Dear Editor,

Many thanks for your E-mail on our manuscript entitled " Incidence, prevalence, and comorbidities of chronic pancreatitis: A 7 - year population - based study (NO.84755). All comments and suggestions from the reviewers are greatly appreciated. We cherish this opportunity for major revisions. According to your suggestions, the manuscript has been revised in point by point way. We try to improve it to meet the publication requirements of World Journal of Gastroenterology.

Enclosed please find the response to the reviewers and the revised manuscript with revised part in blue font. If there are any points unclear, please feel free to contact us.

With kind regarding

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Point-by-point Response

Reviewer 1:

This study provides vital evidence to the increasing incidence of chronic pancreatitis in one province of China and increasing prevalence of it compared to a study in 2009. However, it fails to show the disease pattern and its progression. The following points may need to be looked into.

Comment 1: The definition does not seem to characterize the condition.

Response 1: The definition of CP and its comorbidities have been added in the section of introduction or method.

Comment 2: No diagnostic criteria or disease classification is indicated.

Response 2: The diagnostic criteria and classification of CP have been added in the section of methods.

Comment 3: Risk factors for chronic pancreatitis, comorbidities and sequelae of chronic pancreatitis are described without distinction. Presence of comorbidities does alter the implication of management of any disease and not particularly CP.

Response 3: It is a pity that the database of HIC-SC records could not provide the information on risk factor and sequelae of CP patients. This limitation has been mentioned in the section of discussion.

Comment 4: CP is pictured to present with "recurrent bouts of pancreatitis, with later insidious progression" which is not the norm in all cases.

Response 4: This sentence has been revised as: "Although some CP may begin with one or recurrent bouts of pancreatitis, approximately 50% of CP patients had no history of acute pancreatitis".

Comment 5: It is stated categorically that "no treatment is available to alter the course of the disease", though many studies claim to do so.

Response 5: This sentence has been revised as: "The current strategies for CP include relieving symptoms, preventing disease progression, and management of complications (1). CP may be a heavy health burden worldwide, consuming many medical resources due to less curative treatments that can effectively reverse the course of the disease (2-4).".

Comment 6: The statement that "reliable epidemiological data on the incidence and prevalence is rare" may undermine the strength of published data. So also, the statement that "Population based studies about CP in China is lacking for decades" negates the publications of authors like Wang et al. (13).

Response 6: These sentences have been revised as: "China is one of the most populous countries in the world. However, there are only few epidemiological studies on CP. These data were usually based on one or several databases of hospitals with small sample sizes (5, 6). Population-based epidemiological data may provide a better picture of the incidence and prevalence of CP in China."

Comment 7: Patients with missing data on sex were excluded do not speak well of the data.

Response 7: The missing data have been found and added in the section of result (including tables and figures).

Comment 8: This article is based on the discharge diagnosis of CP obtained from ESR of HIC –SP Records. No diagnostic criteria of CP or classification of CP are indicated.

Response 8: The diagnosis and classification of CP have been added in the section of methods. "It has been widely accepted in China that CP was defined as a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function (4, 7). In clinical practice, CT or MRI has been usually recommended as the first-line test for the patients with clinical symptoms of an inflammatory disorder of the pancreas (such as previous episode of acute pancreatitis, characteristic pain, and/or

maldigestion) because it is universally available, reproducible. The major image characteristics of CP include pancreatic atrophy, fibrosis, duct distortion and strictures, stones in pancreatic ducts or multiple calcifications distributed in the entire pancreas, etc. EUS, because of its invasiveness, often be used only if the diagnosis is in question after CT or MRI. The diagnosis of CP in some patients is established by histopathological examination after surgery due to unexplained pancreatic mass. Therefore, patients were included as individuals with a discharge diagnosis of CP in the HSRs in HIC-SC according to the ICD-10 code K86.102 for CP, K86.852 for pancreatic atrophy, K86.811 for pancreatic calcifications, K86.809 for stones in pancreatic ducts, K86.806/807 for duct distortion and strictures, K86.154 for pancreatic fibrosis, K86.201 for pancreatic cyst, K86.804 for pancreatemphraxis, K86.901/902 for pancreatic mass. Furthermore, this study classified CP according to the ICD-10 codes K86.051 for alcoholic CP, K86.153 for autoimmune pancreatitis, K86.151 for biliary pancreatitis. Patients with conflicting information recorded, i.e., different birth dates at each admission, were excluded."

The data is not verified by independent observers.

The electronic hospitalization summary reports (HSRs) came from various hospitals in Sichuan Province and were uniformly managed by Health Information Center of Sichuan Province. The database is huge, with tens of millions of hospital discharge records. It is impossible to verify the accuracy of CP diagnosis with independent observers. This limitation has been discussed later. As we know, the periodic academic exchanges and routine education and training have made that CP diagnosis in Sichuan Province generally reaches the aforementioned consensus.

The references quoted 22-24 were based on records from one province of SC only.

It has been explained as: "HIC-SC has offered data for many scientific studies, verifying the reliability of the database."

No data on follow up is available.

It is a good suggestion. The follow-up on the basis of these data will be conducted near future.

Comment 9: The incidence described in this study is based on in patients only and hence it may not represent the true incidence of CP. (Though the verification of diagnosis of CP in outpatients is difficult, the fact that CP can be diagnosed in patients who do not need admission and the exact incidence of such is not discussed in this study. However, a multicenter study on CP, focuses on diagnosed patients (not only on admitted patients) and may present a definitive data on incidence than a population-based study based on only discharge records.

Response 9: It is true that the incidence of CP might be underestimated in our study based on only discharge records. So far, no database can fully describe the characteristics of CP prevalence. We fully agree that "CP can be diagnosed in patients who do not need admission". These CP patients may also not be included in outpatient database. Generally, the data quality of outpatient database is rather lower than those in the hospitalization. Therefore, the true incidence of CP may be overestimated with the outpatients and inpatients included according to a study based on commercial insurance databases of inpatients and outpatients in the USA (8). Although a multicenter study on CP focused on diagnosed patients may present a definitive data on incidence than a population-based study based on only discharge records, the incidence can only be predicted from a sample and may also be flawed by sampling error. This point has been discussed later.

Comment 10: No data is shown, to conclude, that "high quality and cost-effective care of CP patients is needed".

Response 10: We are very sorry for the inappropriate sentence, which has been deleted in the manuscript.

Reviewer 2:

INTRODUCTION - It's clear enough. The authors provided the main background. No major comments on this section.

1. METHODS

Comment 1: The authors should start with a subsection entitled "study design and population", where both these aspects are clearly stated and described, respectively.

Response 1: A subsection entitled "study design and population" has been added.

Comment 2: - IRB approval number and date should be provided.

Response 2: IRB approval number: 2022-296 has been added in the last two lines of the subsection of "Study design and population".

Comment 3: Inclusion and exclusion criteria should be clearly listed.

Response: The inclusion and exclusion criteria were added in the revised manuscript: "Therefore, patients were included as individuals with a discharge diagnosis of CP in the HSRs in HIC-SC according to the ICD‐10 code K86.102 for CP, K86.852 for pancreatic atrophy, K86.811 for pancreatic calcifications, K86.809 for stones in pancreatic ducts, K86.806/807 for duct distortion and strictures, K86.154 for pancreatic fibrosis, K86.201 for pancreatic cyst, K86.804 for pancreatemphraxis, K86.901/902 for pancreatic mass. … Patients with missing data on sex or with conflicting information recorded, i.e., different birth dates at each admission, were excluded."

Comment 4: It is not clear how all or which comorbidities were retrieved from the electronic database. This aspect and procedure should be precisely described.

Response 4: According to the suggestion, we added a subsection entitled "Identification of comorbidities" in the Methods section to describe the process of identifying comorbidities.

Comment 5: Overall, the methods section needs some important rearrangement and completion.

Response 5: Yes, we have done this. The methods section has been revised either extensively or intensively.

2. RESULTS

Comment 6: My feeling is that the results description should be expanded. - For instance, the pancreatic tumors and, in detail, malignancies are a very important and debated aspect of CP follow-up. Therefore, I recommend the authors to provide more information about the histological types of pancreatic tumors and the diagnostic timing over the clinical course of CP, which would be an important completion that I am sure can be retrieved from electronic databases. An additional table could help with this task.

Response 6: The data of study were extracted with the ICD-10 codes. Up to now, there is no ICD-10 codes for the histological type of pancreatic tumors (8,10). Also, it is impossible to get the diagnostic timing of pancreatic tumors over the clinical course of CP through the ICD-10 codes. Your suggestion is very important. It will be collected during our follow-up study near future.

Comment 7: Similar recommendation can be given for cardiovascular comorbidities and cerebrovascular comorbidities.

Response 7: According to your suggestion, the data on cardiovascular comorbidities and cerebrovascular comorbidities were listed in Table 3. The cardiovascular disease was defined as coronary heart disease, and the cerebrovascular disease was divided into hemorrhagic and ischemic ones. It is really very sorry that it is impossible to get the diagnostic timing of comorbidities over the clinical course of CP through the ICD-10 codes.

Comment 8: In general, I do not see any statistical analysis, except the descriptive one. - Notably, a comparison with non-CP population admitted during the study period to the same hospital would provide an interesting control group to compare the prevalence and incidence of comorbities and, thus, make additional conclusions. That would greatly increase the scientific value of this research and manuscript.

Response 8: Thanks for your suggestion. Continuous variables were showed as the means ± standard deviation (SD). Since this was a population - based study including all the permanent population of Sichuan Province during the observation period, no confidence intervals were provided for the estimates of incidence or prevalence rates. Statistical analysis such as Student's t test for continuous variables and the chi-squared test for categorical variables were used for comparison of statistics between genders and age groups. To investigate yearly trends, we performed analysis of variance test for linearity of scaled variables and the Cochran-Armitage trend test for categorical data. A 2-sided test with $p < 0.05$ was considered statistically significant.

With regarding to a comparison with non-CP population, the definition of non-CP population is rather difficult. It is unclear what would be the aim of such comparison. Thus, this study was focused on the description of the CP incidence, prevalence and its comorbidities. This study reported that diabetes (26.32%) was the most common comorbidity in CP patients. A comparison between diabetes with CP and without CP population would be interesting. But such comparison needs a well-design study which may be conducted near future.

3. DISCUSSION

Comment 9: This section should be revised according to the new information provided in the results and, thus, can be appropriately assessed after a first round of revision.

Response 9: Yes, the section of DISCUSSION has been revised extensively and intensively.

Comment 10: At first glance, I noticed that some comorbidities are not discussed so much. For instance, the malignancies are only mentioned in the discussion and, as mentioned, represent an important topic in CP patients (e.g. Pancreatitis and Pancreatic Cancer Risk. Technol Cancer Res Treat. 2023 Jan-Dec;22:15330338231164875. doi: 10.1177/15330338231164875).

Response 10: The discussion on comorbidities of CP has been expanded. Pancreatitis and pancreatic cancer risk have also been discussed.

Comment 11: Moreover, in this regard, the authors should at least mention the clinical and epidemiological differences with the other type of chronic pancreatitis, namely the autoimmune pancreatitis for which the oncological risk is also debated (see: Epidemiological aspects and immunological considerations. World J Gastroenterol. 2021 Jul 7;27(25):3825-3836. doi: 10.3748/wjg.v27.i25.3825).

Response 11: According to the suggestion, the clinical and epidemiological differences with autoimmune pancreatitis and its oncological risk were discussed in the special paragraph of the discussion section.

Comment 12: In general, I think that an additional table summarizing the available studies on the association between CP and specific comorbidities would be very useful.

Response 12: Yes, Table 4 has been added to summarize the available studies on the association between CP and specific comorbidities in this manuscript.

4. CONCLUSION

Comment 13: Clear take home messages should be provided, instead of a short summary-abstract of the article

Response 13: The conclusions have been revised completely. We are not clear if "take home messages" as "The implication of high comorbidity of CP with diabetes (26.32%) may be varied with different people." would satisfy the readers.

5. REFERENCES

Comment 14: - to be updated and completed after results completion and revision of the discussion, according to the previous comments and recommendations.

Response 14: Yes, we have updated and completed the references after the revision.

References

1. Cohen SM, Kent TS. Etiology, Diagnosis, and Modern Management of Chronic Pancreatitis: A Systematic Review. JAMA Surg. 2023.

2. Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. Lancet. 2020;396(10249):499-512.

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4. Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG Clinical Guideline: Chronic Pancreatitis. Am J Gastroenterol. 2020;115(3):322-39.

5. Wang LW, Li ZS, Li SD, Jin ZD, Zou DW, Chen F. Prevalence and clinical features of chronic pancreatitis in China: a retrospective multicenter analysis over 10 years. Pancreas. 2009;38(3):248-54.

6. Li JN, Lai YM, Qian JM, Guo T, Lü H, Tang XY. Trends in etiologies of chronic pancreatitis within 20 years: analysis of 636 cases. Chin Med J (Engl). 2011;124(21):3556-9.

7. Zou WB, Ru N, Wu H, Hu LH, Ren X, Jin G, et al. Guidelines for the diagnosis and treatment of chronic pancreatitis in China (2018 edition). Hepatobiliary Pancreat Dis Int. 2019;18(2):103-9.

8. Sellers ZM, MacIsaac D, Yu H, Dehghan M, Zhang KY, Bensen R, et al. Nationwide Trends in Acute and Chronic Pancreatitis Among Privately Insured Children and Non-Elderly Adults in the United States, 2007-2014. Gastroenterology. 2018;155(2):469-78.e1.

Revision reviewer:

The authors improved the manuscript. Some language revisions may further improved the manuscript. At the beginning of the discussion, the authors may list and better highlight the main findings in detail, whereas in the conclusion general, but generalizable, take home messages could be stated.

Comment 1: Some language revisions may further improved the manuscript.

Response: Thanks for your valuable comments! We further modified our words and improved our expressions.

Comment 2: At the beginning of the discussion, the authors may list and better highlight the main findings in detail, whereas in the conclusion general, but generalizable, take home messages could be stated.

Response: We appreciated your helpful suggestion! According to your suggestion, we highlighted the main findings in detail at the beginning of the discussion section and generalized the findings in the conclusion section in order to state the take home messages.