Revision for “Development and validation of a risk prediction score for the severity of acute hypertriglyceridemic pancreatitis in Chinese patients” (Manuscript NO.: 78164, Retrospective Study)

Dear editors：

We thank you and the reviewers for giving us the opportunity to revise our manuscript. We have carefully studied the comments raised by the reviewers and editors, and revised the paper accordingly. The following are point-by-point responses to the editors’ and reviewers’ comments. All the modifications have been highlighted in yellow in the revised manuscript.

Should you have any questions, please contact us without hesitation.

We look forward to your favorable decision.

Yours truly,

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Editors:

1. Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Answer: Thank you for your comment. We had revised the manuscript according to the reviewers' suggestion and sent our revised manuscript to a professional English language editing company AJE (https://www.aje.cn/)to polish the manuscript.

2. Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table

should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Answer: Thank you for your comment. We had revised the manuscript according to you and reviewers' suggestion.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

The study establishes a nomogram that identifying AHTGP patients who may develop SAP at an early stage, which is of great interest for clinical application.

Answer: Thank you for your positive advice.

1. However, The study lacked clinical decision analysis for the development and the validation group.

Answer: Thank you for your constructive comment. Actually, this study was a single-center study, which lacked multicenter data for external validation. We did the clinical decision analysis based on the whole cohort. The relatively small sample size limited our ability to perform the clinical decision analysis for development and the validation group separately. In the follow-up study, we will perform a multi-center, large-sample, prospective study to verify our risk prediction score.

2.Additionally, it is necessary to supplement the full citation source and check the references carefully.

Answer: Thank you for your comment. We had added the relevant citation (highlighted in yellow) in the paragraph 2 of the materials and methods (reference 18), the paragraph 4 of the materials and methods (reference6, 14, 19-30) and the

paragraph 3 of the discussion (reference 35). Thank you so much for your careful review, we modified the inappropriate expressions in the first and second sentences of the first paragraph in the introduction. We corrected the contents of the seventh sentence of the second paragraph in the introduction based on reference 12.

3. The authors must correct many grammatical mistakes in the manuscript.

Answer: Thank you for your comment. I corrected the grammatical mistakes and inappropriate expressions that you marked in my manuscripts. We had sent our revised manuscript to a professional English language editing company AJE (https://www.aje.cn/)to polish the manuscript.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors:

The paper addresses an important issue. HTG is known to cause the most severe pancreatitis. The paper should be published after revision.

Answer: Thank you for the positive evaluation.

1. The list of publications is very incomplete. Many important cohorts are not cited or discussed in this article. Eg: PMID: 32402696, PMID: 35659855, PMID:30237456, etc.

Answer: Thank you for your comment. We went through the relevant literature mentioned above carefully. The evidence indicates that patients with HTG present a more severe form of pancreatitis. These previous studies confirmed that HTG dose-dependently increases the complications and severity of AP. However, a meta-analysis including 11,965 patients from 16 eligible studies found no significant difference in AP severity based on the extent of HTG. We explored the association between HTG levels and the severity of AHTGP using univariable and multivariable logistic regression (Table 2). We found that there was a trend for HTG to dose-dependently increase the severity of AHTGP. However, the *P* values were not significant, probably because of our small sample size. The next step is to conduct a multicenter prospective cohort study with a large sample size to further explore this

important issue. (The relevant content is in the paragraph3 of the introduction, the paragraph2 of the results and the paragraph5 of the discussion)

2. HTG is known to be dose dependent. Besides dose dependence, the metabolic syndrome associated with HTG is also an important factor. How did BMI, Hypertension, Diabetes develop in these patients? It would also be important to discuss it with references.

Answer:

We quite appreciate your constructive comment. We went through the relevant literature carefully (Eg: PMID: 32402696, PMID: 35659855, PMID: 30237456, PMID: PMID: 32425564, PMID: 31620021, etc.). We found that TG levels dose-dependently increase the severity of AP and the presence of metabolic syndrome and its components were associated with increasing AP severity.

We included TG level(group1: < 11.3 mmol/L； group2: 11.3-22.59 mmol/L； group3: ≥ 22.6 mmol/L), BMI, history of hypertension and diabetes in the univariable and multivariable logistic regression to explore the relationship with severity of AHTGP. Compared to patients with TGs lower than 11.3 mmol/L, we found that patients with TGs above 22.6 mmol/L had a higher OR (OR 5.95, 95% CI: 0.56, 62.75) than patients with TGs between 11.3 and 22.59 mmol/L (OR 4.20, 95% CI: 0.40, 44.25). We speculated that there was a trend for HTG to dose-dependently increase the severity of AHTGP. Our study showed that there was a trend that the presence of obesity (OR: 1.08, 95% CI: 0.94-1.24), diabetes (OR: 1.27, 95% CI: 0.38-4.24) and

hypertension (OR: 1.02, 95% CI: 0.99-1.06) increased the risk of SAP. However, the *P* values were not significant, probably because of our small sample size. The small sample size of our study makes it difficult to make extensive recommendations. The next step is to conduct a multicenter prospective cohort study with a large sample size to further explore this important issue. (The relevant content is in the paragraph 2 of the results and the paragraph5 of the discussion)

Our study showed that age, the reduction in ApoA1 and Ca^{2+}, and the presence of pleural effusion were independent risk factors for SAP. Considering that the level of TG, BMI and history of hypertension and diabetes may also be important predictors, we constructed three predictive models based on different combinations of these factors; Model 1 (including age, ApoA1, and pleural effusion), Model 2 (including age, ApoA1, Ca^{2+} and pleural effusion) and Model 3 (including age, diabetes, hypertension, BMI, TG, ApoA1 and pleural effusion). ROC curve analysis was applied to evaluate the diagnostic performance of the three models (Supplementary Figure 1). Model 1 had no significant differences in AUC and IDI between Model 2 and Model 3 (Supplementary Table 1). For clinical convenience and easy application, we selected Model 1 with the fewest factors as the final risk prediction score and constructed the nomogram. (The relevant content is in the paragraph 4 of the results).

3. The EASY-APP (first AI model) has recently been published. Has a comparison been made with this system? This cannot be seen in the figures.

Answer: We quite appreciate your constructive comment. The EASY-APP was

recently developed to predict the severity of AP. It consists of four parts (personal details, anamnestic data, admission data and blood test results) with a total of 23 predictors. We collected the data and calculated the predicted severity scores for all subjects on a web application (http://easy-app.org/) in the Streamlit Python-based framework. An ROC curve analysis was applied to evaluate the diagnostic efficacy of the new risk prediction score (referred to as AAP) and EASY score. The AUC values of AAP and EASY score to predict SAP were 0.929 (95% CI: 0.889-0.958) and 0.807 (95% CI: 0.743-0.871), respectively (Figure 4). IDIs were employed to compare the discriminative ability between the new model and the EASY score. These results demonstrated that AAP has a greater potential for accurately predicting SAP than the EASY score (Table 4).DCA was used to compare the clinical usability and benefits of the scores. DCA plots showed that AAP had greater net benefits than EASY score for predicting the severity of AP patients (Figure 5). Although EASY score achieved a high AUC in predicting SAP, it was still the lowest among the AAP and four commonly used AP scoring systems. This may suggest that the prediction ability of the EASY model is limited for pancreatitis caused by HTG (The relevant content is in the paragraph 3 of the introduction, the paragraph 5 and the paragraph6 of the results and the paragraph 2 of the discussion).