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# Peer Review Report for "Mortality and its Determinants in Adult Patients with End-stage Liver Disease on Waiting List for Liver Transplantation: A Preliminary Report on Baseline Data"

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**Review Timeline:**

| | |
|---|---|
| Submit Date: | 19 Oct 2020 |
| Revised Date: | 29 Nov 2020 |
| Accepted Date: | 7 Jan 2021 |

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

**REFEREE**: Associate Editor | **Revision** (0) 3 Nov 2020

Dear EIC,
This study was designed to assess the predictors of mortality. 544 adult LT, referred from different regions of Iran to the LT center of Shiraz, were followed by mean of 12 months and by 3 months intervals.
In general, this is interesting issue but there are also many important aspects and concerns in various parts of the manuscript, especially the methodology, that authors need to address and revise.
Writing
- English language needs extensive and professional editing.
Methods
- Methods should be fundamentally revised. The main problem is the selection of cases. The case selection of this study is " after exclusion of patients who did not provide consent to participate in this study, 544 adult (≥18 years) patients with ESLD were followed.". What co-morbidities (as important confounding factors) have they had and why they are not

excluded or not considered in the final regression analysis? What was the main reason for referring people to the Tx center? The inclusion and exclusion criteria of this study do not seem to estimate the true mortality and its determinants in adult patients with end-stage liver disease on waiting list.

- The authors designed this research as a prospective cohort study. because this study is prospective, the authors should address the detailed of methods of measurements including Self -health assessment, FB-420 (?), Nutritional Determinants, socioeconomic characteristics, type of nutritional F/U (validated questionnaire?) Portal hypertensive gastropathy, Hepatopulmonary syndrome, Hepatorenal syndrome, and so on.
- Some measurements do not appear to be clinically relevant for mortality analysis and do not require regression, for example gallbladder wall edema and MCV. On the other hand, based on several published studies, it has been confirmed that important conditions such as pulmonary liver syndrome, hepatorenal syndrome, SBP, variceal bleeding and comorbid disorders have a significant impact on pre-Tx mortality, so these conditions should be considered in Multivariate Reg analysis.

Results

- Due to significant problems in methods in selecting individuals, the results may not be generalizable to the community in that area.

Discussion

- Because of important problems in methods in selection of cases, these results could be not generalizability for clinical practice and discussion, so discussion should be re-wright after revising the methods and results.

The authors mentioned that “We did not find other studies on associations of high CA 125.. are probably the first reports on such an association”. Several articles have been published about the association of CA 125 and the prognosis of cirrhosis. (J Clin Transl Hepatol. 2018 Sep 28; 6(3): 241–246. CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension: A Retrospective Study), (Gastroenterol Res Pract. 2015; 2015: 121060. The Significance of Serum CA-125 Elevation in Chinese Patients with Primary Budd-Chiari Syndrome: A Multicenter Study).

Thanks.

**REFEREE**: EIC | **Revision (0)** 8 Nov 2020

Dear Authors,

Revision is required.

Thanks.

**OPEN PEER REVIEW**

**Revision (1)**

## Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

**Dear Reviewer**

**Thanks a lot for your valuable and professional review and your comments about our manuscript entitled ;** Mortality and its Determinants in Adult Patients with End-Stage liver disease on Waiting List for Liver Transplantation: A Baseline-Data Based Preliminary Report.

**For point to point answering, R was considered as Reviewer's comment and A as Authors' answer.**

Respectfully, authors' views are listed below:

**$R_1$**: ***English language*** needs extensive and professional editing.

**$A_1$**: We reedited the manuscript through sending it to a professional editing company.

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**R2:** The main problem is the selection of cases. The case selection of this study is " after exclusion of patients who did not provide consent to participate in this study, 544 adult (≥18 years) patients with ESLD were followed." **What was the main reason for referring people to Tx center**? The **inclusion and exclusion criteria** of this study do not seem to estimate the true mortality and its determinants in adult patients with end-stage liver disease on waiting list.

**A2**: You are right, but considering the so many difficulties that we confronted in conducting interviewing with ESLD patients (who had come from different parts of Iran) in one session and in the same day who had come for assessment by transplantation commission and on the other hand our strict commitment for observing of ethical codes, limited our access to all referring patients. As it was highlighted in the 1st line of the Design and Sampling part of Methods, we did not have any exclusion criteria except non-willing to participate in this study. Our target group

(as it was explained in the Methods part; Designing and sampling) were patients who had been referred from different regions of Iran to the liver transplantation center of Shiraz and were registered as candidates for LT. However, not all of these patients were nominated by commission for transplantation. There were also some patients that were missed in our follow ups, for example due to wrong mobile phones numbers or three times non-responsive phone calling or their cancelling liver transplantation by themselves. Our estimation showed that these dropped out groups and non-volunteered ones were cumulatively around 25% of all referred patients. For further clarification we added and highlighted these points as limitation in the end of discussion part.

……

**R3**: What ***co-morbidities*** (as important confounding factors) have they had and why they are not excluded or not considered in final regression analysis?

**A3**: We studied a lot a variables in this study, as it was explained more, restated and highlighted in the method (data collection part) of the revised version, history of cigarette or hookah smoking, alcohol drinking, drug use, diabetes mellitus, hypertension, hyperlipidemia, asthma, gastrointestinal Diseases (GI diseases), kidney diseases and cancer as well as causes of ESLD were among studied variables. Frequencies of all of these variables were added in and highlighted in the 1st paragraph of result part, but as we highlighted in the 2nd paragraph of result part (for abstinence of verbosity), we only showed the statistically significant variables in the tables 2-1,2-2 and 3 and figure 2. For further clarification, we explained in the result part (2nd paragraph) that other studied variables did not show statistical significant association with mortality of patients.

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**R4:** The authors designed this research as a prospective cohort study. because this study is prospective, the authors should address the detailed of methods of measurements including Self -health assessment, FB-420 (?), Nutritional Determinants, socioeconomic characteristics, type of nutritional F/U (validated questionnaire?) Portal hypertensive gastropathy, Hepatopulmonary syndrome, Hepatorenal syndrome, and so on.

**A4**: This study was a prospective cohort follow up study, that its type is follow up one. We assessed the association of outcome of death and baseline data.

- ***Self -health assessment***: As it was mentioned in the 3rd line of data collection, health assessment was based on the subjective (self) assessment of patients of their health status. A variable that we thought is important and was not assessed before by other studies. This variable was significant in the univariable analysis (as was shown in the table 2-1), and emphasizes on the necessity of mental counselling for LT candidates.
- ***FB-4*** : There are many evidences for FIB-4 as a simple, accurate, and inexpensive method for assessing liver fibrosis as : VALLET-PICHARD eT aL .HEPATOLOGY, Vol. 46, No. 1, 2007 (https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/hep.21669). This evidence was highlighted and added to the end of data collection part of Methods.
- ***Nutritional Determinants*** **and** ***Type of nutritional F/U (validated questionnaire?)***:

In the two last lines of data collection of Methods part of manuscript, it was explained that nutritional status was assessed by 24 hrs dietary recall. This method is a well-known and valid type of nutritional assessment among nutritionists (Jee-Seon Shim et al. Epidemiology and Health,Volume: 36, Article ID: e2014009, http://dx.doi.org/10.4178/epih/e2014009). The validated persian version of this checklist was used in many studies.

- ***socioeconomic characteristics (SEC)***: SEC was queried through interview with patients in the 1st visit as explained in the 6th line of data collection of Method part. These characteristics were shown in the table 1.
- ***Portal hypertensive gastropathy, Hepatopulmonary syndrome, Hepatorenal syndrome, and so on***: These medical data were extracted by recruited GP from the medical records of patients,as was explained in the last lines of the 1st paragraph of the data collection of Method part.

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**R5:** Some measurements do not appear to be clinically relevant for mortality analysis and do not require regression, for example gallbladder wall edema and MCV. On the other hand, based on several published studies, it has been confirmed that important conditions such as pulmonary liver syndrome, hepatorenal syndrome, SBP, variceal bleeding and comorbid disorders have a significant impact on pre-Tx mortality, so these conditions should be considered in Multivariate Reg analysis.

**A5**: We analyzed all studied variables as hepatopulmonary syndrome, hepatorenal syndrome, SBP, variceal bleeding and comorbid disorders. However, as it was explained in the above (**A3**), we only showed the significant ones in the tables 2-1,2-2,3 and figure 2. Only variables with $p<0.2$ in the univariable analysis ( as it was discussed in the Data analysis part of Methods) were entered into multivariable analysis (CPH model). Hepatopulmonary syndrome, weight loss ,MI were became significant in CPH besides some other variables. Regarding MCV and Gall bladder wall edema that became significant in both univariable and multivariable analysis (even with a HR more than MELD score), let us to keep these variables in the study, as we

should not and did not want to assess only previously known determinants of mortality in our study.

- Macrocytic anemia was found to be associated with the severity of liver impairment and might be a predictor for short-term mortality in patients with HBV-related decompensated cirrhosis.( Yang, J., *et al.* Macrocytic anemia is associated with the severity of liver impairment in patients with hepatitis B virus-related decompensated cirrhosis: a retrospective cross-sectional study. *BMC Gastroenterol* **18,** 161 (2018). https://doi.org/10.1186/s12876-018-0893-9) or High MCV may be an indicator of alcoholism -related liver disease (Morgan MY, et al. Macrocytosis in alcohol-related liver disease: its value for screening. Clin Lab Haematol. 1981;3(1):35-44)
- Regarding Gall bladder wall thickening, it was shown that in patients with cirrhosis, ascites, low systemic vascular resistance and hepatic vein pressure gradient were associated with gall-bladder wall thickening. (Wang TF, et al Gall-bladder wall thickening in patients with liver cirrhosis. J Gastroenterol Hepatol. 1997 Jun;12(6):445-9. doi: 10.1111/j.1440-1746.1997.tb00464.x. PMID: 9195402.)

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**R6:** Discussion : Because of important problems in methods in selection of cases, these results could be not generalizability for clinical practice and discussion, so discussion should be re-wright after revising the methods and results.

**A6:** As we explained in the A2, our estimation showed that dropped out groups and non-volunteered ones were cumulatively around 25% of all referred patients. Therefore, we added

and highlighted these points as limitation in the end of discussion part.

……

**R7**: The authors mentioned that “We did not find other studies on associations of high CA 125.. are probably the first reports on such an association”. Several articles has been published about the association of CA 125 and prognosis of cirrhosis. (J Clin Transl Hepatol. 2018 Sep 28; 6(3): 241–246. CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension: A Retrospective Study), (Gastroenterol Res Pract. 2015; 2015: 121060. The Significance of Serum CA-125 Elevation in Chinese Patients with Primary Budd-Chiari Syndrome: A Multicenter Study).

**A7:** Thank you. We corrected our statement and added your recommended two references in the discussion and highlighted them.

**Thank You again for yours time spending for reviewing this manuscript.**

**Authors**

**OPEN PEER REVIEW**

**Revision (1)**

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

**REFEREE**: Associate Editor | **Revision** (1) 7 Jan 2021

Dear EIC,
In my opinion, due to the corrections made, the manuscript with the new format is acceptable.
Thanks.

**REFEREE**: EIC | **Revision** (1) 7 Jan 2021

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.