26 December 2022

Editor in Chief

World Journal of Hepatology

Dear Sir,

We are pleased to have been given the chance to revise our manuscript No. 81063, entitled

"Clostridioides difficile infection in patients with nonalcoholic fatty liver disease - Current Status" for publication in World Journal of Hepatology.

We also appreciate the constructive comments from the reviewers.

We addressed the reviewer' comments and revised the manuscript, accordingly, based on

the recommendations and suggestions.

A response to the reviewer' comments is provided below.

We hope that the revised version will meet the requirements for publication.

Sincerely yours,

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Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Reviewer Comments to Authors The manuscript presented by Yana V Kiseleva et al. aims to give an overview about the current status of research on the association of NAFLD with Clostridioides difficile infection (CDI) severity. The paper sounds easy to read and presents a wealth of information with regard to such a complex area of research. However, there are few issues that remain to be addressed. Major comments: 1) In most studies related to C. difficile/NAFLD, patients with different NAFLD severity stages; often present with heterogeneous lesions and variable demographic characteristics including age, sex and ethnic background, various comorbidities (obesity, type 2 diabetes, …), genetic susceptibility, which are known to influence the gut microbiome; are often overlooked. For example, it has been demonstrated that gut microbiota dysbiosis is exacerbated with increasing obesity severity [Le Chatelier, E. et al. Richness of human gut microbiome correlates with metabolic markers. Nature 500, 541 (2013); Aron-Wisnewsky, J. et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. Gut https://doi-org.bases-doc.univ-lorraine.fr/10.1136/gutjnl-2018-316103 (2018)]. These observations suggest that patients need to be stratified for each metabolic confounding factor. Authors must comment on these questions. 2) A perspective section needs to be included in the text. There are new approaches including metagenomics and multi-omics studies, gut microbiome sequencing, system biology strategies that can be used to study in depth the suggested association of Clostridioides difficile with NAFLD and explore the potential use of microbiome signatures as biomarkers for future metabolic alterations diagnosis. 3) A figure or a table summarizing the main information on C. difficile/NAFLD would help effective data presentation and make it easier for readers to understand the research in the manuscript. Minor comments: - Title: No need for the abbreviation of nonalcoholic fatty liver disease in the title. - Abstract section: first and second lines “Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, leading to fibrosis, cirrhosis and hepatocellular carcinoma (HCC), factors known to be associated with increased….”, the sentence is not clear (factors????). - Core Tip section: The sentence “More retrospective studies and systematic reviews are needed to examine this group of patients as a risk factor for CDI” is not clear, please rephrase. - Page 3, the title of the first paragraph is probably missing (Introduction?) - In this paragraph, the sentence “The current epidemiology of NAFLD is not totally understood ….” Is not clear, please clarify. - Page 4: line 6-7: the sentence “…. in 2017, the incidence was estimated at 223,900 with 12,800 deaths[14].” The citation needs to be checked. In the original reference (Ref #14 in this manuscript), it was written “In addition, nearly 223,900 people in the United States required hospital care for C. difficile and at least 12,800 people died in 2017.” - There are still some grammatical mistakes in manuscript that need to be checked. For example: “Therefore, a low level of secondary bile salts (and consequently a low concentration of secondary bile acid-producing bacteria) and a high level of primary bile salts, results in CDI and its recurrence[38].”

Answer.

Thank the reviewer for this important comment.

Despite the obvious relevance of the topic, there has been very little research on it to date. In this regard, the CDC of patients with NAFLD, a risk factor for CDI, remains unstudied. Moreover, patients with cirrhosis developed as a result of NAFLD often undergo courses of antibiotic therapy with an increased risk of infections, which is an additional risk factor for CDI. In order to prevent CDI in patients with NAFLD, it is necessary to find out whether CDC risk in these patients is increased using modern microbiome sequencing technologies, whether therapeutical correction of CDC in these patients is feasible, and whether this prevents the risk of CDI after antibiotic therapy. All of these questions need to be answered in further studies, which will enable the decrease of CDI among patients with NAFLD.

We have also added a table summarizing the main information on C. difficile/NAFLD would help effective data presentation and reflecting information from the literature sources used.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: My detailed comments are as follows: 1.This manuscript only describes the correlation between CDI and NAFLD. Is there any further research? 2.How can CDI be treated and prevented, and which drugs are effective against CDI? 3. What is the molecular mechanism of CDI?

Answer.

Dear reviewer! Thank you for your thorough review.

Unfortunately, despite its obvious relevance, only 4 studies have been conducted on this topic, most of which included a small number of observations. The purpose of this review is to draw attention to the topic, which will entail more research.

CDI treatment and prevention are highly publicized and included in various international clinical guidelines. They are not covered in this review as we intended to draw attention to the problem of the increased risk of CDI infection in patients with NAFLD.

The molecular mechanisms of CDI are covered in several publications (e.g. Vuotto C, Donelli G, Buckley A, Chilton C. Clostridium difficile Biofilm. Adv Exp Med Biol. 2018;1050:97-115. doi: 10.1007/978-3-319-72799-8_7. PMID: 29383666.). Describing CDI pathogenesis was outside the scope of our review.