

## **Detailed Response to Reviewers**

**Name of journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 11204

**Post-transplant recidivism in liver transplantation for alcoholic liver disease and its medical, public, and ethical perception**

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Our point-by-point replies to all comments of Reviewers #1 and #2 are as follows:

### **Reply to the comments made by Reviewer #1**

*A review paper on liver transplantation for Alcoholic Liver Disease. It would be important: 1) to present more details of the literature data; and 2) to add the ethical aspects of LDLT indication for alcoholic patients. The English language needs revision.*

Thank you for reviewing our manuscript. We totally agree with the comment by the Reviewer #1. We have revised our manuscript as follows.

*1) to present more details of the literature data*

In order to present more details about LT for ALD and emphasize concerns on recidivism, we added a recent topic about LT for alcoholic hepatitis which is more controversial than alcoholic cirrhosis.

(Revised)

***Concerns on LT for acute alcoholic hepatitis without abstinence period***

***Alcoholic hepatitis is a distinct clinical syndrome associated with recent or ongoing alcohol consumption, and its severity leads to high mortality exceeding 50% [35, 43-46].***

Medical treatment including the use of corticosteroids and/or pentoxifylline reduces the mortality rate to approximately 20 %-30%.<sup>[43, 47]</sup> Non-responsive patients suffer high mortality, and thus LT for alcohol hepatitis has been proposed in select patients.<sup>[35, 47, 48]</sup> However, alcoholic hepatitis is a controversial indication or even a contraindication for LT in most institutions<sup>[49, 50]</sup> due to the high potential for alcohol recidivism and conceivably due to the lack of pre-transplant abstinence period. A recent prospective multicenter study showed clear improvement on the odds of survival among patients unresponsive to medical therapy and followed with LT for severe alcoholic hepatitis.<sup>[35]</sup> The 6-month and the 2-year survival rates among LT patients were significantly higher than those among non-LT patients (6 months; 77±8 % vs. 23±8, P<0.001, 2 years; 71±9 vs. 23±8, P<0.001). The survival rate of patients who underwent LT was comparable to that of patients who responded to medical therapy. (77±8 vs. 85±4, P=0.33). The overall recidivism rate with relapse was 12 %, with no case of alcoholic relapse within the initial 6-month follow-up period after LT. Similar survival rate was reported in a retrospective study comparing LT outcomes for alcoholic hepatitis to those of alcoholic cirrhosis.<sup>[48]</sup> The survival rate after LT for patients with alcoholic hepatitis showed no significant difference compared to those with alcoholic cirrhosis (1 year; 93% vs. 88%, P=0.33, 2 years; 91% vs. 84%, P=0.24, 5 years; 80% vs. 78%, P=0.91). However, both studies mentioned visible difference in society's readiness towards transplants for ALD and other self-inflicted liver diseases, despite their comparable mortality. In fact, criticism from the public is not present in response to LT for patients with fulminant hepatic failure stemming from voluntary acetaminophen poisoning, nor intravenous-drug users with acute hepatitis B virus infection.<sup>[35, 48]</sup> In order to gain public acceptance, some sensitive issues surrounding LT for alcoholic hepatitis need to be addressed even though the medical benefits of LT have been proposed for strictly-selected patients. (page 9, line 5 - page10, line 15)

(Revised)

Incidentally, recent studies encourage medical benefits of LT for alcoholic hepatitis whose medical therapy was ineffective, but such patients are likely to have consumed a certain high volume of alcohol recently or on an ongoing basis, with high potential of recidivism anticipated. LT for alcoholic hepatitis is still a highly controversial issue from the public point of view, and needs to be resolved. (page 15, line 16 - page 16, line 3)

*2) to add the ethical aspects of LDLT indication for alcoholic patients*

As the Reviewer #1 pointed out, the ethical aspects were not clearly described. In order to comment on this issue, we have revised the manuscript as follows.

(Revised)

***Public and ethical perspective on LDLT for ALD***

LDLT for ALD may seem to be generally accepted by society from a public point of view because it does not conflict with organs allocation issues as DDLT for ALD does. Nevertheless, ethical issues remain. First, liver transplantation professionals are confronted with difficult situations caused by the dilemma between strong willingness displayed by family to donate and compliance with pre-transplant abstinence rule. For instance, those professionals working in most institutions feel obliged to inform patients and their family member who may have prospective living donors that the requirement of 6-month abstinence period is still applicable, even when some of them are not expected to survive more than 6 months. Secondly, recidivism is not readily accepted by society even if the organ is donated by a family member because LT is supported by national- and/or social- welfare systems in general. LDLT for ALD, inseparable from the public opinion, becomes a complicated topic that requires a viewpoint slightly different from DDLT for ALD when addressing their issues. (page 13, line 11 - page 14, line 6)

(Original)

Although LDLT may not necessarily link to organ allocation issues, considerable efforts to improve post-transplant outcome are required to recompense the potential risks run by living donors. (page 13, lines 5 - 8)

(Revised)

LDLT, **unlike DDLT**, may not necessarily link to organ allocation issues, **but it is nonetheless inseparable from the public eye in an ethical standpoint**. Considerable efforts to improve post-transplant outcome are required to recompense the potential risks run by living donors. (page 15, lines 5-9)

(Original)

Further evaluations on these issues are anticipated to control alcoholic recidivism more effectively to improve the outcome of LT for ALD patients. (page 14, 1-3)

(Revised)

Further evaluations on these issues are anticipated to control alcoholic recidivism more effectively to improve **not only** the outcome of LT for ALD patients **but acceptance from society as well**. (page 16, lines 8-10)

*The English language needs revision.*

As the reviewer #1 pointed out, we revised several descriptions in English again with the support of a professional for grammatical correction. All revised expressions were written using the red color. Please see the revised manuscript.

## **Reply to the comments made by Reviewer #2**

*authors concisely summarized the current data on the problems of liver transplantation for alcoholic liver disease and recidivism. my minor comments are: \*title should be shortened by emphasising the problem of recidivism. \* there are repetition of knowledge even sentences in sections of the manuscript, these should be avoided.*

Thank you for reviewing our manuscript and finding values in our manuscript. We agree with the comment by Reviewer#2. The prevention of post-transplant recidivism is the most important treatment after LT to improve both medical benefits and public acceptance. To reduce the possibility of recidivism, pre-transplant abstinence has been focused. In accordance with the recommendation about the title and the repeated description pointed by the Reviewer #2, we revised the title and the manuscript as follows.

(Original)

**Current Status and Future Perspectives of Liver Transplantation for Alcoholic Liver Disease and Considerations on Living-Donor Liver Transplantation.**

(Revised)

**Post-transplant Recidivism in Liver Transplantation for Alcoholic Liver Disease and its Medical, Public, and Ethical Perception.**

(Original)

Alcohol recidivism, which impairs the long-term outcome of ALD patients after LT <sup>[6-11]</sup>, must be prevented through multidisciplinary approaches to avoid graft loss as well as to recompense potential risks run by living donors. (page4, line 16 – page 5, line 2)

(Revised)

**Nevertheless, prevention of alcoholic recidivism is inevitably the most important factor to enhance medical benefits of LT and to gain more public acceptance as well.** (page 4, line 16-18)

(Original)

Alcoholic recidivism has been considered to negatively impact and result into poor long-term outcomes for recipients, such as through liver damage caused by alcohol toxicity, poor compliance, development of post-transplantation malignancies and occurrence of cardiovascular diseases. (page 7, line 1-4)

(Revised)

**Alcoholic recidivism has been considered to negatively impact postoperative compliance and long-term outcomes of recipients.** (page 7, line1-2)