Peer Review File

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Reviewer A:

In this paper titled " Prevalence and Longitudinal Effects on Mortality associated with Spectrum of Alcohol Intake in Steatotic Liver Disease: A United States Population A United States Population Study", the authors report the frequency of MAFLD, MetALD, and ALD, and the increased mortality associated with ALD in particular, using the NHANES database.

Comment 1.
Clinical events in patients with MASLD, MetALD, and ALD complications are considered, but a control subject group is missing.
Reply 1: Thank you for the comment. We understand the reviewer's concerns regarding a control group in comparison of different clinical subgroups. However, a control subject group was not included as the aim of the current study was to examine the differences in clinical outcomes along the spectrum of SLD, from MASLD to MetALD and ALD, to address the relative literature gap in this aspect. We hope for your kind understanding.
Changes in the text: We have included this under the Limitations section in page 19, lines 375 to 377. We hope that this has improved the clarity of the manuscript.

Comment 2.
Since FIB-4 is measured in this study, it is necessary to examine the classification by FIB-4.
Reply 2: Thank you for the comment. We have included further information regarding FIB-4 in the different classifications under Table 1. We hope that this will improve the clarity and quality of the manuscript.
Changes in the text: The proportion of patients in high, intermediate and low fibrosis (measured by FIB-4) was included in Table 1. We have clarified the differences in FIB-4 scores between MASLD, MetALD and ALD patient in page X, lines 240 to 242. MASLD Predominant patients had the highest median FIB-4 (1.01, IQR: 0.66 to 1.47), followed by MetALD (0.83, IQR: 0.56 to 1.20) and ALD Predominant (0.73, IQR: 0.51 to 1.07).

Reviewer B:
Comment 1: The abstract should mention how SLD was defined in the study.
Reply 1: Thank you for the comment. We have included the definition of SLD in the abstract.

Changes in the text: We have included “SLD was confirmed using either fatty liver index (FLI) or United States Fatty Liver Index (US-FLI).” in lines 100 to 101.

Comment 2: Why the use term ”predominant” in the context of MASLD and ALD?
Reply 2: The term "predominant" was employed to acknowledge the spectrum of SLD encompassing MASLD, MetALD, and ALD. It is recognized that patients positioned on the ALD end of this spectrum may still exhibit minor metabolic influences, and conversely for those on the MASLD side.

Comment 3: Since the FLI/US-FLI incorporate metabolic factors in their definition of SLD, does not the use of these indicies inflate metabolic factors into the definition of SLD? Has FLI been validated for the purpose of SLD subclassification?
Reply 3: Dear reviewer, thank you for the comment. We acknowledge that biopsies or imaging procedures are the preferred methods for diagnosing SLD. Unfortunately, such data was not accessible for the population under study. In support of our approach, we refer to Bedogni et al. (PMCID: PMC1636651), whose work affirms the efficacy of FLI in diagnosing SLD. Nevertheless, we have included the limitation of biopsy and imaging under the Limitations section under page 19, lines 361 to 364. We hope for your kind understanding.
Changes in the text: We have included the limitation of biopsy and imaging under the Limitations section on page 19, lines 361 to 364.

Comment 4: What does ”imputed” refer to here: ”Where applicable, cause of mortality was imputed accordingly based on ICD-10 diagnostic codes:”
Reply 4: Thank you for the comment. We have made changes to the text, amending “imputed” to “ascertain” to improve the clarity of the manuscript.
Changes in the text: Edited “imputed” to “ascertained” on line 199.

Comment 5: The study does not state why liver-related mortality was not analyzed
Reply 5: Dear reviewer, thank you for your comment. Unfortunately, data on liver-related mortality was not available in this cohort. While analysis on liver-related mortality would indeed greatly value-add, we are unable to do so in the present condition and have acknowledged it in the limitations.
Changes in the text: Included the clarification “Similarly, we were unable to analyse liver-related mortality due to inherent limitations in the data.” on page 19, lines 372 to 373.

Comment 6: It seems to me that by prevalence, the authors are in fact meaning the proportion of MASLD/MetALD/ALD of all individuals with SLD at the specific time-point (e.g. MASLD / all with SLD). This is not prevalence of the condition in the entire population (MASLD / all individuals). It seems to come to the somewhat misleading conclusion that MASLD prevalence is decreasing - is not just the proportion of SLD that is attributable to MASLD that is decreasing?

Reply 6: Thank you for the comment. Apologies for the confusion regarding the reference population for prevalence. We have made the necessary changes to the text to improve the clarity of the manuscript.
Changes to text: Changes to text has been made in multiple areas and highlighted in yellow, to clarify the reference population as the SLD population.

Comment 7: Furthermore, it is unclear whether the AAPC approach accounts for possible differences in age structure in the various cohorts over time. Not sure what conclusions can be drawn from these ”prevalence” and temporal trends analyses. This reviewer would be cautious to draw any conclusions.
Reply 7: Thank you for the comment. The AAPC methods was chosen to mitigate the impact of age structure variations over time. Furthermore, we chose AAPC for its ability to facilitate equitable comparisons across the MASLD, MetALD, and ALD cohorts, which experience similar conditions and age-related changes throughout the years.
Changes to text: “Decreasing MASLD prevalence” in line 330 was modified to “The decreasing proportion of SLD attributable to MASLD”.

Reviewer C:

Using data from the NHANES cohort from 1999 to 2018, authors investigated the prevalence trends and mortality due to overall, cardiovascular and cancer-related causes due to steatotic liver disease (SLD) into its three main categories, namely MASLD, MetALD and ALD. The two main findings are the significant decrease of MASLD during the study period and the significantly higher mortality associated to ALD except for cardiovascular causes.

The topic is interesting and timely. The design and analyses are in general sound. Limitations are overall correctly acknowledged. The manuscript is well-written, figures and tables are overall appropriate.

Major comments

1. As in most studies, the time and method for alcohol intake quantification is problematic. It is not stated whether the “label” of MetALD or ALD was assigned based only on baseline data or otherwise (e.g., longitudinal assessment). For instance, if a participant had a FLI >60, overweight, hypertension and a weekly alcohol intake of 230 gr during the last 3 years and was labelled as MetALD but consequently dropped alcohol consumption while gaining weight in the ensuing year would no longer belong to the MetALD category. Of course, this applies to all variables related to metabolic burden and alcohol consumption and therefore to all (mostly MASLD and MetALD) SLD categories. Since the title contains the expression “spectrum of alcohol intake” this point should be discussed and clarified.

Reply 1: Thank you for the comment. Baseline data was used for classification as longitudinal data was largely not available. We have clarified this under the methods section, on page 10, lines 178 to 179. We hope that this will improve the clarity of the manuscript.
Changes to text: Clarified the classification under methods section, on page 10, lines 178 to 179.

2. The main endpoint examined was mortality, as also stressed in the title. However, liver-related mortality (and liver transplant) is not provided. This is key, as the dichotomic comparison between MASLD and ALD has not only relied on CVD complications and death, but largely on liver-related events, considered to be much higher on the latter. In addition, authors should clarify why they decided to focus on mortality and not emerging cardiometabolic and liver-related complications (e.g., difficulties in retrieving complete and high-quality data from ICD-10 codes, etc).
Reply 2: Dear reviewer, thank you for your comment. Unfortunately, data on liver-related mortality was not available in this cohort. While analysis on cardiometabolic complications and liver-related mortality would indeed greatly value-add, we are unable to do so in the present condition and have acknowledged it in the limitations.
Changes in the text: Included the sentence: “Similarly, we were unable to analyse liver-related mortality due to inherent limitations in the data.” on page 15, lines 372 to 373, and “We were also unable to analyse emerging cardiometabolic and liver-related complications due to difficulties in retrieving complete and high-quality data for these conditions from ICD-10 codes.” on page 19, lines 373 to 375.

3. Since 2018, the epidemiology of liver disease has largely changed in the US, with declines in viral hepatitis-SLD, and increases in alcohol-related and metabolic-dysfunction associated SLD boosted by the COVID-19 pandemic. Since authors have found a significant decline in MASLD, which contradicts most reports, this point should be carefully contextualized and reflected in the key findings and conclusions. Also, expression in perfect present tense such as “the prevalence has significantly increased” should be changed by simple past, as 6 years have elapsed since the end of the study period and the epidemiology of SLD is rapidly evolving.
Reply 3: Dear reviewer, we appreciate the comment. We have made changes to the text to improve the expression and ensure clarity of the manuscript.
Changes to the text: Changes to text has been made in multiple areas and highlighted in yellow, to clarify the reference population as the SLD population.

4. Why did authors decide to not conduct a multivariable analysis of potential factors associated with mortality, jointly and by SLD category? This would be especially interesting if including longitudinal data, even if assessed as dichotomic variables (e.g., significant increases in BMI, Hb1Ac, alcohol intake).
Reply 4: Thank you for the comment and we acknowledge that an analysis as described above could value-add to the manuscript. Unfortunately, longitudinal data

was not available for us to perform this analysis. We hope for your kind understanding.
Changes in the text: Added “Baseline data was used for classification as longitudinal data was largely not available.” In line 178.

5. Variables regarding socioeconomic position (in this case, annual household income) should be assessed potential predictors and shown in the main results alongside ethnicity.
Reply 5: Thank you for the comment. We have included description of socioeconomic position across the 3 types of SLD in the results section. We observed that majority of the MASLD and ALD population was in the $25,000-49,999 annual household income bracket, while the highest proportion of the MetALD cohort was in the $75,000 and over bracket. We hope that his will improve the quality of the manuscript.
Changes in the text: Added “The highest proportion of the MASLD (25.14%, 95% CI: 24.19% to 26.12%) and ALD Predominant (27.06%, 95% CI: 24.81 to 29.42) cohorts was in the $25,000-49,999 annual household income bracket, while the highest proportion of the MetALD cohort was in the $75,000 and over bracket (28.82%, 95%CI: 27.01 to 30.70).” in line 238-241.

Minor comments
1. Non-Hispanic White ethnicity should be explicitly mentioned, particularly when referring to the increase in MetALD prevalence, as the mention to “other ethnicities” without clarifying that non-Hispanic Whites were the most common ethnicity in all three subcategories leads to potential misinterpretation.
Reply 1: Thank you for the comment. The change in prevalence in non-Hispanic Whites was described on page 14, lines 261 to 263.

2. Introduction. In the Moon et al study authors found that CVD significantly increased in MASLD, MetALD and particularly ALD. This should be stated and then reassessed in relation to CVD mortality in the discussion.
Reply 2: Thank you for the comment. We have acknowledged the differing study findings as described above and included this under the discussion section on page 18, lines 352 to 356. This study found no significant difference in CVD-related mortality when comparing ALD predominant and MetALD against MASLD, possibly due to other causes such as liver-related or cancer-related having a larger influence on mortality in SLD. We hope that this has improved the quality of the manuscript.
Changes in the text: Discussion section, on page 18, lines 352 to 356.

3. Results. When highlighting the significant difference in total cholesterol across categories, HDL data should also be mentioned, as it is the specific variable considered in the definition of metabolic risk factors for MASLD and MetALD as per the recent consensus definition used in the study.

Reply 3: Thank you for the comment. We amended the manuscript to reflect the HDL data.
Changes in the text: Added “HDL-cholesterol ($p<0.01$)” in line 236.

4. Discussion, second sentence. “While the role between alcohol consumption and hepatic steatosis remains contentious”. Please, rephrase and clarify.
Reply 4: Thank you for the comment. Apologies on any confusion caused, we have edited the sentence and we hope that this improves the clarity.
Changes in the text: Discussion section, page 17, lines 317 to 318.

5. Discussion. The statement “Decreasing MASLD prevalence may be associated with declining rates of 247 diabetes in the US associated with improved screening processes30” is not consistent with NHANES data. Reference 30 should be instead Fang et al, NEJM 2021, which shows and decrease in diabetes control during the same study period.
Reply 5: Dear reviewer, thank you for the comment and we apologise for the discrepancy. We have amended the citation.
Changes in the text: Have added Fang et al, NEJM 2021 as a reference (31).

6. Table 1. The thresholds defining the subcategories of FIB-4 should be included in the footnote.
Reply 6: Thank you for the comment. We have included the threshold values in table 1 for clarification.
Changes in the text: Threshold values included in Table 1.

7. Table 2 (and abstract and results): Change “adverse events” for “mortality”. The “a” superindex corresponding to “adjusted for smoking status, gender, age and ethnicity” as shown in the footnote apparently applies not only to CVD and cancer-mortality but also to overall mortality. Thus, the distinction between HR and sHR needs to be clarified.
Reply 7: Thank you for the comment. We have made the necessary changes Table 2, abstract and results section.
Changes in the text: Modified “adverse events” to “mortality” in the sections mentioned.