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Editors-in-Chief

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Dear Profs Hu, Kang, Pyrsopoulos,

Thank you for the opportunity to transfer our manuscript titled **"Liver disease epidemiology and burden in patients with alterations in plasma protein metabolism: German retrospective insurance claims analysis"** to *World Journal of Hepatology* following peer review feedback from *World Journal of Gastroenterology*. In the table on the following page, we have provided point-by-point responses to each of the reviewers' comments, identifying the location of any associated changes in the manuscript. We hope that you find our responses suitable and that the revised manuscript will now be acceptable for publication in your journal.

Thank you for your consideration of our submission, and we look forward to hearing from you.

Sincerely,

Pavel Strnad, MD

Corresponding author, on behalf of all authors

Liver disease epidemiology and burden in patients with alterations in plasma protein metabolism: German retrospective insurance claims analysis

Reviewer 1 comments		Change/comment	Location of change in tracked document
1.	The Table 2 shows classification of diagnostic procedures. There are no diagnostic criteria in this study. Should diagnostic criteria for APPM be displayed in the method?	We thank the reviewer for their comments. As this was an administrative insurance claims analysis from a German health insurance provider (AOK PLUS) that collected data using German Modification of the International Classification of Diseases – 10th Revision (ICD-10-GM) codes, we are unable to retrospectively evaluate the diagnostic criteria used in real-world practice. This has been highlighted as a limitation in the Discussion section.	Page 13
2.	Are all patients in the APPM cohort diagnosed with AATD? If not, how do other patients diagnose APPM?	As noted in the Methods section (page 6), patients in Germany diagnosed with alpha-1 antitrypsin deficiency (AATD) were identified using the ICD-10-GM code E88.0 for disorders of plasma protein metabolism (which includes AATD and other metabolic disorders such as plasminogen deficiency and bisalbuminaemia). In Germany, E88.0 is the only ICD-10-GM code that can be used for retrospective analyses of patients with AATD, and the associated limitations of this approach are described within the Discussion section (page 12). The following text has been added to the Discussion section along with an accompanying citation: "*In addition, developments of the ICD coding system, such as the addition of the E88.0A code for AATD, could improve the identification of patients with AATD in future administrative*	Page 12

		insurance claims analyses. In a recent registry-based cohort study of the prevalence, incidence and mortality associated with AATD in Denmark using the E88.0A code, a sensitivity analysis demonstrated a predominance of AATD in the E88.0 category for APPM and a near complete shift to the more specific E88.0A code for AATD between 2000 and 2018."	
Reviewer 2 comments		**Change/comment**	**Location of change in tracked document**
This study aims to understand the prevalence, burden and progression of liver disease in patients with APPM, including alpha-1 antitrypsin deficiency. A retrospective analysis of anonymized patient-level was conducted from a German health insurance provider (AOK PLUS). Overall, 2680 and 26,299 patients were included in the APPM (fibrosis [96]; cirrhosis [2584]) and control (fibrosis [1444]; cirrhosis [24,855]) cohorts, respectively. Per 100,000 individuals, annual incidence and prevalence of APPM and liver disease was 10–15 and 36–51, respectively. The authors claimed that among patients with liver disease, those with APPM experience substantial burden and earlier liver disease progression than patients without APPM. Overall, this is an interesting paper. However, I have several concerns as follows.			
1.	The BMI of the subjects should be recorded in Table 1 since this is an important factor. Does the BMI influence the overall result in this study? Eg, a higher BMI with APPM experience substantial burden and earlier liver disease progression than patients with a lower BMI? Please address it.	We thank the reviewer for their comments. As this was an administrative insurance claims analysis that collected data using ICD-10-GM codes, we are unable to assess BMI/body weight. The following text has been added to the limitations within the Discussion section with an appropriate supporting reference (Bowlus CL, et al. *Clin Gastroenterol Hepatol* 2005;3:390–6): "*Lastly, as this was a retrospective insurance claims-based study that collected data using ICD-10-GM codes, we were unable to assess body weight/body mass index, which are known risk factors of early progression to advanced liver disease*".	Page 13

2	I'm not sure if the number of "Patients with fibrosis" is enough for analysis, which will influence the reliability of the results. Could this sample be expanded in the next version?	As noted in the limitations within the Discussion section (page 12), the number of patients in the APPM cohort with fibrosis (n = 96) was lower than anticipated, likely owing to underdiagnosis (patients are often asymptomatic in the early stages of fibrosis) or underreporting. Unfortunately, we cannot expand this subgroup further because current routine clinical practice assumes that most patients with liver disease are not diagnosed until they become symptomatic and progress to cirrhotic liver disease. The development and implementation of structured early screening programmes may be useful to increase the early detection of fibrosis in the general population (page 13).	N/A
3.	I think the selection of the subjects should be presented in the main figure, eg figure 1. It will help the readers to better understand the flow of selection.	As requested, the figure titled "Selection of patient cohorts" has been moved from the supplementary material (previously Supplementary Figure 2) into the main body of the manuscript (now labelled as Figure 1, with all subsequent figures renumbered accordingly).	Page 19
4.	The data comes from the insurance claims-based analyses, which cannot present the general population. A potential selection bias existed as only the subjects can afford insurance participate in this study. It will influence the reliability of the results.	We consider the data to be representative of the German population as ~88% of the general population in Germany are insured by a statutory health insurance (SHI) fund, which have a uniform structure across the country. To clarify this point, the following text has been added to the limitations within the Discussion section: "*In addition, regional differences in morbidity and mortality may exist, and our data may not be representative of geographic regions outside of Germany.* ***However, in Germany, ~73.3***	Page 13

		million people were insured by a statutory health insurance (SHI) fund in 2020, which equates to ~88% of the general population. Owing to the uniform structure of SHI funds in all regions of Germany, we consider the data to be representative of the German population".	
5.	The discussion should be reinforced, especially for the clinical application. How to decrease the disease progression/burden of liver disease in patients with APPM in the community?	Given the low number of patients with fibrosis detected in our database study, we propose to develop and implement structured screening programs to improve early detection of fibrosis in the general population and provide clinical interventions to delay further progression of cirrhosis (page 13). In addition, the following text has been added to the Discussion section: "*The adoption of diagnosis codes specific to patients with AATD may facilitate earlier diagnosis and improved patient management, which may, in turn, contribute to slowing disease progression and decreasing the burden of disease in these patients with a rare, chronic disease*".	Page 12
6.	The authors claimed that the demographics and baseline characteristics were similar between cohorts (Table 1). Please add statistical analysis result.	An additional footnote has been added to Table 1 as follows: "*Patients in the APPM cohort were significantly younger than patients in the control cohort (Wilcoxon rank-sum test: $p < 0.001$). There was no statistically significant difference in the proportion of females between cohorts (Wilcoxon rank-sum test: $p = 0.159$)*" P values have been added to the Demographics and baseline characteristics section of the Results. In addition, the following text has been added to the Discussion section:	Pages 9, 11, 12, 24 and 27

		"*The median age of patients in the APPM cohort was two years younger than in the control cohort, yet the APPM cohort had a higher risk of liver disease-related clinical events. This supports that patients with APPM are at a higher risk of liver disease-related clinical events than patients without APPM irrespective of age*"	
Reviewer 3 comments		**Change/comment**	**Location of change in tracked document**
1.	It is not possible to distinguish the group with APPM but not with AATD, which is big bias as there are already some studies reflecting the more severe behavior of AATD liver disease. - As reported, the patients could be studied in different ways as they were in different hospitals, lacking uniformization of the cohort.	We thank the reviewer for their comments. We believe that our response to Reviewer 1, Comment 2 and the associated revisions to the manuscript have improved the prominence of this limitation in the Discussion section.	Page 12
2.	There are only 96 patients with fibrosis in the APPM group vs 1444 in the control group, being difficult to take any conclusion.	We believe that our response to Reviewer 2, Comment 2 clarifies this limitation within the Discussion section.	Page 12
3.	There is no information how was cirrhosis diagnosed - by fibroscan? liver biopsy?	Table 2 includes all recorded diagnostic procedures within 12 months after the index date. In the APPM cohort, 207 patients (7.7%) had a liver biopsy and 1778 patients (66.3%) had an imaging procedure (including sonography, computed tomography scan, magnetic resonance imaging procedure, angiography of the abdomen and magnetic resonance elastography). Unfortunately, there are no data on the specific imaging procedures conducted (e.g. for fibroscan). Furthermore (and as noted in our response to Reviewer 1, Comment 1), as this was an administrative claims database study using ICD-10-GM codes, it was not possible to retrospectively evaluate the diagnostic procedures; this is now highlighted in the limitations within the Discussion section.	Page 13

4.	How can you explain the group of APPM did not have more respiratory disease? Usually, the more severe the liver disease is, the more severe is the respiratory disease.	Please note that our study was limited to a subpopulation of patients with a diagnosis for APPM (E88.0) and newly diagnosed liver disease. Therefore, we cannot describe the prevalence of respiratory disease in the general patient population diagnosed with APPM. A recent registry-based cohort study of the prevalence, incidence and mortality associated with AATD in Denmark found that 65.6% of patients with AATD (E88.0A) had lung disease and only 5.2% of patients with AATD had both liver and lung disease (Acquavella J, et al. *BMJ Open Respiratory Research* 2022;9:e001281). In addition, other studies have shown no association between the extent of liver and lung disease in patients with AATD (Clark VC, et al. *J Hepatol* 2018;69:1357–1364 and Hamesch K, et al. *Gastroenterology* 2019;157:705–719).	N/A