Response to reviewers and editors

1. Response to peer reviewer

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: jiang et al, conducted a nationwide study using the National Inpatient Sample. We compared the characteristics and inpatient outcomes of patient admitted for Clostridium Difficile Infection (CDI) with the three most common liver diseases: NAFLD, viral liver disease (VLD, including HBV and HCV hepatitis), and alcoholic liver disease (ALD). They demonstrated that patients hospitalized with CDI and coexisting NAFLD had more favorable outcomes when compared to those with ALD and VLD individually. Moreover, they observed higher rates of intestinal complications in the CDI with NAFLD group when compared to the CDI with ALD or VLD groups. The study is written well and organized. I suggest to add to the title "in patients with chronic liver disease hospitalized with Clostridium Difficile Infection"

Answer: Title was modified based on suggestions in the manuscript file "Nonalcoholic Fatty Liver Disease is Associated with Worse Intestinal Complications in Patients with Chronic Liver Diseases Hospitalized for *Clostridioides Difficile* Infection"

2. Language polishing for revised manuscript – submitted by Native English Speakers

Among the authors of manuscript and revised manuscript, three of them are native English speakers with MD, DO, MSc, and BA degrees. The English language of this revised manuscript was reviewed and approved by all the authors including the Native English Speakers.

3. Abbreviations: Everything was modified based on the requirements.

4. Response to Science Editor

1 Scientific quality: (1) Classification: A Grade A. (2) Summary of the Peer-Review Report: The manuscript was well organized and well written. (3) Format: There is four tables and a supplementary table. (4) References: A total of 66 references are cited, including 26 references published in the last 3 years (5) Self-cited references: There is a self-cited reference. (6) References recommendations: None. 2 Language evaluation: Classification: A Grade A. 3 Academic norms and rules: Informed consent was waived. 4 Supplementary comments: None. 5 Issues raised:

(1) This study was interesting, but the association between NAFLD and CDI was unclear.

With the incidence of nonalcoholic fatty liver disease (NAFLD) and *Clostridioides difficile* infection (CDI) on the rise, early intervention is critical for reduction of morbidity and mortality rates. Gut microbiota dysbiosis has been repeatedly observed in other disease types of metabolic syndrome (such as type 2 diabetes and obesity), which strongly intertwined with NAFLD [1]. As such, there is more and more ongoing exploration of the gut-liver axis. As clinicians, the authors started to raise the question about the association of the aforementioned two common diseases more and more ongoing exploration of gut-liver axis. Despite fruitful basic science study results, there are very few clinical studies that have addressed the association between NAFLD and CDI. This study addressed the association of NAFLD and CDI by comparing the inpatient outcomes of CDI in patients with NAFLD, ALD (alcoholic liver disease) and VLD (viral liver disease). The results of this study are statistically significant and multiple confounding factors were adjusted during multivariate regression analysis. In the discussion part, we discussed possible mechanisms of the results and reviewed all related literature. Although the association or causality between NAFLD and CDI is still unclear, the authors hope that our study can create a platform for discussion and stimulate more exploration on the impact of NAFLD on the disease progression and outcome of CDI.

Reference

[1] Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, Nieuwdorp M, Clément K. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol. 2020 May;17(5):279-297. doi: 10.1038/s41575-020-0269-9. Epub 2020 Mar 9. PMID: 32152478.

(2) The classification of NAFLD or VLD was unclear.

The authors acknowledge that, the histological classification of nonalcoholic fatty liver disease (NAFLD) is widely accepted based on pathology from liver biopsy. It reflects the disease progression and helps to identify patients at risk of cirrhosis and liver-related death [1-2]. However, biopsy is not mandatory for the clinical diagnosis of NAFLD, as demonstration of hepatic steatosis by imaging and exclusion of other etiologies can be sufficient [3]. In this study, the diagnosis of NAFLD was based on the International Classification of Diseases-Ninth Edition Revision, Clinical Modification (ICD-9 CM) codes. The ICD codes assignments were based on physicians' clinical judgement and treatment response. The supportive clinical symptoms, signs, diagnostic labs and pathology results were shared between physicians and coding professionals, but not included in the National Inpatient Sample database. The authors did not include the exact histological classification of NAFLD because the percentage of patients underwent biopsies, and the histology results were not included in the database. Notably, despite the limitations of the database, significant efforts were made to evaluate the severity of liver diseases in this study: the percentage of cirrhosis and its related individual comorbidities, and hepatocellular carcinoma were included for analysis.

In regard to viral liver disease (VLD), this study used the combination of ICD-9 CM codes to select chronic liver diseases with positive hepatitis markers. Particularly, we focused on hepatitis B and hepatitis C virus related liver diseases, as hepatitis B and C related chronic liver diseases are commonly seen in the inpatient setting [4-5]. The authors acknowledge that remarkable progress has been made in our understanding of

the natural stages of chronic hepatitis B, which helps with long-term monitoring and optimal timing of antiviral therapy [6]. Hepatitis C related chronic liver disease also has complicated histological classification based on the degree of necroinflammation and the stage of fibrosis, to help guide treatment and determine prognosis [7]. However, due to the limitation of the current database, no lab results (such as HBsAg, HBeAg, HBV-DNA or HCV-DNA levels) or pathology results were available. Therefore, we could not further determine the clinical or pathological classification of VLD. Despite the limitation, our study focused on the different clinical phases of VLD: non-cirrhotic liver disease, cirrhosis, cirrhosis with complications and hepatocellular carcinoma, a comprehensive analysis was performed on a nationwide sample. The authors believe that our findings have good generalizability. In the meantime, this study opened the door for the design of future prospective studies. For example, future studies can include pathological study stages and classification in the inclusion criteria, and the possibility of subgroup studies to compare different pathological stages in chronic liver diseases, etc.

Reference

[1] Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. Drug Metab Rev. 2017 May;49(2):197-211. doi: 10.1080/03602532.2017.1293683. Epub 2017 Mar 17. PMID: 28303724; PMCID: PMC5576152.

[2] Hashimoto E, Tokushige K, Ludwig J. Diagnosis and classification of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: Current concepts and remaining challenges. Hepatol Res. 2015 Jan;45(1):20-8. doi: 10.1111/hepr.12333. Epub 2014 May 20. PMID: 24661406.

[3] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases.

Hepatology. 2018 Jan;67(1):328-357. doi: 10.1002/hep.29367. Epub 2017 Sep 29. PMID: 28714183.
[4] Kim WR. The burden of hepatitis C in the United States. Hepatology. 2002 Nov;36(5 Suppl 1):S30-4. doi: 10.1053/jhep.2002.36791. PMID: 12407574.
[5] Kruszon-Moran D, Paulose-Ram R, Martin CB, Barker LK, McQuillan G. Prevalence and Trends in Hepatitis B Virus Infection in the United States, 2015-2018. NCHS Data Brief. 2020 Mar;(361):1-8. PMID: 32487291.
[6] Shi YH, Shi CH. Molecular characteristics and stages of chronic hepatitis B virus infection. World J Gastroenterol. 2009 Jul 7;15(25):3099-105. doi: 10.3748/wjg.15.3099. PMID: 19575488; PMCID: PMC2705731.
[7] Dhingra S, Ward SC, Thung SN. Liver pathology of hepatitis C, beyond grading and staging of the disease. World J Gastroenterol. 2016 Jan 28;22(4):1357-66. doi: 10.3748/wjg.v22.i4.1357. PMID: 26819505; PMCID: PMC4721971.

5. Response to Company Editor-in-chief

(1) Core-tip audio is missing – it was recorded and uploaded.

(2) Please update manuscript format per journal guidelines. – format checked and modified in the manuscript file.

(3) Please provide Copyright License Agreement and *Conflict-of-Interest Disclosure Form.
- CLA provided by individual author, COI disclosure uploaded.