Dear Editor,

We have enclosed the revised version of our manuscript –entitled "NONINVASIVE MARKERS OF LIVER STEATOSIS AND FIBROSIS AFTER LIVER TRANSPLANTATION - WHERE DO WE STAND?"

We thank you and the reviewers for the very helpful comments. We accepted all the comments and have included our responses below. We hope the revised version is acceptable for publication.

Rewier 1

This review by Dr. Mikolasevic and collaborators focused on steatosis and fibrosis after liver transplantation. The topic is of interest, given the high prevalence of both conditions after transplantation, and the significant improvement of patient outcomes after introduction of specific treatments for viral hepatitis. My comments: - The Authors cited a study by Baghat et al (ref #11) saying that recurrent steatosis and steatohepatitis were more frequent after LT in patients with NASH than in those with alcoholic liver disease. The latter group may experience a de novo steatohepatitis, and not a recurrent. - A high rate of BPAR is not a common finding in patients with NAFLD. - I suggest to use the term NAFLD more frequently, replacing, whenever possible, the term NASH (i.e., transplant for NAFLD instead of "transplant for NASH"), in order to make the manuscript easy to understand. Similarly, the term NAFL appears only at page 19, whereas steatosis is adopted throughout the manuscript. - In my opinion, the section "Nonalcoholic Fatty Liver Disease After Liver Transplantation" should be re-considered, highlighting results provided by cited metanalysis and summarizing current gaps of knowledge on NAFLD (both de novo and recurrent) after LT. For instance, prevalence of post-LT NAFLD differed across studies also because of different follow-up time, different diagnostic tools used, etc.. - The Authors said that non-invasive tools as APRI, FIB-4, NFS are not so useful in the post-LT setting due intrinsic pitfalls (i.e., thrombocytopenia). Nevertheless, they cited many studies which demonstrated a good accuracy also in the post-LT setting. A further interpretation given by the Authors may be important for the Readers on this issue. - The Authors well described potential pitfalls of Transient elastography for a non-invasive assessment of fibrosis. Nevertheless, they mentioned studies on pre-LT setting. I suggest to focus more on post-LT patients, shortening the first paragraph. Moreover, the usefulness of TE for ACR or during donor graft evaluation is interesting, but in my opinion goes beyond the scope of this manuscript. - I agree with the Authors that no drugs are currently available for the management of NAFLD, especially in the post-LT setting. Nevertheless, monitoring NAFLD may be useful also in the setting of immunosuppression management. - English language polishing needed. There are some redundant sentences that would be shortened or deleted. Minor: - ref#11: Baghat instead of Baghet - per protocol instead of protocolary - page 18: post-transplant instead of non-transplant ? - Ref # 76: the follow-up time should be mentioned, in order to better understand the high prevalence of post-LT cirrhosis

Response: Thank you. We have done it.

Rewier 2

In the invited review the authors aimed to summarize the data on evaluation of steatosis and fibrosis after liver transplant settings in particular in the context of recurrent NAFLD. Overall, the review is well written although it is quite lengthy and has only two tables, no figures, which are, to my view, necessary to attract the readership. The review has multiple parts that can be probably better structured

to allow the reader better orientation. Having the main focus on non-invasive markers of liver steatosis and fibrosis after liver transplantation, almost 5 pages are related to overall Non-alcoholic fatty liver disease after LT. While the information is important it may be important to include a figure or at least table to summarize the lengthy content. The key message is to provide the global overview on existing methods to evaluate fibrosis and steatosis in post LT subjects. Surprisingly, the TE and CAP (Fibroscan) receive the largest attention while SWE and MRI elastography receive very little attention. Since the focus is set to global non-invasive methods and markers, it is recommended to expand on this topic. Alternatively, the title needs to be adjusted to the transient elastography. It is also important to expand on the point that identification of NAFLD in post LT settings does not mean to have therapeutic options and it is quite questionable to reflect on economic burden and potential consequences. No doubt that biochemical markers including APRI and Fib4 are and will be useless in such a complex condition as post LT. A clear statement in the related chapter may be helpful. I would recommend revising the sentence:. “It has been suggested that LB is the best available standard of reference for fibrosis evaluation, although it is an imperfect gold standard because we do not have a better reference standard”. At present it is well accepted that histology is the gold standard (it is not suggested), the second part of the sentence makes no sense. Besides, histology provides also additional information regarding the other common questions including rejection etc. Separating chapter on CAP may be recommended to allow better structuring of the paper. The authors state the potential of CAP to replace the liver biopsy for assessment of liver fat assessment. Unfortunately, at present it is not sufficient evidence to support this message. While TE (including SWE) indeed helps the evaluation of fibrosis, the CAP values are still very heterogeneous and it is too early to state the value of CAP in post liver transplant. One of the most significant limitations so CAP is the missing outcome based on the CAP-values. Page 18: sentence needs revision- “...ill defined”. Please consider revising similar sentences.

Response: Thank you. We have done it.

Rewier 3

This review article summarized clinical tools that are currently available for assessment of graft steatosis and fibrosis after liver transplantation. These tools included various laboratory markers and imaging modalities, mainly ultrasound-based technology. 2. The article spent more spaces in discussing the background of steatosis than fibrosis. This created a sense of imbalance, since steatosis and fibrosis were both stated in the title. Whether the word "fibrosis" specifically referred to "fibrosis related to NAFLD" need to be clarified. If not, it seems that the article omitted substantial contents regarding graft fibrosis. 3. The first three paragraphs of TRANSIENT ELASTOGRAPHY mentioned the utility of TE and CAP for assessment of NAFLD in the pre-LT status, which is not the main focus of this article (post-LT). It is probably better try to reduce the length of this section and make it more concise for the readers. 4. pSWE/SWE are widely utilized in current practice. MR elastography is also an emerging imaging modality. The article only mentioned these tools briefly, which is probably inadequate to provide a general picture for the readers interested in this field. 5. MRI is also capable of assessing liver steatosis using different kinds of methods, and are currently available for clinical application. 6. In the third paragraph of “Usefulness of transient elastography in the post-LT setting” - “…..TE with CAP in diagnosing fatty liver disease in nontransplant patients.”: nontransplant ? 7. In the last sentence of the last paragraph of “Usefulness of transient elastography in the post-LT setting” - “Until then, imaging methods could identify NAFL, but LB should be used to identify NASH [16].”: NAFL ?

Response: Thank you. We have done it.