

Number ID: 03475636

Manuscript NO: 39635

World Journal of Hepatology,

May 24th, 2018

**Re: World Journal of Hepatology, Invited Manuscript NO: 39635 entitled
"Liver Transplantation and Atrial Fibrillation: A Systematic Review and Meta-analysis"**

Dear Editor,

Thank you for the thoughtful input and review of our manuscript. The reviewers' inputs are extremely helpful. We believe as a result of this review, our study would have more value for your readers. We revised the manuscript based on the reviewer's suggestions. We have attached our point by point response.

As the invitation and our status Number ID: 03475636 as a contributor to the F6Publishing system, we are thankful that it is acknowledged by waiving of the publication fee for "Review Articles" authored and submitted that are accepted for publication in the BPG journals.

Thank you for your time and consideration. We look forward to hearing from you.

With many thanks for your attention, I remain.

Sincerely yours,

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Response to Reviewer

Comment #1 (Number ID 03538158)

Chokesuwattanaskul et al. performed the meta-analysis about atrial fibrillation in liver transplantation. Authors should discuss the cause of AF in liver transplantation more.

Response: Thank you for your response. The following text has been added to the discussion part of full article. We also construct the diagram, presented as **Figure 6**, illustrating the postulated mechanism of AF in liver transplantation.

There are also several mechanisms explained why liver transplantation promote the occurrence of atrial fibrillation during postoperative period (Figure 6). Firstly, conventional postoperative hemodynamic challenge could provoke atrial fibrillation through hemodynamic instability or inotropic administration (50). Also, some preexisting liver diseases, such as nonalcoholic fatty liver disease (NAFLD), share a common risk factor, that is diabetes and obesity, with the AF patients (53). In addition, NAFLD could also occur as de novo after liver transplantation and subsequently enhances the postoperative complications, contributed by systematic inflammatory mechanism (54-56). Furthermore, immunosuppressive therapy increases the risk to develop insulin resistance which eventually leads to metabolic syndrome (57). Various kind of cirrhosis-specific heart diseases, such as a well-known entity called congestive hepatopathy, prior to transplantation play a substantial arrhythmogenesis role as a substrate for pathogenesis of atrial fibrillation (50, 58). Various underlying medical problems including AF would,

in the future, be used to identify high-risk patient population that needs to be optimized the treatment to achieve higher outcome after liver transplantation.

Comment #2 (Number ID 00058381)

Major Comments: This manuscript provides a review and a meta-analysis on atrial fibrillation before and after liver transplantation. Limitations are mentioned by the authors at the end of the discussion. Minor Comments: First Page, "Authors' Contributions": The contribution of each of the authors should be specified in more detail. Introduction, first sentence: "peoples" -> people. Results, first paragraph: "After the exclusion of 83 articles based on title and abstract for clearly not fulfilling inclusion criteria on the basis of type of article, study design, population or outcome of interest, leaving 38 articles for full-length review." - Please complete this sentence. Discussion, first paragraph: "to those patients who underwent heart transplantation (incidence of AF up to 40%) (39-44) other open-heart surgeries (incidence of AF up to 50%) (5, 45, 46)." -> to those patients who underwent heart transplantation (incidence of AF up to 40%) (39-44) or other open-heart surgeries (incidence of AF up to 50%) (5, 45, 46). Discussion, penultimate paragraph: "Our study has a several noteworthy limitations. Firstly, heterogeneities in definition, for an example how to define AF, early and late development of AF, among the different studies precludes to draw the definite causality, in addition to association. Secondly, duration of follow up over the postoperative period, by some study trace forward for just 30 days post-transplantation, does not long enough to reveal the long-term morbidity and mortality outcome." - Please correct/improve these three sentences. Discussion, last paragraph: "In conclusion, our study demonstrated the prevalence of preexisting AF in patient underwent liver transplantation, incidence of AF post-liver transplantation and association of AF with

higher morbidity and mortality among liver transplant recipients. Further studies are needed to explore in detail of AF in these patients, which we strongly believe that AF management would be an important part in the care of liver transplant.” - Please correct/improve this paragraph as well. Table 1: All the abbreviations should be explained (AKI, ATTRm). Table 1 (20-23), “Outcomes”, rightmost column: “Study aim to compare outcome as CV event after liver transplant between patient with NASH and those with alcoholic cirrhosis who receive liver transplant” -> ...patients... Table 1 (20-23) and (28-31), second column, Newcastle-Ottawa scale: “E3”? Figure 3: “Nicolau-raducu” -> Nicolau-Raducu.

Response: Thank you so much for your response. Reviewer is correct. We have made the following change according to recommendations. Also, we replied every question in this comment with supporting information provided below.

We have added detail for author’s contribution to be more specified in detail on the first title page. We categorized our job into conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis and supervision.

We have corrected the penultimate paragraph and added the following text into the discussion section of full text: **“Our study has noteworthy limitations. Firstly, an inconsistent in definition, for an example how to define the timing of atrial fibrillation as an early or late onset, among the different studies preclude to draw the generalized conclusion. Such this limitation, data use needs tailoring to the individual patient. Secondly, duration of follow up during the postoperative period**

by some study prospectively monitored a cardiovascular event for just 30 days post-transplantation, which this time frame does not long enough to reveal the long-term morbidity and mortality outcome.”

We also have corrected the last paragraph of discussion section in full text. The following text has been replaced the prior version of this paragraph: **“In conclusion, our study demonstrated the actual prevalence of preexisting AF in patient underwent liver transplantation, incidence of AF post-liver transplantation. Our study also highlighted the association of AF with higher morbidity and mortality among liver transplant recipients. Further well-designed studies are needed to explore the impact of AF in liver transplant patients, which we strongly believe that AF management, specified to liver transplant patients, would be an important strategy to augment standard of care in this particular population.”**

We have explained all abbreviations under Table 1.

E3 is corrected assessment by Newcastle-Ottawa quality assessment scale for case-control study, which is done by both Bargehr et al. and VanWagner et al.

We have corrected the name of author in Figure 3 by changing “Nicolau-raducu” to **“Nicolau-Raducu”**. Please find new Figure 2 attached with this submission.

Comment #3 (Number ID 00051373)

A meta-analysis to investigate the relationship between AF and liver transplant patients. An interesting topic and an extensive review. It should be benefit to the most of the readers in the

liver transplantation setting. Well manuscript written and organized regarding to easily understanding.

Response: Thank you for your response. We tried our best to provide the most updated and comprehensive review in the purpose of expanding the reader's horizon regarding this particular "growing-interest" issue.

Comment #4 (Number ID 03253490)

Chokesuwattanaskul et al. investigated 'Liver Transplantation and Atrial Fibrillation'. The topic is interesting. The author should discuss the mechanisms and types of cardiovascular complications and AF in advanced liver diseases more.

Response: Thank you for your response. Even though we intended to emphasize role of AF in liver transplant patients, we cannot deny that cardiovascular complications other than AF is also associated with higher morbidity and mortality in post-transplant patient. Therefore, the following text has been added to discussion section of full text.

"Leading cause of long term mortality in patients with liver transplantation is cardiovascular complications which, other than AF, includes heart failure and myocardial infarction. These complication is predominantly driven by the development of metabolic syndrome after liver transplantation. However, this topic of interest is beyond the scope of our study and could be explained elsewhere (50). More or less, these cardiovascular

complications were also considered as potential risk modification that should not be overlooked.”

Thank you for your consideration.

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