

ANSWERING REVIEWERS

Dear Editor,

Thank you and the reviewers for the useful suggestions and comments regarding our manuscript entitled: Host Factors are Dominant in The Development of Post-Liver Transplant Non-Alcoholic Steatohepatitis.

We are enclosing point by point responses to all of the queries below and have incorporated the changes into the manuscript as indicated. We hope that this revised version of the manuscript will be acceptable for publication in the "World Journal of Hepatology".

We also want to mention that we are ready to make any change that reviewers would further suggest to consummate our manuscript.

Kindest regards,

Salih BOGA, MD

Responses to Reviewers' Comments

Reviewer 1:

This is an interesting case report about post transplant NASH comparing two different scenarios (two different hosts) from a unique donor from a split liver transplant. It proposes that split liver transplant might be an interesting tool to study the pathogenesis of NASH in the post transplant period. I do agree that this might be a very interesting tool to study the pathogenesis of NASH in the post transplant, but more than this split liver transplant may reinforce the importance of the host factors and also donor factors on the long-term outcome of liver transplant. The present case report shows two completely different scenarios one of a baby and the other a host who already has metabolic syndrome in the pretransplant period. The outcome is obviously expected and there is a lot of data considering host factors as crucial for the development of NASH. Although the manuscript lacks originality in this aspect

(host factors as predictive factor for NASH development) it proposes an interesting tool to study NASH in the post transplant which is the split liver transplant graft. It is well written and the content is clearly stated. Minor comments: on page 9 line 10-12 there is some mistake concerning the segment of recurrence of the HCC – this should be revised and the phrase rewritten

Response: The data regarding the size and segment of recurrence of HCC is included to the manuscript.

Reviewer 2:

Split liver transplantation is an interesting experimental system to examine the host factors affecting the development of steatohepatitis in transplanted liver. As authors described in this reports, host factors are divided into changeable factors and unchangeable factors. 1. Authors should compare the changeable and unchangeable host factors in the two recipients. 2. Description of the post transplant clinical course is too simple. Details of the post transplant clinical course should be illustrated in figures that is helpful to accentuate the difference of the both cases. 3. Nowadays, Several SNPs and genetic factors related to the development of NASH have been revealed. Clarify the genetic background as far as possible.

Response: The changeable and unchangeable host factors are included to the 'Discussion' segment of the manuscript as: "Of the factors mentioned above; age, genetic background and even pretransplant history of alcoholic cirrhosis may be considered as unchangeable host factors where as post-transplant life style changes, diet, glycemic control by anti-diabetic medications, control of weight gain, hyperlipidemia therapy and immunosuppressive medications are changeable host factors that can affect the presence and progression of post-LT NASH."

We are sorry but we could not realize how to illustrate the post-transplant clinical courses of the patients in figures. However, post transplant clinical courses of

patients were presented in details including post-transplant operations, interventions and medications.

The only known genetic background was the heterozygosity for genetic hemochromatosis of the adult patient. Because we did not find iron accumulation in the liver biopsy of the adult recipient, we suggest that iron did not play any additional role in the genesis of steatohepatitis.

Reviewer 3:

Although there are several differences in the background between two recipients, for instance, child/adult, primary liver disease, and treatment after transplantation, this report is a valuable case report to understand the pathogenesis of steatohepatitis after transplantation. Minor revisions are needed. 1.Higher magnification of histology from the donor liver and case 1 should be shown. 2.There are missing words in the line 11, page 9.

Response: Higher magnifications of histology from the donor liver and case 1 are added to the manuscript and figures are re numbered again as figures 1a-1b, 2a-2b and 3a-3b. The data regarding the size and segment of recurrence of HCC is included as well.

Reviewer 4:

This is a very interesting case report of post-transplant NASH. The split liver transplantation revealed that NASH affected livers but had non-liver causes. Most hepatologists had thought it but had no direct evidence. This report provides the direct evidence to the hypothesis. To amplify the scientific value, latest related articles should be cited. For example, "Prevalence and risk factors of steatosis after liver transplantation and patient outcomes" (Hejilova I et al., Liver Transpl 2015), seems a very important paper for the present case report. In page 9, the size of recurrent HCC should have been described

Response: The article recommended by the reviewer was cited with the reference number '18' and was mentioned in the discussion part of the manuscript as :
“Recently Hejlova et al. examined 2360 post-transplant biopsies of 548 LT recipients to identify risk factors for the development of significant steatosis and found alcohol induced cirrhosis as a pre-transplant factor that is associated with significant post-transplant steatosis^[18].” The data regarding the size and segment of recurrence of HCC is included as well.