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OPEN PEER REVIEW

The Optimal Cut-Points of Alanine Aminotransferase for Screening Metabolic Syndrome in Iranian Adults

Samaneh Asgari, Fereidoun Azizi, Farzad Hadaegh

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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Contents

1 **Original submission** Referee 1 2
2 **Revision 1** Yadollah Mehrabi 3
Authors' reply to reviewers 4
Reviewer and editor comments 8
3 **Revision 2** 9
Authors' reply to reviewers 10
Reviewer and editor comments 12

1 Original submission

1 comment · 2 Sep 2024

Referee 1 Reviewer

MINOR REVISION 2 Sep 2024

This cross-sectional study aimed at determining gender-specific ALT cut-off points for screening metabolic syndrome in Iranian adults. Although the topic is not novel, the manuscript is well written, and the internal validity is acceptable. Moreover, the authors validated the suggested cut-off points in the American population. My comments are provided below:

Major:

1. The main concern is the different approaches used to determine cut-off points in other studies. For instance, the ACG used a statistical approach, which is entirely different from the current study. If this is true, the comparisons do not make sense.
2. Different definitions have been used in various studies. How did the authors account for these differences?
3. It seems that individuals with diabetes were included in the study. Considering the importance of diabetes, I recommend excluding them and redoing the analysis.
4. Why was "physical activity" not included in the adjustments?

Minor:
1) Regarding external validation, there is no comment in the statistics.
2) It is better to include a flow chart to illustrate the sampling process.
3) Page 9, line 130: Why was the “usage of triglyceride” lowering drug not mentioned?

2

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.

Reviewers' Comments:

Reviewer 1:
This cross-sectional study aimed at determining gender-specific ALT cut-off points for screening metabolic syndrome in Iranian adults. Although the topic is not novel, the manuscript is well-written, and the internal validity is acceptable. Moreover, the authors validated the suggested cut-off points in the American population. My comments are provided below:

Major:

1. The main concern is the different approaches used to determine cut-off points in other studies. For instance, the ACG used a statistical approach, which is entirely different from the current study. If this is true, the comparisons do not make sense. Different definitions have been used in various studies. How did the authors account for these differences?

Response: Thanks for your concern. Each study established its own cut-off points for the specific outcomes it examined. For instance, the ACG provides clinical guidelines for reporting abnormal liver chemistries, reviewing multiple studies that documented abnormal values associated with liver-related mortality. Our study aimed to evaluate various abnormal ranges of ALT in relation to the prevalence of METS, taking into account both our findings and previously reported ranges. Given that the outcomes differ, we did not directly compare the studies with one another. Instead, we utilized their defined cut-off points to assess our study's performance in identifying the optimal abnormal range for detecting METS prevalence in the Iranian population. Thus, this comparison is not statistically related.

3. It seems that individuals with diabetes were included in the study. Considering the importance of diabetes, I recommend excluding them and redoing the analysis.

Response: Thanks for your comment. In the current study elevated FPG was defined as FPG ≥100 mg/dl or using anti-diabetic medications. However, as a sensitivity analysis we excluded 442 adults on anti-diabetic medications on TLGS data and 664 individuals in ARIC data. The results were largely consistent. When considering the optimal cutoff point analysis, the recommended value for females decreased to 14.5 mg/dl, with a sensitivity of 73.8% and specificity of 50.5%, yet the discrimination power remained unchanged. For males, the results were consistent with the main analysis. (Page 8 lines 162-163; Page 10 lines 195-199; supplementary Tables 1 and 2).

4. Why was "physical activity" not included in the adjustments?

Response: Thanks for your valuable comment. We accounted for physical activity in the main analysis, but unfortunately, it was omitted from the text. We have now added it to both the text and the table.

Minor:

1) Regarding external validation, there is no comment in the statistics

Response: Thanks for your comment. As part of the external validation, the diagnostic performance of various cut-off points was assessed using the ARIC dataset. (Page 8, lines 161-162)

2) It is better to include a flow chart to illustrate the sampling process

Response: Thanks for your comment. Study flow chart was included in the manuscript (Figure 1).

3) Page 9, line 130: why “usage of triglyceride” lowering drug was not mentioned

Response: Thanks for your comment. In the TLGS study, the primary focus was on lipid-lowering medication, so we made the necessary adjustments accordingly.(Page 7, line 130)

Reviewer 2:

Manuscript Title: The optimal cut-points of alanine aminotransferase for screening metabolic syndrome in Iranian adults

1. The authors of this manuscript have tried to determine the alanine aminotransferase (ALT) thresholds for screening of metabolic syndrome (Mets) in men and women separately, in a cross sectional study. Since TLGS is a longitudinal cohort study, the main question that arises here is that why they have not taken incident cases of Mets instead of prevalent cases?

Response: Thanks for your valuable comment. Unfortunately, due to limited resources, ALT lab measurements were only conducted during the final phase of TLGS (7th phase, 2018-2021). As a result, it was not possible to identify incidence cases, as no further measurements were taken beyond this phase. While prognostic cut-off points derived from longitudinal data are more accurate, establishing diagnostic cut-off points using cross-sectional data enhances their applicability in public health settings. (Page lines 243-244)

2. The results are not that promising. Determining cut points, when the models have low discrimination power, seems not to be that helpful for screening of Mets. In this study the area under ROC curve models are as low as 62 percent. How the authors justify this?

Response: Thank you for your concern. The discrimination power of ALT alone is 65% for screening MetS. Our proposed cutoff points effectively identify approximately 62% of MetS cases, which represents a significant portion of the overall discrimination capability. We also want to highlight that even modest predictive power can have clinical relevance by identifying individuals at risk for MetS and facilitating targeted interventions. While we acknowledge the methodological limitations of our study, we believe that further research could improve predictive accuracy. Ultimately, our findings offer valuable insights into MetS screening and emphasize the necessity for ongoing development in this field. (Page lines 242-246)

3. Footnote of the table 2 says that "model 1: adjusted only with ALT". Since ALT is the main exposure in this study, adjusting for that is not reasonable. Please clarify.

Response: Thanks for your comment, By "adjustment," we refer to its inclusion in the model. We can rephrase the sentence to: "Model 1 included ALT."(Table 2)

4. Table 2: how do you justify adjusting for BMI for Mets, since WC (as a measure of obesity) is one of the components. Sharp drop of ORs for model 3 (compared to model 2) when elevated WC has been taken as the response variable may be due to this adjustment. Instead, physical activity can be a reasonable replacement for BMI. Please check it.

Response: Thanks for your comment. All analysis repeated with excluding BMI. (Table 2).

Physical activity: We accounted for physical activity in the main analysis, but unfortunately, it was omitted from the text. We have now added it to both the text and the table.

5. Line 117: two reference categories have been defined for education level (<6 and >=12).

Response: Thanks for your comment. It was corrected.

Associate Editor's Comments:

Associate Editor 1:

Associate Editor Comments:

1. As far as I know, population-based reference values are primarily determined from cross-sectional studies to specify healthy persons and cut-off values are valuable in cohort studies in relation to a specific outcome. Please explain why a cross-sectional study was used to determine cut-off values.

Response: Thanks for your valuable comment. Unfortunately, due to limited resources, ALT lab measurements were only conducted during the final phase of TLGS (7th phase, 2018-2021). As a result, it was not possible to identify incidence cases, as no further measurements were taken beyond this phase. While prognostic cut-off points derived from longitudinal data are more accurate, establishing diagnostic cut-off points using cross-sectional data enhances their applicability in public health settings. (Page lines 242-246)

2. According to comments raised by reviewers, the manuscript needs major revision. Please provide a point-by-point response to reviewers.

Response: A point-by-point response was provided.

References

1. Abbate LM, Stevens J, Schwartz TA, Renner JB, Helmick CG, Jordan JM. Anthropometric measures, body composition, body fat distribution, and knee osteoarthritis in women. Obesity. 2006;14(7):1274-81.

2 Revision 1

1 comment · 28 Oct 2024

Yadollah Mehrabi Reviewer

ACCEPT 28 Oct 2024

Many thanks to the authors for their point-by-point response to the comments. The authors have answered most of the questions raised in the first review and mentioned some of them as limitations of the study.

3

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.

Title: NEEDS ACTION: ID 151542 Needs Minor Revision, rev [1]

- **Journal:** International Journal of Endocrinology and Metabolism
- **Manuscript ID:** 151542
- **Manuscript Title:** The optimal cut-points of alanine aminotransferase for screening metabolic syndrome in Iranian adults
- **Revision:** [1]

Dear Dr. Farzad Hadaegh,

Thanks for submitting your valuable manuscript to the journal. As a result of this, we would like to inform you that the review of your manuscript is finished, and based on the editorial decision, you need to do a "**Minor Revision**" on your manuscript. Even though this manuscript has enough quality to enter the review process, it needs some significant (Minor) revisions in some points of view.

How to Submit Revision?

Below you may find those comments. Please read them and answer them one by one.

The **corresponding author** needs to prepare replies as below:

1. In a Word file, reply to all comments one by one (reply to reviewer)
2. In the Word file of your manuscript, reply and apply all comments as marked or highlighted lines/paragraphs.

Instruction: **click here**

Reviewers' Comments:

Reviewer 1:

In the revised manuscript the majority of comments given for the different sections have been satisfactorily responded to and accordingly altered.

However, there is one point that still requires attention. I understand that the comparisons made are not statistically related. However, as I mentioned previously, ACG employed a statistical approach in which normal values are defined as the mean value of a healthy population ± 2 standard deviations. This method encompasses 95% of subjects and differs significantly from the outcome-based approach utilized in this work.

Response: Thanks for your comment. The ALT threshold for liver related mortality among US population was reported by Ruhl.CE and Everhart.JE (1) that is referenced in the ACG guideline studies (2) (Table 3, Page 22). In this study, we consider these outcome-based thresholds. Previously, we had used the "ACG thresholds" in the manuscript; however, to be clear, we revised them to reflect the liver-related mortality thresholds for the U.S. population, following the reviewer's recommendation.

References:

1. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and γ-glutamyltransferase and mortality in the United States population. Gastroenterology. 2009;136(2):477-85. e11.
2. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Official journal of the American College of Gastroenterology| ACG. 2017;112(1):18-35.

3 Revision 2

0 comments

No public comments in this round.