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Name of journal: World Journal of Gastroenterology

Manuscript NO: 41946

Title: Risk factors and prediction score for chronic pancreatitis: a nationwide population-based cohort study

Reviewer's code: 00832596

SPECIFIC COMMENTS TO AUTHORS

Overall, this is an interesting study is the paper is well-designed and well-written. I have three comments. 1. Regarding the drinking and smoking habits, it is essential to see the habits after the development of AP. This point should be clearly presented. 2. the discussion related to genetic mutations are irrelevant to this study, because this study does not deal with genetic information. 3. Regarding early CP, it is difficult to accurately diagnosis this disease entity soon after AP, because transient fibrosis is often observed during the wound repair period of AP. The discussion should be revised.

Answering Reviewers:

1. Thanks for your kind reminder. We defined drinking or smoking habit according to ICD-9-CM coding. If the patients with AP enrolled in our study have drinking-related coding or smoking-related coding during their follow-up period after the first AP episode, we considered them have drinking or smoking habit. I have made this point clear in the section of method.

2. I have deleted the following section about genetic mutation in Discussion.

(The mechanism underlying the interaction between genetic and environmental risk factors remains underinvestigated; however, Wittel et al. have noted that cigarette smoke is responsible for the increased ratio of trypsinogen to the protective pancreas-specific trypsin inhibitor that

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increases the vulnerability to pancreatic autodigestion in rats. They suggested that the increased expression of PRSS1 in the carriers of the wild-type genotype augmented this mechanism and the toxic constituents of cigarette smoke mediate their effects on the pancreas)

3. I have revised the discussion as below:

Using our prediction score model for CP, we were able to stratify our patients into different categories and arrange further examinations such as functional test or EUS after acute stage for the high-risk category (incidence rate of about 31 per 1000 person-years, based on our study) to detect CP as early as possible and determine the optimal follow-up interval according to this scoring system for the patients with AP with a nonbiliary, nonobstructive etiology.

Reviewer's code: 03261315

SPECIFIC COMMENTS TO AUTHORS

Interesting study but I have some concerns of population selection (limited data on acute pancreatitis diagnosis and chronic pancreatitis diagnosis: criteria for AP are missing, criteria for CP are incomplete). Here are my comments: Abstracts conclusions are too long The introduction does not highlight the issue. Why did the authors use only 4 years of look-back? How was acute pancreatitis diagnosed (please specify criteria used for diagnosis of AP)? Why did the authors exclude biliary pancreatitis and pancreas divisum-related pancreatitis but checked for drug-related pancreatitis? There are patients with one or more episodes of biliary pancreatitis which can develop CP. If I understood correctly, the authors included in this study only patients with alcoholic and/or cigarette smoking –related pancreatitis and idiopathic or/and drug-related pancreatitis, why? Please provide the reason to check the income of the patients (the data are presented at results section but the discussions on this issue are missing). In my opinion the authors should erase this part. The methods used for CP diagnosis were only

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imaging tests? No faecal elastase or other functional tests were made? Please specify at the methods section: what does it mean validation and deviation cohort. There are some typing errors.

Answering Reviewers:

Thanks for your recommendations, we do appreciate it. Please let us answer the questions one by one:

1.About the criteria for diagnose AP

The diagnosis of AP is based on ICD-9-CM disease coding (ICD-9-CM code 577.0), we only enrolled inpatient claims data to ensure the reliability of diagnosis. A total of 5971 patients with one or more episodes of AP recorded in the inpatient claims data from 2000 to 2013 were identified from the database. A 4-year look-back period was applied from 1996 to 1999 to ensure that all cases in our cohort were newly diagnosed and to reduce false incident cases.

Exclusion criteria: patients with a previous diagnosis of AP during the look-back period were excluded. Patients who had CP before the index date, those aged <18 or >100 years, those with a follow-up duration of <1 year, and those with biliary pancreatitis or obstructive pancreatitis(such as pancreatic cancer and pancreas divisum) were also excluded.

This diagnosis of AP is based on ICD-9-CM coding

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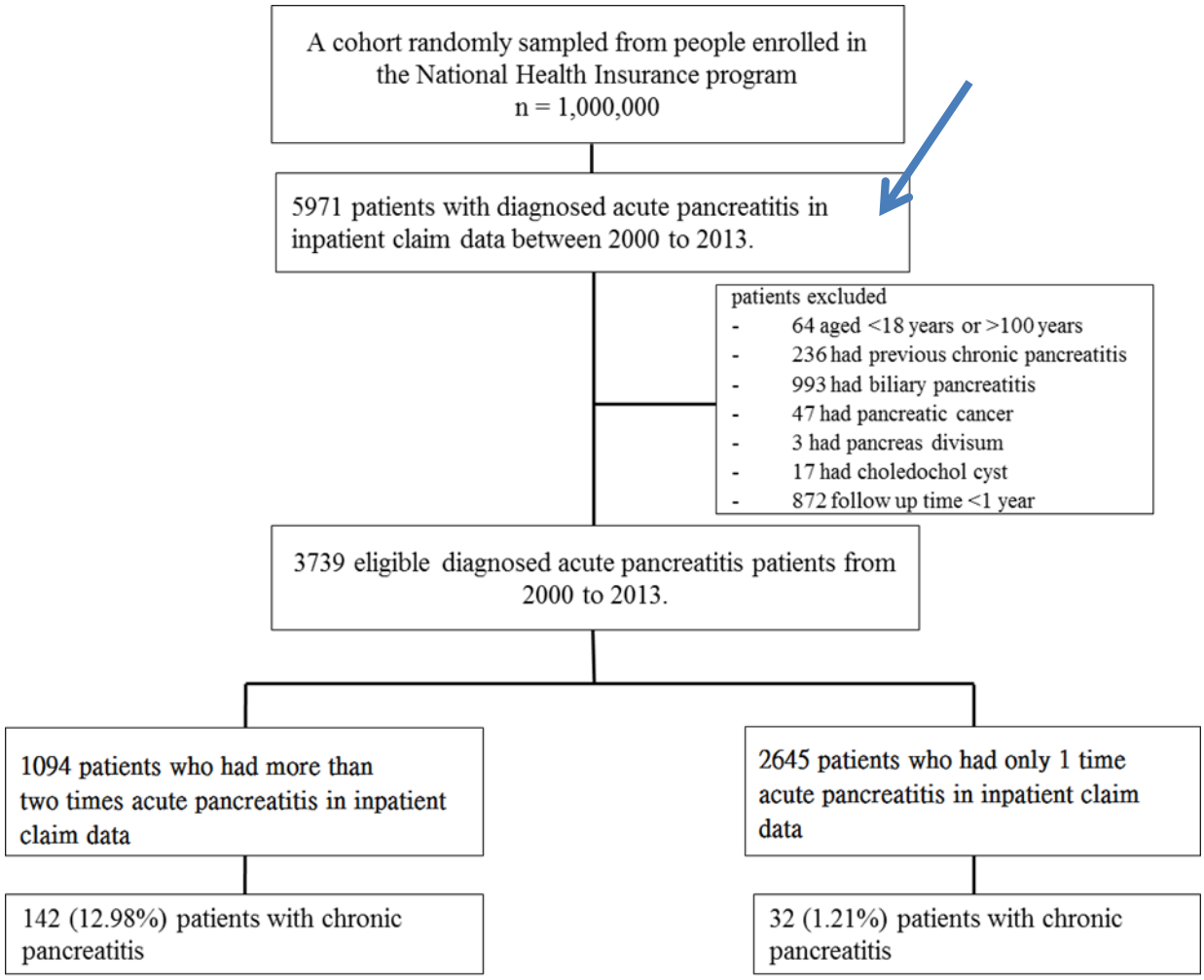

2. About the criteria for diagnose CP

Chronic pancreatitis (CP) was defined using ICD-9-CM codes (ICD-9-CM code 577.1).To avoid over-diagnosis of CP by ICD-9-CM coding alone, we excluded all patients without abdominal computed tomography(CT) or abdominal magnetic resonance imaging(MRI) performed within 3 months before the diagnosis of CP.

In other words, our diagnosis of CP is based on image study in addition to ICD-9 coding, for there are no information about pancreatic functional test of pancreas in our national data base. That is, the diagnosis of chronic pancreatitis in our study can be considered as more advanced chronic pancreatitis, which could already be diagnosed by abdominal

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CT/MRI study.

2. To response to your recommendation, I have revised the section of conclusion and introduction

The revised conclusion of abstract is as follows:

In the study, we identified the risk factors of CP and developed a novel prediction score model for CP.

The revised introduction is as follows:

……*Because only a small proportion of patients with AP progress to CP, and CP has been proven to be an important risk factor of pancreatic duct adenocarcinoma(PDAC),it is critical to predict the development of CP in a patient with AP. However, till date, no prediction scores for CP have been addressed in the English literature, although there were some prognosis scores for CP and AP. Therefore, in this population-based, large-scale cohort study, we developed and validated a scoring system for predicting CP using data from the National Health Insurance Research Database (NHIRD) in Taiwan.*

3. We thank the reviewer for allowing us to explain more. Our study data were retrieved from the Taiwan National Health Insurance Research Database (NHIRD), which released by the Taiwan National Health Research Institute for scientific research. However, the Taiwan National Health Insurance (NHI) program was started since 1996. Therefore, we used a look-back period from 1996-1999 for identifying incident AP patients. This 4-year look-back period was used to ensure that all AP patients in our cohort were newly diagnosed and to reduce false incident cases.

4. We thank the reviewer for the kind remainder. Indeed, there are some patients with one or more episodes of biliary pancreatitis which can develop CP. However, it is quite rare (Lankisch, Paul Georg, et al. "Natural history of acute pancreatitis: a long-term population-based study." The American journal of gastroenterology 104.11 (2009): 2797.) To assess the reliability of our results and response to your question, we included the

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patients with biliary pancreatitis and obstructive pancreatitis in the sensitivity analysis. The results of sensitivity analysis were consistent with those of our primary analyses, indicating the robustness of our study (shown in supplementary 2). Because we have excluded those with biliary pancreatitis and obstructive pancreatitis in the original analysis, the prediction score can't be applied in patients with biliary pancreatitis or obstructive pancreatitis. (I have mentioned this in the section of limitation).

5.We checked the income and socioeconomic factors of each patients in our cohort because an American study have addressed that alcoholic liver disease (ALD) was more prevalent in the low- to middle-income men (Tao, Nico, et al. "Demographic characteristics of hospitalized patients with alcoholic liver disease and pancreatitis in los angeles county." Alcoholism: Clinical and Experimental Research 27.11 (2003): 1798-1804.) However in our study, the impact of income on the development of CP is not significantly in the univariate analysis of our study, therefore we did not discuss this issue in the later section.

6. The "deviation cohort" in the methods section is typing error. Thanks for your kind reminder.