Journal of Clinical and Translational Research
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A global multi-center propensity matched analysis of mortality risk and palliative care referral due to cirrhosis in hospitalized patients with COVID-19

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1st Editorial decision
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Ref.: Ms. No. JCTRes-D-22-00103
A Global Multi-Center Study of Mortality Risk and Palliative Care Referral in Hospitalized Patients with Cirrhosis and COVID-19
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Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Sep 23, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: the manuscript entitled A Global Multi-Center Study of Mortality Risk and Palliative Care Referral in Hospitalized Patients with Cirrhosis and COVID-19 is original , unfortunatly the effectvof liver insuffisiancy ie ; effect of child pugh score cannot be assessed ; it will be intersting to know ift the effect of
hepatocellular carcinoma could be assesed the paper is of interest

EDITOR:
Dear authors,

Thank you for submitting this paper to JCTR.

I have the following comments:

1) The manuscript requires thorough proofreading. Please engage a native speaker, a third-party contractor, or contact the editor (m.heger@jctres.com). JCTR has editorial staff that could perform a deep dive on language, structure, and content for a fee.

2) To make Table 1 optically more intuitive, please make the statistically significant P-values boldface in both the propensity score-unmatched and propensity score-matched columns. Also, in the propensity score-matched column, color the cell of the P-value red to designate an increase in the COVID + cirrhosis group relative to the COVID group and red for a decrease in the COVID + cirrhosis group relative to the COVID group.

3) Why did the authors not perform hazard ratio analysis on different cirrhosis-causing comorbidities and behavioral patterns, such as NAFLD, hepatitis, and alcohol abuse? It would be interesting to see whether the primary outcome parameters (palliative care and mortality) are further influenced by any of these prevailing causes and alcohol abuse. NAFLD, alcohol abuse, and chronic HepC accounted for cirrhosis in 45.3%, 27.5% and 23.9% of the patients, respectively, which should yield enough data points (from N = 1968) for the subanalysis. These subgroup analyses, including the one described in the Results only (ascites), could be presented in a separate table.

4) Please only use abbreviations for phrases that recur frequently in the manuscript and ensure that all abbreviations are written out in full at first mention.

5) When referring to statistics related to PC, please indicate which country the stats pertain to.

PC as a concept itself and its practical implementation differs per country.
"PC referral rate in cirrhosis is variable and can range from 1% in 2006 to 7%
in 2012 (16,17)" is an exemplary sentence for such specification. The database used covers global statistics, whereas the practical application of the results is focused on a specific region.

Authors' response

Reply to the reviewers

Our sincere thanks to the reviewers and editorial team for reviewing our manuscript. I have answered all the questions/observations point wise (as below). Corresponding changes (except English language correction) are highlighted in yellow in the revised manuscript.

Reviewers' comments:

Reviewer #1: the manuscript entitled A Global Multi-Center Study of Mortality Risk and Palliative Care Referral in Hospitalized Patients with Cirrhosis and COVID-19 is original , unfortunatly the effectvof liver insuffisiancy ie ; effect of child pugh score cannot be assessed ; it will be intersting to know ift the effect of
hepatocellular carcinoma could be assesed the paper is of interest

Thanks for this pertinent question- the data available did not include the details of hepatocellular carcinoma and we could not analyze this specifically, but we have addresses this in another paper of ours. We did not have clinical details on severity of hepatic encephalopathy on individual patients, so calculation of CTP score for individual subjects were not feasible (Clin Gastroenterol Hepatol. 2021 Nov;19(11):2450-2451.e1. doi: 10.1016/j.cgh.2021.05.010. Epub 2021)

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1) The manuscript requires thorough proofreading. Please engage a native speaker, a third-party contractor, or contact the editor (m.heger@jctres.com). JCTR has editorial staff that could perform a deep dive on language, structure, and content for a fee.

We have reviewed manuscript with a native speaker and made changes in language as appropriate, thanks for recommending that

2) To make Table 1 optically more intuitive, please make the statistically significant P-values boldface in both the propensity score-unmatched and propensity score-matched columns. Also, in the propensity score-matched column, color the cell of the P-value red to designate an

increase in the COVID + cirrhosis group relative to the COVID group and red for a decrease in the COVID + cirrhosis group relative to the COVID group.

Thanks for the suggestion, P values that were statistically significant in propensity matched group was made bold. We did not change the values in unmatched group to bold, as many variables like age, gender, comorbidities appear significant, which by propensity matching were excluded as non-significant. We are happy to change those (to bold) if you feel that helps with better understanding

3) Why did the authors not perform hazard ratio analysis on different cirrhosis-causing comorbidities and behavioral patterns, such as NAFLD, hepatitis, and alcohol abuse? It would be interesting to see whether the primary outcome parameters (palliative care and mortality) are further influenced by any of these prevailing causes and alcohol abuse. NAFLD, alcohol abuse, and chronic HepC accounted for cirrhosis in 45.3%, 27.5% and 23.9% of the patients, respectively, which should yield enough data points (from N = 1968) for the subanalysis. These subgroup analyses, including the one described in the Results only (ascites), could be presented in a separate table.

Very good observation

Identification of etiology in global data samples have inherent data recording variability. Some patients have concurrent multiple etiologies, like alcohol use, obesity and chronic viral hepatitis. But most of the time one of them get coded into diagnosis, this could be the condition the provider felt as the main etiology for progression of liver disease. That is why we did not include the etiology into hazard ratio analysis. Alcohol use disorder could not be objectively quantified as we do not have granular data for that variable, and the definition of non-alcohol use fatty liver and alcohol use fatty liver is variable in different regions of the world.

4) Please only use abbreviations for phrases that recur frequently in the manuscript and ensure that all abbreviations are written out in full at first mention.

Yes, we made respective changes, thanks for suggesting that

5) When referring to statistics related to PC, please indicate which country the stats pertain to. PC as a concept itself and its practical implementation differs per country. "PC referral rate in cirrhosis is variable and can range from 1% in 2006 to 7% in 2012 (16,17)" is an exemplary sentence for such specification. The database used covers global statistics, whereas the practical application of the results is focused on a specific region.

Yes, very pertinent observation. The two studies I mentioned in the above references were from Europe and US respectively. But I did not specify regions because, this was not representative of Europe or US. Within Europe and US, we see different rates of referral in different regions and within same region rates are variable based on the institutional set up. I further clarified this sentence as below.

PC referral rate in cirrhosis is variable and can range from 1% in 2006 to 7% in 2012, and the referral rates depends on geographic area and national or regional institutional policies (16,17)

2nd Editorial decision
30-Aug-2022

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A Global Multi-Center Study of Mortality Risk and Palliative Care Referral in Hospitalized Patients with Cirrhosis and COVID-19
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: