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OPEN PEER REVIEW

Evaluation of the Relationship Between the Characteristics and Dimensions of Calcified Plaques and Coronary Artery Stenosis in Patients Undergoing Coronary Computed Tomography Angiography

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About this report

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1 Original submission

1 comment · 17 Apr 2022

Editor-in-Chief

MINOR REVISION 17 Apr 2022

Dear authors,
Before the review process for your article begins, it is necessary to clarify the following items:

Given the importance of conflict of interest clarification, the corresponding author should fill out the “ICMJE form” and upload it during the submission process. (The form is available in the “conflict of interest” section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html.)

References 19, 17, 15, 6, and 5 are old. Please replace them with newer references.
Regards

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editorial board

Thank you for your useful comment

All your comments were done except for replacing references 15 and 17. Because these are two critical and evolutional studies that are eligible to compare with this study. Please skip this comment.

Thank you in advance

2 Revision 1

3 comments · 16 Nov 2022 – 21 Jan 2023

Referee 1 Reviewer

MINOR REVISION 16 Nov 2022

Thanks to the authors for their submission to the IJR.
Overall, this manuscript is relatively suitable in terms of the importance of the title, scientific writing structure, and sample size, but it needs some revisions as follows:
Abstract
1. It should be written according to the journal guidelines.
2. Background: All abbreviations, such as CT, should be written in full at first use.
3. Methods:
3.1. At present, the study design is cross-sectional, and this term should replace the term "prospective descriptive-analytic" in all sections of the manuscript.
3.2. It would be better to use a case-control design by selecting patients with more and less than fifty percent carotid stenosis as the case and control groups, respectively.
3.3. Please clarify whether 212 is the number of samples or plaques. The number of samples should be mentioned.
3.4. What is the meaning of prospective and retrospective ECG-gated CCTA?
3.5. The patient inclusion and exclusion criteria and the calendar period of the study should be added.
3.6. The statistical analysis software and significance level should be added as the last sentence.
4. Results:
4.1. First, important demographic characteristics of the patients should be presented.
4.2. For binary variables, such as less or more than 50%, the value for only one category should be reported.
4.3. When describing a significant or nonsignificant relationship, also indicate that the significance is statistical.
4.4. The term correlation should be replaced with association or relation.
4.5. The P-value should be written as less or more than 0.05, 0.01, or 0.001.
4.6. The most important index of ROC analysis is the positive predictive value, which shows the probability of truly having the outcome when the test is positive. Sensitivity, negative predictive value, accuracy, and the area under the ROC curve should also be reported.
5. Conclusion: Only specificity indices are reported, and these relate only to the accurate diagnosis of samples without the outcome. Therefore, this sentence "In this regard, plaques with width more than 4.35, length more than 10.75, and thickness more than 2.45 may be significant." should be edited according to the sensitivity value.
Main Text
6. The objective should be moved to the last paragraph of the background.
7. Statistical analysis
7.1. The first sentences of the statistical analysis section should address descriptive measures, including categorical variables described by number and percentage and continuous variables expressed as mean and standard deviation (SD).
7.2. To adjust for possible confounding, it would be better to use multivariate logistic regression, including other important factors such as age, sex, etc. A regression model can also be used in ROC analysis.
7.3. The significance level should be added as the last sentence.
8. Tables
8.1. Important demographic and clinical variables should be added to table 1.

8.2. All ROC analysis indices mentioned in the abstract should be reported in a table as table 2.
9. Figures: All figures 1-4 should be merged into one figure.

Referee 2 Reviewer

MAJOR REVISION 6 Dec 2022

Dear authors
The subject of this manuscript is of importance due to the prevalent use of coronary CT angiography in patients with suspected symptoms of coronary artery disease. However, it is of intermediate novelty.
The abstract should be reevaluated with respect to the word count limit.
The following sentence should be omitted from the objective section: "no comprehensive study was conducted in this regard yet"
I could not find the registered ethical code on the Iran National Committee for Ethics in Biomedical Research website. Please recheck the code and provide a website link.
The manuscript needs to be evaluated by an English editing service.
Are there any available conventional angiography data? If so, it is better to include them. As is known, the gold standard modality for stenosis estimation is conventional angiography.
The plaque location should be mentioned precisely; for example, LAD plaque is not a precise description, and it should be stated whether the plaque is in the proximal, mid, or distal LAD.
I suppose that the following sentences are inappropriate for the 2.3. Image acquisition and analysis section: "To evaluate plaque dimensions as a criteria of luminal stenosis, first the status of variable normality was assessed using One-Sample Kolmogorov-Smirnov Test. Since the hypothesis of normality of variables has been rejected, Mann-Whitney U test was used for comparison. Indeed, ROC curve was used for determination of cut points and sensitivity and spec specifity. ROC curve was used for significant variables."
The analysis is incomplete, and some predictive regression analyses are needed rather than a simple Mann-Whitney test.
Best Wishes!

Editor-in-Chief

MAJOR REVISION 21 Jan 2023

Dear authors,
Your article needs Major Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Chief Editor of the Journal

At first, thank you for your attention and your letter comments because we know that you are too busy. We are tremendously grateful to this assessment which provides helpful comments that making this manuscript significantly better. Our responses to the comments are as follows. The changes in revised manuscript are highlighted in **Red.**

Reviewer 1:
Dear authors
The subject of this manuscript is of importance due to the prevalent use of coronary CT angiography in patients with suspected symptoms of coronary artery disease. However, it is of intermediate novelty.

The abstract should be reevaluated for the limitation of word count. Thanks. It has been done.

The following sentence should be omitted from the objective section; "no comprehensive study was conducted in this regard yet". It has been deleted.

I could not find the registered ethical code in the Iran National Commitee for Ethics in Biomedical Research website; Please recheck the code and provide a website link.
https://ethics.research.ac.ir/ProposalCertificate.php?id=72054&Print=true&NoPrintHeader=true&NoPrintFooter=true&NoPrintPageBorder=true&LetterPrint=true

The manuscript needs to be evaluated by an English editting service. It has been done.

Is there any available conventional angiography data? If so, it is better to include them. As known, the gold standard modality for stenosis estimation is conventional angiography.
Angiography was not performed in all of our participants and it seems reasonable since angiography was just performed in cases with critical lesions detected by CTA.

The plaque location should be mentioned precisely; for example, LAD plaque is not a definite explanation and it should be mentioned that the plaque is in the proximal, mid, or distal LAD.
First, all of our patients did not undergo angiographic evaluation and the possibility of examining them could not be evaluated due to the non-random conditions of the plaques.

I suppose that the following sentences are inappropriate for the 2.3. Image acquisition and analysis section;
"To evaluate plaque dimensions as a criteria of luminal stenosis, first the status of variable normality was assessed using One-Sample Kolmogorov-Smirnov Test. Since the hypothesis of normality of variables has been rejected, Mann-Whitney U test was used for comparison. Indeed, ROC curve was used for determination of cut points and sensitivity and spec specifity. ROC curve was used for significant variables."
Thanks. It has been deleted.

The analysis is incomplete and some predictive regression analyses are needed rather than a simple Mann-Whitney test.
Thanks. It has been done.
Best Wishes!

Reviewer 2:
Thanks to the authors for their submission to the IJR.
Totally it can be mentioned that this manuscript is relatively suitable according to, importance of title, scientific writing structure, and sample size; but it needs some revisions as follows:
Abstract
1. It should be written according to journal guideline. Thanks. It has been done.

2. Background: All abbreviations like as CT should be written in full form for the first time. Thanks. It has been done.

3. Methods:
3.1. At present, the design of study is cross-sectional, and this term should be replaced rather than "prospective descriptive-analytic" term in all sections of manuscript. Thanks. It has been done.

3.2. It is better that it is used of case-control design by selection of patients with more and less than fifty percent carotid stenosis as case and control groups, respectively.
Carotid artery was not within the scope of this study, but it is a good idea that we appreciate it.

3.3. It be cleared that 212 is number of samples or plaques? The number of sample should be mentioned. This is the number of plaques. The number of cases were 54.

3.4. What is meaning of prospective and retrospective ECG-gated CCTA?
The X-ray beam is on about 20% and 100% of the R-R interval with prospective vs. retrospective gating, respectively. Indeed, the maximal tube current is on 65-85% of the R-R interval using retrospective gating.

3.5. Inclusion and exclusion criteria of patients and calendar time of study should be added.
Patients with measurable calcified plaques were randomly selected and patients without plaques were excluded. The quality of CTA for measurement of plaque volumes was the only inclusion criteria, while unqualified CTA was considered as exclusion criteria.

3.6. Statistical analysis software and significance level should be added as last sentence.
Thanks; it has been added.

4. Results:
4.1. At first, important demographical characteristics of patients should be presented.
Thanks, it has been added.

4.2. 4.2. For binary statues variables like as less or more than 50%, it should be written only one state value.
Plaques were divided into four categories (1-24%, 25-49%, 50-70% and 70-99%). It is corrected.

4.3. When to be written about the significant or non-significant relationship, also added the world of statistical between them. Thanks, it has been added.

4.4. The correlation term should be replaced with association or relation. Thanks. It has been corrected.

4.5. P-value should be written as less or more than 0.05, or 0.01, or 0.001. Thanks. It has been corrected.

4.6.Most important indices of ROC analysis is positive predictive value that shows the probability of truly having outcome, when the test is positive. Also, sensitivity, negative predictive value, accuracy, and area under ROC should be reported.
Thanks. It has been done.

5. Conclusion: Since, only specificity indices reported and it only related with accurate diagnosis of samples without outcome. Therefore, this sentence "In this regard, plaques with width more than 4.35, length more than 10.75, and thickness more than 2.45 may be significant." should be edited according to sensitivity value.
Thanks. It has been done.

Main Text
6. Objective should be transferred as last paragraph of background. Thanks. It has been added.

7. Statistical analysis
7.1. First sentences of statistical analysis should be about descriptive measures including categorical variables described by number and percentage and continuous variables expressed as mean and standard deviation (SD).
Thanks. It has been done.

7.2. It is better that for adjustment of possible confounding, it used of multivariate logistic regression by including of other important factors like as age, sex, ... Also. it can be used of regression model in ROC analysis.
Thanks. It has been done.

7.3. Significance level should be added as last sentence. It has been added.

8. Tables
8.1. Important demographical and clinical variables should be added to the table 1.
Thanks. It has been done.

8.2. All ROC analysis indices that mentioned in the abstract should be reported in a table as table 2.
Thanks. It has been done.

9. Figures: All figures 1-4 should be merged in one figure. It has been done.

3 Revision 2

2 comments · 9 Apr 2023 – 19 Apr 2023

Associate Editor

ACCEPT 9 Apr 2023

All comments were correctly and completely applied. As a result, this manuscript is now methodologically approved.

Editor-in-Chief

MAJOR REVISION 19 Apr 2023

Dear authors,
Your article needs Major Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Chief Editor of the Journal

At first, thank you for your attention and your letter comments because we know that you are too busy. We are tremendously grateful to this assessment which provides helpful comments that making this manuscript significantly better. Our responses to the comments are as follows. The changes in revised manuscript are highlighted in **Red.**

Associate Editor 3:
1-in line 5 of abstract: the part "cardiac computed tomography (CT) angiography (CCTA)" should be written as: "cardiac computed tomography angiography (CCTA)"
Thanks. It has done.
2-please add objective part to abstract according to journal format.
Thanks. It has added.
3-this sentence seems unclear: "There was a statistically significant relationship between stenosis and area of plaques lumen and lumen of normal coronary artery before or after plaque" [… between stenosis and area of plaques lumen …..???]
Thanks. It has cleared.
4-in lines 18 and 19, the authors mentioned: "There was also a statistical significant relationship 18 between width and thickness of plaque with stenosis (P>0.01, P>0.05)." while P>0.05 means a non significant statistical relationship. Please clarify. [in abstract and result section. Please note that the P>0.01 does not mean a significant relationship, as it could be P>0.05. in fact P>0.01 should be written as 0.01<P<0.05. please correct.]
Thanks. It has done.
5-please write references in sequential order. For example, reference 2 is mentioned before reference 1. Please correct.
Thanks. It has corrected.
6-this part is unclear: "larger volume of plaque is other high risk for CAD"
Thanks. It has cleared.
7-in the line 2 of background, I think disease is better than diseases.
Thanks. It has done.
8-the authors have mentioned: "Coronary artery calcification, greater proportions of non-calcified materials and higher remodeling indices (3) are associated with higher risk of CAD in these patients." While two first items are in contrast. [I mean Coronary artery calcification and greater proportions of non-calcified materials]. Please clarify. Is more calcification a risk factor or less calcification?
Thanks. It has clarified.
9-this part is unclear: "… responsible for linkage between clinical outcomes and angiographic findings"
Thanks. It has clarified.
10-please add objective part to paper according to journal format.
Thanks. It has added.
11-what do you mean by "easy non-random method"? sequential method?
Thanks. It has clarified.

12-please check and correct SPSS manufacturer data based on the IBM site. I think SPSS 21 is for IBM Inc. not SPSS Inc.

Thanks. It has corrected.

13-in the statistical analysis part, please correct: "…. was rejected, Mann-Whitney U ….."

Thanks. It has corrected.

14-it seems the part related to normality check [K S test] is repetitive in stat analysis section. Please correct.

Thanks. It has corrected.

15-authors have mentioned: "In addition, ROC curve was used to determine the cut of points, sensitivity and specificity" but it is unclear what is the target of diagnosis here? Which condition is the goal of diagnosis in which the authors have used ROC? Please explain in this regard.

Thanks. It has explained.

16-please add full term of abbreviations for the first time usage for example ROC, ….

Thanks. It has done.

17-sample size is 212 or 211? [… stenosis degree less and more than 50% was 100 (47.3%) and 111 patients (52.6%),….]

Thanks. It has corrected.

18-authors mentioned: "All of our patients did not undergo angiographic evaluation and the possibility of examining them could not be evaluated due to the non-random conditions of the plaques." This sentence seems unclear, especially its second part. [and the possibility of …..…]

Thanks. It has corrected.

19-this part is wrong: "8 top locks in the proximal LCX". In addition, "3 plates" and "4 plates" are wrong.

Thanks. It has corrected.

20-in the table, number of plaques with lower and higher 50% stenosis are 99 and 112 while they are 100 and 111 in text. In addition, total plaques are 211 while in text they are 212.

Thanks. It has corrected.

21-please replace +_ with ± in all paper.

Thanks. It has done.

22-what is difference between width and thickness in table? The authors should mention definition of these variables and the method of their measurement in paper.

Thanks. It has done.

23-authors mentioned: "Diameter of normal coronary after or previous plaque (mean+_SD)" in table. This part reminds us two measurements [before and after] while there is only one data in table. Please clarify.

Thanks. It has corrected.

24-in figure legend, please correct specifity to specificity.

Thanks. It has corrected.

25-the part related to ROC curves is totally unclear both in stat. method, result and figure. The authors should explain exactly why did they used ROC and what is their goal [diagnostic goal]? I mean for which condition, the authors used ROC analysis? Are they going to detect more than 50% stenosis? Did they use this in all vessel segments together or in terms of each segment? Please carefully clarify this part in paper.

Thanks. It has clarified.

26-figure legend is unclear as I mentioned in previous question. Please clarify. pLease exactly explain each part in figure legend [parts A-D]

Thanks. It has done.

27-based on the figure 1, it seems the ROCs A,B and D are not efficient as their AUC are near 0.5. the authors have not mentioned AUCs and we can not judge in this regard. In fact, they should mention the AUC of variables to assess their efficacy, while they did not mention the AUC, P-Value of ROC and the criteria for selecting cut off point. In addition, it is unclear which condition is going to be diagnosed by ROC. Regarding the diagnostic indices, we have PPV, NPV, PLR and NLR in addition to sensitivity and specificity. So, the part related to ROC analysis is better to be completed and corrected.

Thanks. It has done.

28-in LAD, LCx and RCA the stenosis more than 70% needs treatment [in LM, 50%] while the authors considered 50% for all arteries. Is this rational?

Thanks. It has checked.

29-in the response to a question, the authors mentioned: "Patients with measurable calcified plaques were randomly selected" while they mentioned sampling was "easy non-random method". This is paradox. Please clarify.

Thanks. It has done.

30-authors mentioned stenoses as four categories (1-24%, 25-49%, 50-70% and 70-99%) while they mentioned only cut off point of 50% for stenoses. I think for the other stenoses, the results could be mentioned in the paper. Otherwise, the reason for this mentioning is unclear.

Thanks. It has clarified.

31-Most important indices of ROC analysis is positive predictive value that shows the probability of truly having outcome, when the test is positive. Also, sensitivity, negative predictive value, accuracy, area under ROC, and p-vlue should be reported. All indices should be reported with %95 confidence intervals.

Thanks. It has done.

32-Conclusion: Since, only specificity indices reported; and, it only related with accurate diagnosis of samples without outcome. Therefore, this sentence "In this regard, plaques with width more than 4.35, length more than 10.75, and thickness more than 2.45 may be significant." should be edited according to sensitivity value.

Thanks. It has done.

33- It is better that for adjustment of possible confounding, it used of multivariate logistic regression by including of other important factors like as age, sex, ... Also, it can be used of regression model in ROC analysis.

Thanks. It has done.

34- All ROC analysis indices that mentioned in the abstract should be reported in a table as table 2.

Thanks. It has done.

35-please correct relationbetween. [add space]

Thanks. It has done.

36-please follow journal format in references.

Thanks. It has done.

37-Please cite refs in sequential order(Background and Discussion section).

Thanks. It has done.

38-Please cite ref No.16

Thanks. It has corrected.

4 Revision 3

1 comment · 7 Jun 2023

Editor-in-Chief

MINOR REVISION 7 Jun 2023

Dear authors,
Your article needs Minor Revision.
Regards

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Chief Editor of the Journal

At first, thank you for your attention and your letter comments because we know that you are too busy. We are tremendously grateful to this assessment which provides helpful comments that making this manuscript significantly better. Our responses to the comments are as follows. The changes in revised manuscript are highlighted in **Red.**

Associate Editor 1:
1-this sentence does not have verb: "Very few available studies regarding the relationship between plaque characteristics, such as plaque dimensions and stenosis, in patients undergoing CCTA (9)."
Thanks. It has corrected.

2-please cite SPSS manufacturer based on this address: https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss
Thanks. It has corrected.

3-this part seems wrong: "In order to compare the dimensions of plaque with the variable introduced as a criterion for vascular stenosis, logistic regression has been used (table 2)." Logistic regression is not for comparison. Comparison could be done by t-test, mann whitney ……
Logistic regression was used to investigate the impact of different characteristics and dimensions of calcified plaques on coronary artery stenosis. A binary variable indicating the stenosis greater than 50 or less than 50 was used as the dependent variable in this model, while characteristics and dimensions of calcified plaques were used as quantitative independent variables.

4-this part does not have verb: "First, the crude model without confounding and then the adjusted model with the presence of the sex variable"
Thanks. It has corrected.

5-this part in statistical analyses belongs to result section and should be moved to result of paper: "First, the crude model without confounding and then the adjusted model with the presence of the sex variable. In both models, the same variables were not significant, so in the adjusted model, width (OR=1.73), plaque luminal area (OR=0.64), Diameter of a normal coronary after or previous plaque (OR=1.70) was significant (p-value<0.05) (table3). But in the crude model, the length(OR=1.10) variable is also significant"
Thanks. It has done.

6-many required statistical analyses method have been deleted that is not correct. Please get a consultation from methodologist and statistician.

Writing of paper have been ruined

7-result section is not classically written. Many parts are deleted and some parts have been added. The authors should mention at first a brief of demographic data.
Thanks. It has corrected.

8-please review carefully the result section. Some parts have been deleted and some parts are added. We have no comparison.
Thanks. It has corrected.

9-this sentence is unclear: "After performing statistical analysis, it was concluded that there is a significant relationship between stenosis and the area of the lumen of the normal vessel and atherosclerotic plaque and plaque width." What is the stat method here? Please get a statistical consultation.
Thanks. It has corrected.

10-i am confused regarding the main results of paper. In previous version diagnostic efficacy indices [including sensitivity and specificity] has been mentioned. of course, the ROC analysis in previous version was unclear and we asked about diagnostic efficacy assessment from the authors. They deleted this approach and presented in current version the results using log. regression analysis. Please explain and clarify.
Because the variable of vascular stenosis in this article is defined as having or not having stenosis and this was considered as our main dependent variable. The purpose of logistic is to determine whether there is a relationship between the variables and if there is, it analyzes how much our dependent variable (arterial stenosis) will change based on the increase or decrease of the independent variable (the dimensions and characteristics of the classified plaques). and in addition, if there is a distortion variable, how will these changes be applied.

Because this is the purpose of the study, logistic regression has more advantages than rock.

11-please write the results in a classical and appropriate style. Move the results from statistical analysis section to result section and explain about the analysis approach in the statistical section of the paper. The paragraph beginning with: "All of our patients did not…." Seems to be mentioned at the first part not second part of results. In addition, please add mean age and gender data. Please express the data of logistic

regression in detail and complete. This part seems to be extracted from log regression but it is so vague: "After performing statistical analysis, it was concluded that there is a significant relationship between stenosis and the area of the lumen of the normal vessel and atherosclerotic plaque and plaque width. This association can be interpreted as follows For one unit increase in any of the significant variables (width (OR=1.73), plaque luminal area (OR=0.64), Diameter of normal coronary after or previous plaque (OR=1.70)) the probability of reducing plaque stenosis increases by 1.73, 0.64, and 1.7, respectively." It is better the author mention what was the dependent variable in logistic regression. What were the independent variables in log regression? Did they use univariate or multivariate or both methods? Please write results correct and appropriate.

Logistic regression was used to investigate the impact of different characteristics and dimensions of calcified plaques on coronary artery stenosis. A binary variable indicating the stenosis greater than 50 or less than 50 was used as the dependent variable in this model, while characteristics and dimensions of calcified plaques were used as quantitative independent variables.

12-did the authors compared sub-groups by t-test or U mann-whitney?
Thanks. It has done.

13-please replace +_ with ± in all paper
Thanks. It has corrected.

14-please mention the tables sequentially in text. Table 1 is after tables 2 and 3.
Thanks. It has corrected.

15-authors mentioned stenoses as four categories (1-24%, 25-49%, 50-70% and 70-99%) while they mentioned only cut off point of 50% for stenoses. I think for the other stenoses, the results could be mentioned in the paper. Otherwise, the reason for this mentioning is unclear.

Thank you for this comment. Essentially, it explained that the stenosis that we wish to say needs more attention is one that is greater than 50%. Additionally, we divided the stenosis into significant and non-significant stenosis, or either below or above 50%.

5 Revision 4

1 comment · 3 Jul 2023

Editor-in-Chief

ACCEPT 3 Jul 2023

Dear authors,
Your article is acceptable for publication in IJR.
Regards