Author’s response to reviews

Title: Prevalence and Long-term Outcomes of Non-alcoholic Fatty Liver Disease Among Elderly Individuals from the United States

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Prevalence and Long-term Outcomes of Non-alcoholic Fatty Liver Disease Among Elderly Individuals from the United States

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Answers to reviewer’s Comments:

Reviewer 1: In this study, the authors analyzed a NHANES-III to determine the prevalence of fatty liver (as determined by US-FLI score) in US citizens aged 60 years or older, and explored the association of fatty liver with incidences of mortality according to age subgroups. They demonstrated a high prevalence of fatty liver in the elderly and found the diagnosis was associated with cardiovascular outcomes and mortality in individuals aged between 60-74 years, but not in those older than 74 years. Overall, this study is and mainly descriptive and straightforward. It might provide useful information to clinicians taking care of patients with fatty liver. Several caveats were noted and discussed below.
Major comments:

Q1. The novelty is Medicare as it has been well known that the prevalence of fatty liver increases with age and that fatty liver is associated with increased risks of cardiovascular outcomes.

A1. Thanks for your comment. The association of NAFLD with mortality has been controversial. Our study demonstrated that NAFLD is independently associated with all-cause and CVD mortality within the adults aged 60-74 years. Also, our supplementary analyses showed that risk factors among elderly NAFLD patients are generally the same as those of general NAFLD subjects (Supplementary Table 3).

Q2. Using US-FLI score to define fatty liver in the elder may be problematic, given that the formula includes age as an explanatory variable. Has US-FLI been independently validated in the elderly? Was the diagnostic accuracy (referenced by gold standard such as histology or MR spectroscopy) similar across different ages, particularly in those older than 70 years? Is there supportive reference?

A2. There is no study that separately validates US FLI in the elderly population. However, in our own study we performed a small validation using ultrasound for a subgroup of patients with NAFLD. In fact, NAFLD by US-FLI did not differ from NAFLD patients who were defined by ultrasound (Supplementary Table 1). In this context, beside US-FLI there is no other non-invasive test to diagnose NAFLD in the multiethnic U.S. population. Since ultrasound examinations in NHANES were performed only on adults aged 20 to 74 years (NHANES III), US FLI provided the best option to study NAFLD in the elderly population who were included in the NHANES.

Q3. What was analyzed, in fact, was a scoring formula that consisted of age, race-ethnicity, waist circumference, gamma-glutamyltransferase, fasting insulin, and glucose. In a sense, the findings regarding the association with metabolic and cardiovascular disorders might simply reflect the component variables.

A3. We agree with the reviewer. Recently, Ruhl and Everhart have evaluated the FLI in the multiethnic U.S. population and derived an improved index, which is more appropriate for the U.S. population (US-FLI) including age, race/ethnicity, waist, GGT, insulin and glucose. Although the individual components may be associated with outcomes, the full algorithm (US-FLI), which represent NAFLD has the best performance.

Minor points:

Q1. How many patients were excluded because of insufficient data? The authors did not explain why they believed "elders (aged 60 and over) who were excluded from the study were similar to the final study cohort."
A1. Demographic characteristics and health-related behaviors, and history of comorbidities by inclusion criteria are presented in Supplementary Table 2. Characteristics did not differ between the groups.

Reviewer 2: This is a well-designed study that provides important data regarding NAFLD in the elder U.S. peoples.

I have a few queries on this paper.

Q1. Have the authors examined the competing risk factors of mortality that confounding the analysis in this study? If not, the authors need to examine the competing risk factors of mortality.

A1. The authors would like to thank the reviewer. After this comment, we examined the competing risk factors of mortality. Multivariate models were adjusted for sex, current smoker, hypertension, hyperlipidemia, advance fibrosis (NFS > 0.676), and history of cardiovascular disease and cancer (Table 4). Additionally, we assessed the risk factors among NAFLD elders. In these models, we controlled for age, male, race, current smoker, diabetes, hypertension, hyperlipidemia, advanced fibrosis (defined as NFS > 0.675), history of cancer, and CVD. Our findings were presented at Supplementary Table 3. Different risk factors were found compared to general NAFLD subjects.

Q2. Because age is a factor for calculating NAFLD fibrosis scores, the authors should take care of this when examining the association of liver fibrosis and NAFLD in elder patients.

A2. We agree with reviewer. That’s the reason that APRI (calculated by AST, ALT, and platelet count) was also reported. Additionally, when we examined the risk factors of mortality, components of US-FLI and NFS scores were not considered in multivariable models.