ANSWERING REVIEWERS

October 11, 2019

Name of Journal: World Journal of Hepatology
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Manuscript Type: CASE CONTROL STUDY
Title: "Clinical characteristics and treatment outcomes in patients with liver cirrhosis and lymphoma"

Dear Editors and Reviewers,

First of all, we thank you for taking the time to review our manuscript. We welcome and appreciate your comments regarding our study and we believe they have enriched our manuscript.
Below please find a point-by-point response to the comments made by each of you.
We appreciate the consideration of our work for your journal.

Best regards,

Ricardo Ulises Macías-Rodríguez

Correspondence to: Ricardo Ulises Macías-Rodríguez, M.D., M.Sc., Ph.D., Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Belisario Domínguez Sección XVI, Tlalpan, Mexico City, 14080, Mexico.
Telephone: +52 55-54-87-09-00, ext. 2711
Fax: +52 55-56-55-22-24
Email address: ricardomacro@yahoo.com.mx

Reviewer #1: The manuscript is about a case-control study in patients with cirrhosis and lymphoma treated with chemotherapy. This is an interesting and well written manuscript about a clinical situation barely treated in the literature. The retrospective nature of the study and the number of patients imply important limitations as the authors state but other limitations and bias risks have not been considered and them must be taken in account before value the results.

- Concretely, the selection bias (data are from patients treated out of guidelines recommendations at the time. So, a selection of patients cannot be excluded) neither an immortal time bias by which selected patients were more prone to survive and to respond to chemotherapy. Authors must analyze both bias and discuss its possible influence in the results. It would be very interesting to compare survival and adverse events appearance between the case group and a control group formed by paired patients with cirrhosis and lymphoma non-treated with chemotherapy.

- We appreciate this important comment, we agree that case-control studies have several bias, mainly information bias and selection bias. We have added to the discussion the possible bias in our study. We considered that immortal time bias is not present because all patients had a minimum follow up of 2 years. Also, Kaplan-Meier Curves show how most patients reached an outcome.
- On the other hand, we completely agree with the reviewer on how it would be very interesting to add a group of cirrhosis and lymphoma without chemotherapy, however given the lack of available cases as described in Figure 1 and throughout the study, supported by the few available cases in the literature consisting only of case reports we are not able to add this group.

- It is important that authors define in the text accurately the minimum and maximum time difference between cirrhosis and lymphoma diagnosis to consider them as concomitant diagnosis.

- We have added this information in the results section, the median time between the diagnosis of cirrhosis and lymphoma was 2.16 years, with a range between the same diagnostic time and 8.6 years after the diagnosis of cirrhosis.

- In the "Characteristics of lymphoma in the population" section authors state that "the predominant histologic subtype was diffuse large B cell (80%) in 24 patients". This figure must be wrong.

- Thank you for pointing this out, with 24 cases we are referring to the cases in both groups, therefore to avoid confusion we specified that 7 cases belong to the case group and 17 to the control group.

- A detailed description of number and severity of infection cases in both groups must be included in the text. There were significant differences in the number of infections between groups?

- Thank you for your comment, in the results section we mention that in the case group there was only one infection in a patient who developed atypical pneumonia, whereas in the control group there were no infections. In Table 4 we show that infections occurred more in patients with cirrhosis (1 cases vs. 0 controls, p = 0.103), although it was not statistically significant.

- In the discussion section, categorical statements such as "these patients have risk factors related to both the development of cirrhosis (such as HCV infection) and disease per se (alterations in immune surveillance), which confers an increased risk of developing neoplastic diseases, including lymphomas" must be supported by references.

- Thank you for you observation, we added three references (19-21) to support this statement. [Negri E, et. al. B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review. Int J Cancer 2004;111:1-8 & Sorensen HT, et. al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide

cohort study in Denmark. Hepatology 1998;28:921-925 & Lombardo L, et. al. Malignant lymphoproliferative disorders in liver cirrhosis. Ann Oncol 1993;4:245-250]

- The conclusion paragraph should be more prudent and consider the numerous limitations and bias of the study.

- We agree with the reviewer and we have softened the conclusion statement, as can be now seen in the modified manuscript.

Reviewer #2: Authors constantly refer to C-P classification without giving further details. To better appreciate the importance of the decompensation of the studied patients, key point, Authors are warmly requested to refer to a modern classification as that presented in both...What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? BMC Gastroenterol. 2009 Nov 24;9:89 ...and... Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol. 2009 Mar 17;9:21. Deepening this aspect makes it clear what was the class to which belonged the patients (appropriate Table) and skips the doubts about the value of the median C-P score that is 7.5 (low for a decompensation) and explain in this way why the patients were classified as decompensated (80%).

- We appreciate your comment and agree that it was unclear how decompensation was defined. We have added the decompensation criterion in the materials and methods section.
- We considered decompensated cirrhosis as a CTP class B or C (Garcia-Tsao G, et. al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2017;65:310-335), or by the presence of an overt clinical decompensation (D'Amico G, et. al. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 patients. J Hepatol

2006;44:217-231 & D'Amico G, et. al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563-576).

Reviewer #3: Gonzalez-Regueiro JA et al attempted to reveal clinical characteristics and treatment outcomes in patients with liver cirrhosis and lymphoma and found in this manuscript that it was possible to administer chemotherapy in cirrhotic patients, regardless of their severity, obtaining satisfactory clinical outcomes. English writing is fair (few grammatical error) and this work is worth enough for possible publication in WJH. Major comments. 1. Please explain or even speculate the reason why the incidence of H. pylori infection is significantly higher in lymphoma with liver cirrhosis compared to lymphoma without it. Minor comments. 1. Provide page number in the manuscript. 2. Page 6, lines 21. It is well know … is It is well known … 3. Table 3, lines 8. The cases of Hodgkin lymphoma in controls are 2 (10%) instead of 2 (20%) since the total number of controls are 20.

- Major comment: Thank you for your comment, we agree with the relevance of the finding from the association between Helicobacter pylori and liver cirrhosis. Prompted by your comment, we made an extensive search in the literature and found two studies with adequate methods that have demonstrated a higher prevalence of Helicobacter pylori in patients with liver cirrhosis, especially in those with viral etiology, probably due to disturbances of immunologic functions. Therefore, we have made the relevant changes in the discussion section and added two references (22,23). [Helicobacter pylori infection among patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2017;29:1161-1165 & Association between cirrhosis and Helicobacter pylori infection: a meta-analysis. Eur J Gastroenterol Hepatol 2014;26:1309-1319].
- Minor comments: We added the page numbers to the manuscript, made another careful revision of the spelling and corrected the spelling error of "known", as

well as, the number of cases of Hodgkin lymphoma in the control group in Table 3.

Reviewer #4: This is an interesting study about chemotherapy of lymphomas in cirrhotic patients. There are not many informations about this. Were the HCV viremic cirrhotics treated for the viral infection along the chemotherapy or after the end of this? This would be very interesting to be mentioned.

- We agree with the reviewer in regards to the importance of HCV. There were five patients with viral cirrhosis due to HCV, four of them were treatment naïve at the time of lymphoma diagnosis, and one of them had been treated previously and achieved sustained virologic response before the onset of lymphoma. Only one treatment naïve patient could receive antiviral treatment after chemotherapy. The reason the other three patients were not treated for HCV is that were diagnosed before the era of new direct acting antivirals and interferon was contraindicated in decompensated patients. We have added this information in the results section.