PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between triglyceride glucose-related markers and the risk of metabolic-associated fatty liver disease: a cross-sectional study in healthy Chinese participants
AUTHORS	chang, mingxing; Shao, Zhihao; Shen, Guifang

VERSION 1 – REVIEW

REVIEWER	Yustisia, Ika Hasanuddin University, Biochemistry
REVIEW RETURNED	06-Dec-2022

GENERAL COMMENTS	MAFLD is a health threat often overlooked because it is silent, and its prevalence in non-obese individuals is quite high. This interesting study evaluated the TyG-related indices as a predictor for MAFLD. It revealed that the TyG-BMI index had the best sensitivity and specificity among TyG-related indices, especially for lean MAFLD and female MAFLD. So these results will be useful for the early detection of MAFLD in an easy and non-invasive way. I have a few comments for the authors: Language and writing issues: 1. On line 22, page 4: "formly" should be "formerly". The author should double-check other parts of the manuscript to detect other typos. 2. On line 48, page 4, SAM should be written in unabbreviated form because it was first mentioned in the introduction section. 3. The word "flowchart" in line 39, page 6, seems inappropriate. It should be replaced with the correct word related to the context. 4. In Table 1, line 54, page 6, it was written "Gender (M)" with certain numbers in the MAFLD and non-MAFLD columns. For me, it's a bit difficult to understand. Why not write "Male" and "Female" and then write specific numbers in related columns? 5. The P-values in Table 2, rows 4 – 12, page 8, which were written 0.000, should be written <0.0001 to show very high significance results. Methods 1. The authors should construct a detailed flowchart to determine the number of 20,922 subjects in this study. How many participants who underwent medical examinations between January 2021 – December 2021 at the Affiliated Hospital of Xuzhou Medical University met the inclusion and exclusion criteria? 2. Were the TyG-related indices equations written in lines 45 – 51, page 5, formulated by the authors or referring to previous studies? If the authors formulated them, they should write each equation's derivation. If referring to previous research, the source(s) should be cited.

	3. In diagnosing MAFLD, the authors referred to the flowchart for the proposed "positive" diagnostic criteria for MAFLD (Figure 1) from Eslam M et al. J Hepatol. 2020 Jul;73(1):202-209. DOI: 10.1016/j.jhep.2020.03.039, but it must be added to the reference list and cited in the text. 4. Because the diagnosis of NAFLD in this study only used hepatic ultrasonography and not in other ways as written in the diagnostic criteria, the authors should clearly write it in the "Diagnosis of MAFLD" section, as stated in the abstract. Results: 1. It is better to write how many male and female subjects were diagnosed with MAFLD and non-MAFLD, respectively. 2. It is also better to write how many of each BMI subgroup were diagnosed with MAFLD and non-MAFLD. Discussion The author concluded that TyG-BMI might be ideal for predicting lean MAFLD. Based on the formula in the methods section, the TyG-BMI index is obtained by multiplying the TyG index by the BMI, which means that the higher the subject's BMI, the higher the TyG-BMI index. However, the authors need to clearly write down the interpretation and rationale for the conclusions above so that the TyG-BMI index can be an ideal predictor for lean MAFLD and how it compares with the TyG-WC? Reference Reference No. 8 and 24 are the same.

REVIEWER	Tarantino, Giovanni Federico II University Medical School, ClinandExpert Medicine
REVIEW RETURNED	30-Jan-2023

GENERAL COMMENTS	WC should be presented according to gender and consequently also TyG-WC. NAFLD and MAFLD do not always are the same disease, thus a note of caution should be posed. NAFLD/MAFLD with their main mechanism that insulin resistance is linked also to extra-hepatic cancer, such as bladder cancer, as evident in...Association of NAFLD and Insulin Resistance with Non Metastatic Bladder Cancer Patients: A Cross-Sectional Retrospective Study. J Clin Med. 2021 Jan 18;10(2):346. doi: 10.3390/jcm10020346. PMID: 33477579; PMCID: PMC7831331.

REVIEWER	Lyu, Quanjun Zhengzhou University, Nutrition and Food Hygiene
REVIEW RETURNED	10-Feb-2023

GENERAL COMMENTS	Chang evaluated the relationship of Triglyceride glucose-body mass index with MAFLD. and found that TyG-BMI was associated with higher odds of MAFLD. The topic is interesting and useful for identifying participants with higher risk of MAFLD. However, I have several concerns: 1. The 95%CI is too wide, especially for the 4th quartiles(263.25-551.05), which suggested that the result is not robust. Maybe the number of cases is to small? Please clarify the reason. At least, please discuss this as a limitation. 2. The is a cross-sectional study, so the predictive value shoud be discuss carefully. 3. Please clarify whether the study was approved by the local ethic board.

	4. Page 6 line 8, please specify the detailed criterion of liver steatosis

VERSION 1 – AUTHOR RESPONSE

Reviewer1: Dr. Ika Yustisia, Hasanuddin University

Comments to the Author:

MAFLD is a health threat often overlooked because it is silent, and its prevalence in non-obese individuals is quite high. This interesting study evaluated the TyG-related indices as a predictor for MAFLD. It revealed that the TyG-BMI index had the best sensitivity and specificity among TyG-related indices, especially for lean MAFLD and female MAFLD. So these results will be useful for the early detection of MAFLD in an easy and non-invasive way.

I have a few comments for the authors:

Language and writing issues:

1. On line 22, page 4: "formly" should be "formerly". The author should double-check other parts of the manuscript to detect other typos.

- Thanks for your careful review, we revised this spelling mistake and double-check the whole manuscript carefully to avoid language errors.

2. On line 48, page 4, SAM should be written in unabbreviated form because it was first mentioned in the introduction section.

- We are sorry for this kind of mistake, SAM is abbreviated form San Antonio Metabolism, we revised it on line 4, page 4 in the revised manuscript and revised the whole manuscript to avoid similar mistakes.

3. The word "flowchart" in line 39, page 6, seems inappropriate. It should be replaced with the correct word related to the context.

- Thanks for your comment, the word "flowchart" here is indeed inappropriate. We have replaced the original sentence with the following: "The baseline characteristics of the study subjects is shown in Table 1" on lines 16-17, page 6 in the revised manuscript.

4. In Table 1, line 54, page 6, it was written "Gender (M)" with certain numbers in the MAFLD and non-MAFLD columns. For me, it's a bit difficult to understand. Why not write "Male" and "Female" and then write specific numbers in related columns?

- Thanks for your suggestion, we have replaced "Gender (M)" with "Male (%)" to better describe the certain numbers and proportions of males in the MAFLD and non-MAFLD group in Table 1 in the revised manuscript.

5. The P-values in Table 2, rows 4 – 12, page 8, which were written 0.000, should be written <0.0001 to show very high significance results.

- We revised these expressions in Table 2 and double-check the whole manuscript carefully to avoid similar errors.

Methods

1. The authors should construct a detailed flowchart to determine the number of 20,922 subjects in this study. How many participants who underwent medical examinations between January 2021 –

December 2021 at the Affiliated Hospital of Xuzhou Medical University met the inclusion and exclusion criteria?

- Thanks for your critical review and suggestion, we constructed a detailed flowchart (Figure 1, Flowchart of the study design) to show the detailed process of inclusion and exclusion.

2. Were the TyG-related indices equations written in lines 45 – 51, page 5, formulated by the authors or referring to previous studies? If the authors formulated them, they should write each equation's derivation. If referring to previous research, the source(s) should be cited.

- The TyG-related indices equations were derived from previous studies, which have been cited as references 15-16 in the revised manuscript.

3. In diagnosing MAFLD, the authors referred to the flowchart for the proposed "positive" diagnostic criteria for MAFLD (Figure 1) from Eslam M et al. J Hepatol. 2020 Jul;73(1):202-209. DOI: 10.1016/j.jhep.2020.03.039, but it must be added to the reference list and cited in the text.

- Thanks for your reminder, we have added it to the reference list (reference 18) and cited in the revised manuscript.

4. Because the diagnosis of NAFLD in this study only used hepatic ultrasonography and not in other ways as written in the diagnostic criteria, the authors should clearly write it in the "Diagnosis of MAFLD" section, as stated in the abstract.

- Thanks for your careful and helpful suggestion, we replaced the original sentence: "The proposed criteria were based on liver steatosis (detected either by medical imaging, blood biomarkers/scores or by liver histology)" with the following: "The diagnosis of MAFLD was based on the ultrasonically diagnosed hepatic steatosis" after careful consideration on lines 17-18, page 5 in the revised manuscript.

Results:
1. It is better to write how many male and female subjects were diagnosed with MAFLD and non-MAFLD, respectively.

- Thanks for your suggestion, which made the "Results" section more comprehensive. Thus, we supplemented the analysis of MAFLD prevalence in the enrolled participants and described the numbers and proportions of MAFLD individuals in males and females on lines 17-19, page 6 in the revised manuscript.

2. It is also better to write how many of each BMI subgroup were diagnosed with MAFLD and non-MAFLD.

- Similarly, we also supplemented the analysis of the prevalence MAFLD in all three BMI subgroups on lines 19-21, page 6 in the revised manuscript.

Discussion
The author concluded that TyG-BMI might be ideal for predicting lean MAFLD. Based on the formula in the methods section, the TyG-BMI index is obtained by multiplying the TyG index by the BMI, which means that the higher the subject's BMI, the higher the TyG-BMI index. However, the authors need to clearly write down the interpretation and rationale for the conclusions above so that the TyG-BMI index can be an ideal predictor for lean MAFLD and how it compares with the TyG-WC?

- Lean MAFLD is not a benign or stable state as expected, and reduced BMI levels are necessarily representative of a metabolically healthy state. BMI alone cannot provide a comprehensive reflection of MAFLD because of the neglect of IR. Similarly, although based on the formula of TyG-BMI, we could reasonably infer that the higher the subject's BMI, the higher the TyG-BMI index. However, our study observed that increased TyG-BMI levels were positively correlated with the risk of MAFLD in lean individuals. Perhaps this is why the role of "TyG" has not been addressed, we may ignore its dynamic changes in various metabolic states. The effect of "TyG" increase might be far greater than BMI decrease in lean individuals with MAFLD. That is to say, IR caused by excessive accumulation of visceral fat may be more pronounced in the development of MAFLD in lean individuals. Therefore, simply focusing on decreased BMI or increased TyG does not seem to be suitable for the prediction of lean MAFLD. Only by considering the TyG-BMI index as a whole can we better understand its predictive value in lean MAFLD. The revised parts have been marker in red and green colors in the revised manuscript.

As for the comparison of TyG-BMI and TyG-WC, we performed the nonparametric DeLong test to assess the AUC differences of predictive values in each subgroup analysis. Although the TyG-WC index also presented some predictive value for MAFLD, we observed that it was not quite stable and fluctuated in different subgroups. In lean MAFLD, the predictive value of the TyG-BMI index was significantly higher than than of the TyG-WC (Figure 5). From the analysis results of the whole and each subgroup, the TyG-BMI index seems to be more promising in predicting MAFLD than the TyG-WC index. Therefore, did not describe the TyG-WC index in detail in the Discussion section, but gave a brief description of its performance in the first paragraph, the added part has been marked in red.

Reference
Reference No. 8 and 24 are the same.

- We are sorry for our carelessness, we have removed the duplicate reference and renumbered the reference list in the revised manuscript, thanks for your careful review again.

Reviewer 2: Prof. Giovanni Tarantino, Federico II University Medical School
Comments to the Author:
WC should be presented according to gender and consequently also TyG-WC.

- Thanks for your suggestion, we supplemented the analysis of WC and TyG-WC according to gender in both Table 1 and on lines 27-29, page 6 in the revised manuscript.

NAFLD and MAFLD do not always are the same disease, thus a note of caution should be posed. NAFLD/MAFLD with their main mechanism that insulin resistance is linked also to extra-hepatic cancer, such as bladder cancer, as evident in...Association of NAFLD and Insulin Resistance with Non Metastatic Bladder Cancer Patients: A Cross-Sectional Retrospective Study. J Clin Med. 2021 Jan 18;10(2):346. doi: 10.3390/jcm10020346. PMID: 33477579; PMCID: PMC7831331.

- Thanks for your comment and helpful reminder, MAFLD is linked to a variety of adverse clinical sequelae, your comment really helped us to better understand the the dangers of MAFLD and meanwhile, helped us to enrich the "Introduction" section. Thus, we added "Association of NAFLD and Insulin Resistance with Non Metastatic Bladder Cancer Patients: A Cross-Sectional Retrospective Study. J Clin Med. 2021 Jan 18;10(2):346. doi: 10.3390/jcm10020346. PMID: 33477579; PMCID: PMC7831331" to our reference list and properly cited it in the revised manuscript.

Reviewer 3: Dr. Quanjun Lyu, Zhengzhou University, The first Affiliated Hospital of Zhengzhou University

Comments to the Author:

Chang evaluated the relationship of Triglyceride glucose-body mass index with MAFLD. and found that TyG-BMI was associated with higher odds of MAFLD. The topic is interesting and useful for identifying participants with higher risk of MAFLD. However, I have several concerns:

1. The 95%CI is too wide, especially for the 4th quartiles (263.25-551.05), which suggested that the result is not robust. Maybe the number of cases is too small? Please clarify the reason. At least, please discuss this as a limitation.

- Thanks for your careful and critical review, this comment is really helpful. The study was conducted at Health Management Department in our local hospital from January 2021 to December 2021. We included all subjects meeting the eligibility criteria for the year, but only 20,922 patients were excluded after careful screening of exclusion criteria. However, the results showed that some 95%CIs were too wide, especially for the 4th quartiles (263.25-551.05) of the TyG-BMI index. After a double-check of the analysis process and careful consideration, we all agreed with you that this may be due to insufficient sample size. Thus, we discussed this as a limitation and revised some original descriptions concerning "large-scale sample size" or "large-scale population" throughout the whole manuscript. The revised parts have been marked with red and green colors.

2. The is a cross-sectional study, so the predictive value should be discuss carefully.

- Thanks for your helpful reminder. Cross-sectional studies cannot establish causality, thus the predictive value should be discussed carefully. To make this clear, we supplemented a limitation in the "Strengths and limitations of this study" section on lines 21-22, page 3 in the revised manuscript and modified some descriptions that were too specific and replaced them with cautious words throughout the manuscript including "might be", "promising" and so on.

3. Please clarify whether the study was approved by the local ethic board.

- Thanks for your suggestion, we supplemented a ethical approval statement both in the sections of "Methods" and "Declarations".

4. Page 6 line 8, please specify the detailed criterion of liver steatosis

- Thanks for your suggestion, we supplemented a detailed criterion of liver steatosis on lines 23-26, page 5 in the revised manuscript.

We hope that your comments have been addressed accurately. If any further action is needed, please let us know immediately. Thanks for your careful review and the constructive comments again, and we look forward to hearing back from you.

VERSION 2 – REVIEW

REVIEWER	Yustisia, Ika Hasanuddin University, Biochemistry
REVIEW RETURNED	21-Mar-2023

GENERAL COMMENTS	Congratulations and success to the authors. I am delighted to have had the opportunity to review your manuscript so that it adds to my knowledge and insight.

REVIEWER	Tarantino, Giovanni

	Federico II University Medical School, ClinandExpert Medicine
REVIEW RETURNED	07-Mar-2023

GENERAL COMMENTS	Authors correctly answered comments

REVIEWER	Lyu, Quanjun Zhengzhou University, Nutrition and Food Hygiene
REVIEW RETURNED	13-Mar-2023

GENERAL COMMENTS	1.The abstract need to be written again according to the structure. 2.The strengths and limitations of this study should be list in the last paragraph in the discussion 3. The 2. Methods should be changed into 2.Subjects and Methods and then the 1.1 Populations or Subjects 4. The author should describe the software they used in the data analysis including the name and their source. 5. As a general comment, there are MANY mistakes in written and grammar. It is better for the author to review the whole article carefully and find the errors or mistakes in grammar or ask someone whose native language is English to correct the errors.

VERSION 2 – AUTHOR RESPONSE

Reviewer1: Dr. Ika Yustisia, Hasanuddin University

Comments to the Author:

Congratulations and success to the authors. I am delighted to have had the opportunity to review your manuscript so that it adds to my knowledge and insight.

Our reply: Thanks for your careful review and approval.

Reviewer 2: Prof. Giovanni Tarantino, Federico II University Medical School

Comments to the Author:

Authors correctly answered comments.

Our reply: Thanks for your careful review and approval.

Reviewer 3: Dr. Quanjun Lyu, Zhengzhou University, The first Affiliated Hospital of Zhengzhou University

Comments to the Author:

1.The abstract need to be written again according to the structure.

Our reply: Thanks for your suggestion, we carefully studied the formatting guidelines of BMJ open for abstract. A structured abstract should include all the following where appropriate, objectives, design, setting, participants, interventions (not applicable), primary and secondary outcome measures, results and conclusions. Consider these requirements as well as recently published articles in BMJ open, we rewrote this section to meet these requirements and improve the readability and clarity. The current

layout and format of "ABSTRACT" fully meet the requirements of the journal after consulting a professional editing service.

2.The strengths and limitations of this study should be list in the last paragraph in the discussion

Our reply: We have discussed the strengths and limitations of this study at the end of the article. However, the journal requires that each article should include a "Strengths and limitations of this study" section after the abstract. Therefore, this section is per journal guidelines and should not be deleted. Thanks for your kind reminder sincerely!

3. The 2. Methods should be changed into 2.Subjects and Methods and then the 1.1 Populations or Subjects

Our reply: Thanks for your suggestion. Based on your suggestion and the formatting guidelines, we revised the "2. Methods" section to "PARTICIPANTS and METHODS" and then "Study design and populations", "Health survey examinations and laboratory measurements", "Patient and public involvement" ,"Diagnosis of MAFLD" and "Statistical analysis".

4. The author should describe the software they used in the data analysis including the name and their source.

Our reply: Thanks for your kind reminder, we have attached a detailed description of the software used. We revised "Statistical analysis was performed with SPSS 22.0 and MedCalc 16.2." to "Statistical analysis was conducted using SPSS 22.0 (IBM Corp, Armonk, NY, USA) and MedCalc 16.2 (MedCalc Software Ltd, Ostend, Belgium)."

5. As a general comment, there are MANY mistakes in written and grammar. It is better for the author to review the whole article carefully and find the errors or mistakes in grammar or ask someone whose native language is English to correct the errors.

Our reply: We revised the whole manuscript carefully to avoid mistakes in written and grammar. In addition, we consulted a professional editing service to check and improve the quality of writing with an Editing Certificate.