PEER-REVIEW REPORT

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear authors Although the topic is interesting, as a retrospective study based in an insurance database, there are a lot of limitations in this study: - 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. - There are only 96 patients with fibrosis in the APPM group vs 1444 in the control group, being difficult to take any conclusion. - There is no information how was cirrhosis diagnosed - by fibroscan?liver biopsy? - 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.

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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 follow: 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. 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? 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. 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. 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? 6. The authors claimed that the demographics and baseline characteristics were similar between cohorts (Table 1). Please add statistical analysis result.

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SPECIFIC COMMENTS TO AUTHORS

Comment 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?   Comment 2：Are all patients in the APPM cohort diagnosed with AATD？If not, how do other patients diagnose APPM？