADS grading system which is a method for reporting the results of coronary CT angiography. This is a well designed and accurately performed study. The title is precise and complete. All statements have correct citations. The tables are clear and complete. The method is perfectly explained and leaves no ambiguity. Clear examples are presented . The results are presented in an organized form and are easy to understand. In the discussion section, authors have indicated that there are several explanations for the "obesity paradox"; in which obesity is not associated with the severity of coronary artery disease. But none of theses explanations are presented. It would be reasonable if at least one of these explanations are mentioned in the manuscript. Regarding the writing style of the manuscript, it is clear, concise, easy to follow and informative. Overall, the manuscript can be considered for publication after minor revision.

REVIEWER	Jonathon Leipsic University of British Columbia
REVIEW RETURNED	29-Nov-2019

GENERAL COMMENTS	Thank you for taking the time and effort needed to improve this manuscript. It is significantly improved and have no further concerns.

VERSION 2 – AUTHOR RESPONSE

REVIEWER 1

1. In general, the English needs correcting and some sentences could be removed because they are redundant.

   We thank the reviewer for this comment. We have revised the entire manuscript and corrected the English. Also, we have removed some of the redundant words from the manuscript.

2. It is not clear whether ethical approval was sought and obtained from each patient.

   We thank the reviewer for this observation and we agree that this information was not stated very clearly in the manuscript. Our Institutional Review Board waived the requirement for obtaining informed consent. *Therefore, w*e have added the following statement on “Ehics approval” section: “The Institutional Review Board approved this retrospective, HIPAA-compliant study and waived written informed consent. (1339/25.09.2018)”.

3. Now that the prognostic modelling has been removed, the introduction does not fit with the paper.

   We thank the reviewer for this comment. We have revised and rewritten the introduction. We removed the paragraph related to prognostic value of CCTA and added some information about the importance of CCTA in diagnosing CAD and also about the current situation of cardiovascular risk factors and CAD in Romania.

4. In the tables, there is no need to put stars to indicate statistical significance.

   We thank the reviewer for this observation. We removed all the stars from the tables.

5. Tables 1 and 2 are essentially showing the same thing. Consider removing one of them (or if you find it necessary to keep both, then move one t the appendix).

   We thank the reviewer for this suggestion. We agree that the content of the two tables is similar. However, we consider that the information presented in Table 1 emphase the different distribution of cardiovascular risk factors among the CAD-RADS groups. For instance, we removed Table 1 from the main text and we put it as Supplementary Table 1.

6. P7, line 12 - The interpretation with respect to age is wrong. The correct interpretation is that the mean (SD) ago of those with a CAD-RADS score of 3+ is 6.3 (SD).

   We thank the reviewer for this comment. We have rewritten the interpretation regarding the age as following: “Our results show that a CAD-RADS score between 0-2 was more frequent in younger patients, with a mean age of 55.41 ± 13.11 years in this subgroup, while patients with CAD-RADS score ≥ 3 had a higher mean age of 63.1 ± 10.55 years.” (page 7, lines 30-32)

   We hope that these responses can address the problems that you posed; if not please feel free to contact us. Thank you again for all your observations and suggestions.

REVIEWER 2

1. Thank you for taking the time and effort needed to improve this manuscript. It is significantly improved and have no further concerns.

   We kindly thank the reviewer for his consideration and for his time and effort to review this manuscript. We greatly appreciate your helpful suggestions, which were very valuable for improving the quality of the manuscript.

REVIEWER 3

1. In the discussion section, authors have indicated that there are several explanations for the "obesity paradox"; in which obesity is not associated with the severity of coronary artery disease. But none of these explanations are presented. It would be reasonable if at least one of these explanations are mentioned in the manuscript.

   We thank the reviewer for this observation. We have added some explanations and theories about the obesity paradox: “One hypothesis for this paradox is that obese patients tend to be diagnosed at an earlier age and stage of CAD, therefore having lower morbidity and mortality rates (42, 43). Another potential reason for better outcomes of obese patients compared to those of underweight ones is that the latter group is more likely to have post procedural complications due to excessive anticoagulation which is usually not weight adjusted (44, 45).

Moreover, underweight patients usually have more concomitant comorbidities which lead to worse prognosis (46). Another theory is that obesity is associated with higher amounts of lean mass and which can have a protective effect when not associated with increased systemic inflammation (47).” (page 9, lines 43-52).

We thank you for your kind words and suggestions and for approval for publication.

VERSION 3 – REVIEW

REVIEWER	Dr Louise Marston University College London
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	Thank you for your changes to this paper. It is much improved. Only one comment, because the data are not longitudinal, you cannot say that variables predict the outcome, you can only say they are associated with the outcome.

VERSION 3 – AUTHOR RESPONSE

REVIEWER 1

1. Thank you for your changes to this paper. It is much improved. Only one comment, because the data are not longitudinal, you cannot say that variables predict the outcome, you can only say they are associated with the outcome.

   We thank the reviewer for this comment and for all the time and effort to review this manuscript. We have revised our manuscript and rewrote the title and the phrases where it was stated that the variables predict the outcome, replacing prediction with association (page 2 lines 46-50, page 6 lines 25-26, page 7 lines 54-55, page 9 lines 10-11).
   We greatly appreciate your helpful suggestions, which were very valuable for improving the quality of the manuscript.