ONGResponse Letter

To Whom It May Concern:

Responses to comments from reviewer number: 503243

1. **Only one point to be added: what to do with patients with ALD and HCV infection:** We aimed to focus our paper on those transplanted for ALD alone, however we discussed HCV as a risk factor for alcohol relapse in a new section: "**HCV infection** HCV infection and ALD often co-exist and approximately 8-10% of liver transplantation performed was for mixed HCV and ALD cirrhosis [47]. Aguilera et al, compared post-transplantation outcomes among patients transplanted for alcoholic cirrhosis, mixed alcoholic cirrhosis and HCV and HCV alone. Interesting, there was no significant difference in rate of alcohol relapse between the mixed HCV and alcoholic cirrhosis group (8%) and the alcoholic cirrhosis group (18%). Alcohol relapse also does not affect liver histology or liver functions tests in recipients with concomitant HCV versus ALD alone [48]. Additionally, rates of rejection and graft loss were not significantly different between the mixed HCV and ALD and ALD groups. While recurrence of HCV is a major cause of reduced survival in patients transplanted for HCV cirrhosis, 5-year survival was comparable between the mixed HCV and ALD group (73%) and alcoholic cirrhosis group (76%) [49, 50]. Though further studies are warranted, based on these studies, presence of HCV does not appear to result in greater risk of alcohol relapse or worse post-transplantation outcomes."

Responses to comments from reviewer number: 504392

1. **State what the most frequent indication is for liver transplantation … Give a percentage of alcohol liver disease as indication for liver transplantation:** I included in the introduction that Hepatitis C virus (HCV) infection was the most

frequent diagnosis for liver transplantation and I also included the percentage of liver transplantation for alcoholic liver disease: "Alcohol use disorder (AUD) affects nearly 10% of the general population in both the United States (US) and Europe and is one of the most frequent causes of liver cirrhosis in the Western world [1]. After Hepatitis C virus infection, alcohol liver disease (ALD) is the second most common indication for liver transplantation (LT) in the US and Europe [2, 3]. According to the OPTN/SRTR 2015 annual report, 21% of liver transplantation was for alcoholic liver disease [4]."

2. **Probably it might make sense to distinguish between intrinsic (internal) and extrinsic risk factors for recidivism:** I clarified which patient factors were intrinsic versus extrinsic. The main extrinsic factor discussed is social support so I reworded my sentences: "Lack of social support is an extrinsic factor that has consistently been associated with an increased risk of relapse for patients transplanted for ALD [13, 28, 37, 38]." Our main intrinsic factor is comorbid psychiatric conditions so I reworded the sentence: "The presence of psychiatric comorbidities or previous diagnosis of a mental illness has been found to be an important intrinsic risk factor associated with an increased risk of alcohol relapse for patients transplanted for ALD [19, 28, 37]." Since the ARRA scoring system includes several different intrinsic and extrinsic risk factors for recidivism, I reworded the section where I listed the 9 risk factors to: "In terms of the Alcohol Relapse Risk Assessment (ARRA), a study hypothesized 25 risk factors and found 9 to be significantly predictive of alcohol relapse. This scoring system includes both intrinsic and extrinsic risk factors of alcohol relapse. The

intrinsic factors include low motivation for alcohol treatment and poor stress management skills. The extrinsic factors include limited social support, engagement in social activities with exposure to alcohol and lack of nonmedical behavioral consequences. The remaining factors are absence of hepatocellular carcinoma, dependence on tobacco and ongoing alcohol use after diagnosis of liver disease."

3. **Make clear, that the 6 month rule will open the chance for improvement of liver function so that transplantation will no longer be needed in a considerable percentage of cases with alcoholic liver disease:** We believe this is an important point to include. I changed the "6 month rule" paragraph to include the presumed purposes for the 6-month rule based on EASL guidelines. "Many centers require 6 months of abstinence to be listed for liver transplantation. The 6 month rule has two presumed purposes: to allow patients to recover from their liver disease and preclude the need for liver transplantation and to identify patients who are likely to remain abstinent after liver transplantation [1]. Nonetheless, there are conflicting findings as to whether this length of abstinence is needed to reduce the risk of relapse [11, 25-27]."
4. **Is there a difference between noncompliance and nonadherence with regard to liver transplantation?** I believe this is regarding the section "Noncompliance with clinic visits." I clarified the definition of noncompliance with clinic visits based on the Egawa et al paper: "Egawa et al found noncompliance with clinic visits, defined as 3 absences without notice, after LT to be associated with both alcohol relapse and harmful drinking [39]." Additionally, for the cross-sectional study by Lamba et al, I

changed “non-adherence to clinic appointments” to “missed clinic appointments” to avoid any confusion between noncompliance and nonadherence throughout the paragraph: “Furthermore, a cross-sectional study found that those who missed clinic appointments had lower adherence to immunosuppressive medications after liver transplant for any etiology ($p<0.001$) [45]. In the study, non-adherence to immunosuppressive medications was liberally defined as any missed doses of transplant medications [45]. This finding is significant because strict adherence to immune suppressant agents is a very important factor in long-term outcome after liver transplant [46]. In multivariate analysis, missing physician appointments was the only independent factor associated with non-adherence to immune suppressants.” I also defined how the study determined non-adherence to medications by adding the sentence, “Non-adherence to immunosuppressive medications was liberally defined as any missed doses of transplant medications [44].” This was determined by self-report on a survey.

5. **The SIPAT has not yet been studied ‘exclusively’ or separately in liver transplant patients … ?** So far studies on SIPAT include liver, lung, kidney and heart transplant recipients. There are no studies of the SIPAT in liver transplant patients only. I changed the term exclusively to separately to avoid confusion: “The SIPAT has not yet been studied separately in liver transplant patients.”
6. **What is the frequency of occasional slips, abusive and harmful drinking after liver transplantation. This details could be introduced into table 1:** For the “Definitions” section and Table 1, I wanted to focus on the definitions of the various terms rather than the frequency. Since frequency of the various amounts of drinking

is important to mention, I included the general frequency of any drinking, harmful/abusive drinking and occasional slips in the introduction: "In terms of patterns of alcohol use, there are varying frequencies given the different definitions and follow-up periods, but in general approximately 12-33% of liver recipients for ALD relapse to abusive or harmful amounts of drinking [11-14] and 6-26% relapse to occasional slips after transplantation [12, 14, 15]." I also included the frequency of slips and continuous heavy drinking in the section "Consequences of alcohol use on allograft outcomes" from the Rice et al study: "In the study, 20.8% of patients had a single slip and 33.3% of patients relapsed to continuous heavy drinking [36]."

Sincerely,

Jane Lim, Michael P Curry and Vinay Sundaram