

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between TyG index and long-term mortality of critically ill patients: a retrospective study based on the MIMIC database
AUTHORS	Dai, Lingli; Yu, Yun; Wang, Kunling; Hu, Cuining; Wu, Dan; Shan, Shan

VERSION 1 – REVIEW

REVIEWER	Liu, Yihai Nanjing Medical University
REVIEW RETURNED	09-Jun-2022

GENERAL COMMENTS	<p>Shan et al utilized a large database (MIMIC III) to explore the association between TyG index and long-term mortality of critically ill patients. They found that TyG index was negatively associated with 360-day mortality, not in-hospital or 30-day mortality of critically ill patients. This study is innovative and meaningful, which could be considered publication after correcting some mistakes.</p> <p>1. Abstract, Line 37: "were" as "was"</p> <p>2. Introduction, Line 60: "outcome" as "outcomes" Line 61: "is" as "was" Line 62: delete "admission"</p> <p>3. Results Line 120: "hospital" as "ICU" Line 136: "1-unit" as "one-unit"</p> <p>4. Discussion Line 155: "surrogated" as "surrogate" Line 171: "in" as "of" and "have predicted" as "predict"</p>
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REVIEWER	Wei , Zhonghai Nanjing Drum Tower Hospital
REVIEW RETURNED	07-Jul-2022

GENERAL COMMENTS	<p>1. The patients in the ICU includes various diseases, which would influence the mortality. The current study did not consider this factor</p> <p>2. In the Table 1, when the author completed the comparisons among the four groups, the mutiple comparisons between any two group should be performed to identify the origins of the differences. The trend test might be more suitable.</p> <p>3. In Figure 3C, there were apparent cross among the KM curves. Therefore, the authors should further analyze and illustrate the</p>
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	<p>origins of the statistical differences in the KM plot.</p> <p>4. Many previous studies have found that higher TyG is associated with the higher mortality, which is opposite to the current study. The author should discuss the issue in the discussion section.</p> <p>Furthermore, the contents in the discussion should be enriched.</p>
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REVIEWER	Tarantino, Giovanni Federico II University Medical School, ClinandExpert Medicine
REVIEW RETURNED	22-Aug-2022

GENERAL COMMENTS	<p>Authors should be congratulated for approaching this interesting topic.</p> <p>Authors could add in the introduction that TyG, as surrogate marker of insulin resistance, has been found associated to bladder cancer that is widespread among men, 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.</p> <p>Multicollinearity, as authors know very well, is a common problem when estimating linear or generalised linear models, including multivariate Cox regression. It occurs when there are high correlations among predictor variables, leading to unreliable and unstable estimates of regression coefficients.</p> <p>How did they deal with this problem?</p> <p>Finally, this is only an observation and not a deep criticism, i.e, if your variable of interest is continuous, you almost always lose information by splitting the variable into a categorical effect.... What about it?</p> <p>Lacking the HOMA determination is not a limitation because for some authors TyG is as reliable as HOMA in assessing insulin resistance, as evident in...TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. Diabetes Res Clin Pract. 2011 Sep;93(3):e98-e100. doi: 10.1016/j.diabres.2011.05.030. Epub 2011 Jun 12. PMID: 21665314.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Yihai Liu, Nanjing Medical University

Comments to the Author:

Shan et al utilized a large database (MIMIC III) to explore the association between TyG index and long-term mortality of critically ill patients. They found that TyG index was negatively associated with 360-day mortality, not in-hospital or 30-day mortality of critically ill patients. This study is innovative and meaningful, which could be considered publication after correcting some mistakes.

1. Abstract,

Line 37: "were" as "was"

Response: We have corrected it.

2. Introduction,

Line 60: "outcome" as "outcomes"

Line 61: "is" as "was"

Line 62: delete "admission"

Response: We have corrected them.

3. Results

Line 120: "hospital" as "ICU"

Line 136: "1-unit" as "one-unit"

Response: We have corrected them.

4. Discussion

Line 155: "surrogated" as "surrogate"

Line 171: "in" as "of" and "have predicted" as "predict"

Response: We have corrected them.

Reviewer: 1

Competing interests of Reviewer: None.

Reviewer: 2

Zhonghai Wei , Nanjing Drum Tower Hospital

Comments to the Author:

1. The patients in the ICU includes various diseases, which would influence the mortality. The current study did not consider this factor

Response: Referring to previous publications, we have added chronic kidney disease (CKD) in Table 1. Therefore, comorbidities include coronary artery disease (CAD), hypertension (HBP), diabetes (DM), chronic obstructive pulmonary disease (COPD), and CKD. We have also adjusted these factors in multivariable logistic models.

2. In the Table 1, when the author completed the comparisons among the four groups, the multiple comparisons between any two group should be performed to identify the origins of the differences. The trend test might be more suitable.

Response: We agreed with your suggestions. The multiple comparisons between any two groups generate 6 kind of p value, which influence the layout of labels in Table 1. Besides, these comparisons don't affect our results of multivariable regression models. Therefore, we only label the trend test in Table 1.

3. In Figure 3C, there were apparent cross among the KM curves. Therefore, the authors should further analyze and illustrate the origins of the statistical differences in the KM plot.

Response: We have added the multiple comparisons as you suggested and labeled them in the Figure legend.

"Figure 3. The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B), $P < 0.05$: Q2 vs. Q1, Q2 vs. Q3, Q2 vs. Q4; and 360-day mortality (C), $P < 0.05$: Q1 vs. Q2, Q1 vs. Q3, Q1 vs. Q4, Q2 vs. Q4, Q3 vs. Q4."

4. Many previous studies have found that higher TyG is associated with the higher mortality, which is opposite to the current study. The author should discuss the issue in the discussion section. Furthermore, the contents in the discussion should be enriched.

Response: We have added the explanations in the discussion.

“The difference could be that we included more diseases in ICU and followed a longer time. Besides, a higher TyG index may be related to a good nutrition status and be compensatory for the development of various diseases.”

Reviewer: 2

Competing interests of Reviewer: no competing interests

Reviewer: 3

Prof. Giovanni Tarantino, Federico II University Medical School

Comments to the Author:

Authors should be congratulated for approaching this interesting topic.

Response: Thanks for your review.

Authors could add in the introduction that TyG, as surrogate marker of insulin resistance, has been found associated to bladder cancer that is widespread among men, 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.

Response: We have added the reference in the introduction as you suggested.

Multicollinearity, as authors know very well, is a common problem when estimating linear or generalised linear models, including multivariate Cox regression. It occurs when there are high correlations among predictor variables, leading to unreliable and unstable estimates of regression coefficients.

How did they deal with this problem?

Response: Thanks for valuable suggestions. We have established a linear regression model setting TyG index as a dependent variable and found that the coefficients of all variables are <0.8 and the VIFs are <2, suggesting that the included variables in multivariable models have no significant multicollinearity with TyG index.

Finally, this is only an observation and not a deep criticism, i.e, if your variable of interest is continuous, you almost always lose information by splitting the variable into a categorical effect... What about it?

Response: We have also analyzed the association between TyG index as a continuous variable and 360-day mortality in Table 2. As shown, it suggested that per one-unit increasement of TyG was associated with 0.85-fold lower risk of mortality (HR 0.85, 95% CI [0.79, 0.92]; P<0.001).

Lacking the HOMA determination is not a limitation because for some authors TyG is as reliable as HOMA in assessing insulin resistance, as evident in...TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. Diabetes Res Clin Pract. 2011 Sep;93(3):e98-e100. doi: 10.1016/j.diabres.2011.05.030. Epub 2011 Jun 12. PMID: 21665314.

Response: We have deleted the limitation as you suggested.

Reviewer: 3

Competing interests of Reviewer: No conflicts of interest

VERSION 2 – REVIEW

REVIEWER	Liu, Yihai Nanjing Medical University
REVIEW RETURNED	09-Sep-2022

GENERAL COMMENTS	The authors have addressed my questions, and I recommend it for acception.
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REVIEWER	Wei , Zhonghai Nanjing Drum Tower Hospital
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REVIEW RETURNED	25-Sep-2022
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GENERAL COMMENTS	No more comments
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REVIEWER	Tarantino, Giovanni Federico II University Medical School, ClinandExpert Medicine
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REVIEW RETURNED	09-Sep-2022
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GENERAL COMMENTS	Authors correctly answered comments.
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