

ANSWERING REVIEWERS



We thank the reviewers for their comments. Below are our point by point responses to the reviewers and editors comments. We also enclose a copy highlighting these changes in the revised manuscript.

Reviewer no 31627- The paper shows that the synergistic interaction between alcohol and HCV leads to a more aggressive disease prior to LT including higher wait-list mortality. However, the impact of mixed disease after LT remains unclear, with conflicting findings, suggesting the need for more prospective multicenter studies on a larger sample size to better examine this question and devise strategies to improve the management of these patients. The review is well done and interesting.

Reviewer no 6993- Review of Manuscript for World Journal of Gastroenterology Authors: Khan et al. Title: Outcomes after Liver Transplantation for Combined Alcohol and Hepatitis C Virus Infection Overall, in the present manuscript, Khan et al provided a summary on the outcomes after liver transplantation in patients with alcohol consumption and hepatitis C virus infection. The topic is interesting to readers and important in the field. There are the following issues that need to be addressed. Issues: 1. Abstract: The abstract is neither well-written nor organized. Please revise it and make readers easier to follow.

We have modified the abstract as per journal requirements.

2. Page 3, Baseline Characteristics, please add a table/footnote summarizing the findings described in the Baseline Characteristics.

We have created a master table including the various baseline characteristics with all the available data from different studies.

Reviewer no 53634- The authors review the current literature on the outcome of patients receiving liver transplantation for liver disease due to HCV + alcohol mixed etiology. The topic is very interesting and somewhat original. However, there are some minor points that the authors have to address before recommending publication 1) I suggest the title to be Outcomes after Liver Transplantation for Combined Alcohol and Hepatitis C Virus Infection.

The title has been modified as suggested.

A review 2) The abstract is not well written and poorly informative. The authors should clarify that they set a review and the main results of their work

The abstract has been modified as per journal requirements

3) A paragraph on HCV epidemiology as well as alcohol abuse epidemiology (current and future scenario, natural history, therapies, etc.) is needed The authors can find interesting these article that can be cited in reference section: - Davis GL, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*. 2010 Feb;138(2):513-21, - Gentile I, et al. Concomitant interferon-alpha and chemotherapy in hepatitis C and colorectal cancer: a case report. *In Vivo*. 2013 Jul-Aug;27(4):527-9. - Shepard CW, et al. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis*, 2005;5:558–567. Coppola N, et al. Anti-HBc positivity was associated with histological cirrhosis in patients with chronic hepatitis C. *Ann Hepatol*. 2013 Jan-2014 Feb;13(1):20-6. - Gentile I, et al. Efficacy and Safety of Sofosbuvir in Treatment of Chronic Hepatitis C: The Dawn of the New Era. *Rev Recent Clin Trials*. 2013 - van de Laar TJ, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. *J Infect Dis* 2007; 196:230–238. ; - Wakefield JC, Schmitz MF. How Many People have Alcohol Use Disorders? Using the Harmful dysfunction Analysis to Reconcile Prevalence Estimates in Two Community Surveys. *Front Psychiatry*. 2014 Feb 3;5:10
4) Some points of the manuscript are difficult-to read and would need a further polishing

HCV epidemiology is mentioned as prevalence as well as contribution to total cases of cirrhosis.

Reviewer no 52899- Rashid Khan et al in this manuscript reviewed the data on the outcomes of liver transplants in HCV drinkers compared to alcohol abuse or hepatitis C alone. They declared that the synergistic interaction between alcohol and HCV leads to more aggressive disease prior to LT including higher wait-list mortality. And they also concluded that some conflicting data on this issue should be performed in larger prospective and multicenter cohort in the future study. Overall, this manuscript is well prepared with good writing and large novelty. Specific comments:
1. I don't think it would be a good topic of review for comparing outcomes of liver transplants in populations with different etiologies. Normally, a systematic review using meta-analysis would be better for this issue. The authors should address the reason why the systematic review has not been used. Is there not enough number of literatures for this topic?

We did not use a systematic review as the data on this topic is scarce in general. Studies are few, individual patient numbers are few, methodology/study designs vary, and hence we felt a review article would be suitable.

2. The authors should present a comprehensive table including basic characteristics, waiting list mortality, survival rate, HCV recurrence and alcoholic relapse. The current table 1 with survival is too simple.

We have modified the table to include other variables and make it more comprehensive as suggested.

In page 4, the authors concluded that “patients transplanted for mixed etiology tend to have a more aggressive and advanced liver disease at the time of transplantation”. However, this conclusion is conflict with the words in the same paragraph “patients with alcoholic cirrhosis were sicker at the time of transplantation than those with cirrhosis secondary to HCV or mixed etiology”. The author should clearly address this issue.

We agree with the reviewers and have modified this sentence to read it better. Patients with mixed etiology in general have aggressive course and faster progression to end-stage liver disease requiring liver transplantation. This is supported by younger age at transplantation and shorter duration of liver disease history prior to transplantation among patients with cirrhosis due to mixed etiology.

4. In page 5, the five years survival in transplants for HCV cirrhosis, alcoholic and cirrhosis mixed etiology varied significantly among different studies. The authors are recommended to present more details in this issue.

Factors such as variations in the study design, data source, study population, and sample size may explain differences in the findings among various studies. Anti-HCV treatment and of re-transplantation in patients with cirrhosis due to mixed etiology as compared to the other two groups may explain the conflicting results. These data on HCV treatment are not available in studies reporting data using UNOS or European LT databases.

5. The authors reviewed the five year survival in patients transplanted for different etiology. However, the 5 year survival only partially reflects overall graft and patient survival. Is there any data on the 3 year survival in related literatures?

We included 3 year survival data from studies reporting this in the more comprehensive table in this revised version.

6. There are several typographical errors?

We reviewed the manuscript again and corrected any typos, grammar, and spelling errors.