

- ✓ (1) Please add the Core tip section. The number of words should be controlled between 50-100 words.
- ✓ (2) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text (and directly before the References).
- ✓ (3) Please provide the PMID numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.
- ✓ (4) Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.
- ✓ (5) Please provide the primary version (PDF) of the Institutional Review Board’s official approval, prepared in the official language of the authors’ country - - Not Applicable

Blue color: Reviewer #1 comments

Red color text: Reviewer #1 questions to the authors

Black color text: Response to the reviewer from the authors

Yellow color text: Specific revised sections in the manuscript based on the reviewers’ questions.

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

The study is aimed to investigate the relationship between non-alcoholic fatty liver

disease and major cardiovascular and cerebrovascular events (MACCE) in subgroups

using a nationally representative US inpatient sample. The title is “Sex and Racial

Disparities in NAFLD-Related Cardiovascular Events: National Inpatient Sample Analysis

(2019)".

1. Several factors influence the outcome of the study. Please discuss these.

Ans: Thank you for reviewing and pointing out the fact to discuss other influential factors to our study. I have included the following section the discussion part of the section by citing additional references:

“Furthermore, In a study using data from NHANES, patients with NAFLD demonstrated to develop increased odds of developing cardiovascular disease²⁰. Their study lacked to control for conditions like hyperlipidemia or systemic hypertension. However, this limitation was addressed in our study through adjustments for a comprehensive range of comorbid conditions, including hyperlipidemia and hypertension, thereby enhancing the robustness of our findings. Patients with NAFLD often have one or more components of the metabolic syndrome, which is a known risk factor for cardiovascular disease²¹. This makes NAFLD independently associated with cardiovascular disease. Moreover, our study revealed that the prevalence of hypertension, diabetes with and without chronic complications, hyperlipidemia, and obesity were significantly higher in all racial groups among NAFLD patients. While the relationship between NAFLD and diabetic complications remains unclear, it is worth noting that individuals with steatosis and type 1 diabetes may be at a heightened risk of developing cardiovascular disease and subsequent cardiovascular complications²². Therefore, it is of utmost importance to screen high-risk groups for NAFLD-related fibrosis, and the American Association of clinical endocrinology clinical practice guideline for the diagnosis and management of NAFLD strongly recommend screening patients with type 2 diabetes using the Fibrosis (FIB)-4 index²³. Other metrics such as

the NAFLD activity score, a validated grading system for disease activity²⁴ and noninvasive assessments of hepatic fibrosis, like the NAFLD fibrosis score, are specific to NAFLD. The NAFLD fibrosis score considers factors such as age, body mass index, hyperglycemia, aminotransferase levels, platelet count, and albumin²⁵. Elevated NAFLD fibrosis scores may correlate with heightened cardiovascular disease mortality²⁶. These assessment tools are essential for stratifying the NAFLD population into distinct grading categories, enabling targeted screening for adverse cardiovascular outcomes. Establishing a causal relationship between NAFLD and cardiovascular disease will be challenging due to the complex interplay of overlapping metabolic disturbances in these individuals, such as obesity, diabetes, hypertension, atherogenic dyslipidemia, and visceral adiposity. Further research is necessary to clarify this mechanistic link. Nevertheless, regardless of causality, it is crucial for endocrinology and primary care clinicians to recognize individuals with NAFLD as being at a heightened risk of cardiovascular complications.”

2. Please review the literature and add more details in the discussion section

Ans: Thank you for pointing out that our article requires additional information and literature write-up on particular risk factors and outcomes of NAFLD population. I have added the following in the discussion section with citing latest references.

“In a striking revelation, a study focusing on Native American patients with Medicare in the US uncovered that nearly half of the patients grappled with severe cardiovascular conditions, while also bearing a heightened load of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia³². These alarming findings parallel our own study, which demonstrated that Native Americans faced elevated odds of in-hospital mortality. This stark correlation

underscores the profound and widespread racial disparities in cardiovascular health across the United States³³. Consequently, there is a pressing need for the implementation of comprehensive multilevel interventions in healthcare, encompassing individual- and community-level factors for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD, to enhance cardiovascular health. This approach must be complemented by strategic investments in communities to tackle the socioeconomic determinants of health, ultimately leading to improved cardiovascular outcomes within these populations.”

The following was added to the clinical implications section:

“Early diagnosis and proper management of NAFLD and related risk factors are essential to prevent atherosclerosis and other cardiovascular outcomes, particularly in high risk and underserved racial and ethnic groups. Furthermore, comprehensive multilevel interventions in healthcare, addressing individual and community level factors, are urgently needed for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD to enhance cardiovascular health and reduce disparities. These efforts must be complemented by strategic investments in communities to address the socioeconomic determinants of health, ultimately leading to improved cardiovascular outcomes within these populations and promoting health equity.”

3. Please add more details of the limitations of the study.

Ans: Thank you for reviewing the limitations section and advising on the addition of specific details. The following was added to the limitations section

“The study's use of a 2019 sample might not be entirely representative of the broader NAFLD patient population over time.”

“Notably, the study did not consider the severity of NAFLD, including crucial factors such as NAS score, NAFLD fibrosis score, FIB-4 index, and ultrasonography findings. The absence of this information in the NIS database hinders a comprehensive understanding of the disease's nuances. Furthermore, the lack of established screening guidelines for NAFLD exacerbates the issue, as its asymptomatic nature and the absence of a correlation with elevated liver function enzymes make it easily overlooked in clinical settings. “

4. What is the new knowledge of the report?

Ans: Thank you for asking this specific question, to which I responded by adding the article highlights at the end of the manuscript just before the reference section.

ARTICLE HIGHLIGHTS

- NAFLD is associated with a higher risk of major adverse cardiovascular events (MACCE), including all-cause mortality, AMI, cardiac arrest, and stroke.
- Older males with NAFLD are at a greater risk of MACCE.
- Native Americans and Asian Pacific Islanders with NAFLD have higher all-cause mortality.
- There are significant sex and racial disparities in outcomes related to NAFLD.
- Early detection and comprehensive management of cardiovascular risk factors in NAFLD patients are crucial.
- Lifestyle interventions, such as weight loss and physical activity, can improve patient outcomes for NAFLD.

5. Please recommend to the readers “How to apply this knowledge?”

Ans: Thank you for reviewing and requesting additional information on how this article would the clinicians. The following information was added to the clinical implication section which can guide the clinicians on how to manage this patient population.

“Early diagnosis and proper management of NAFLD and related risk factors are essential to prevent atherosclerosis and other cardiovascular outcomes, particularly in high risk and underserved racial and ethnic groups. Furthermore, comprehensive multilevel interventions in healthcare, addressing individual and community level factors, are urgently needed for Native Americans and Asian/Pacific Islanders diagnosed with NAFLD to enhance cardiovascular health and reduce disparities. These efforts must be complemented by strategic investments in communities to address the socioeconomic determinants of health, ultimately leading to improved cardiovascular outcomes within these populations and promoting health equity.”