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Professor Clara Balsano, Ph. D.; Professor Wan-Long Chuang, M.D., Ph. D.
Editors-in-Chief

World Journal of Hepatology

Dear Sirs:

Please find attached our revised manuscript entitled "THE SYSTEMIC-TO-PULMONARY ARTERY PRESSURE RATIO AS A PREDICTOR OF PATIENT OUTCOME FOLLOWING LIVER TRANSPLANTATION" for consideration of publication in World Journal of Hepatology. This paper should be of interest to all your readers. The manuscript has been revised incorporating all the reviewer's comments and suggestions.

All authors have contributed to the design and conduct of this original manuscript which has not been previously published, and has not been submitted for publication elsewhere. All authors have written, read and approved of the submitted manuscript.

The authors thank the reviewers for the thoughtful and helpful comments which serve to strengthen the manuscript. All of the suggestions have been addressed in the revised manuscript. Specifically, the following issues have been considered:

see blue.
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Reviewer 02936520

Thank you for your comments:

> *The authors attempt to assess the usefulness of mean AP/mean PP in cases of OLTx. This is not an entirely new idea as pulmonary hypertension is a known adverse risk factor and a predictor of bad outcomes in cases of cardiac surgery. ?* De Pietri L1, Montalti R, Begliomini B, Reggiani A, Lancellotti L, Giovannini S, Di Benedetto F, Guerrini G, Serra V, Rompianesi G, Pasetto A, Gerunda GE. ? Pulmonary hypertension as a predictor of postoperative complications and mortality after liver transplantation. Transplant Proc. 2010 May;42(4):1188-90. doi: 10.1016/j.transproceed.2010.03.068. ? Zhen-Dong Xu,1,* Hai-Tao Xu,2,* Wei-Wei Li,2 Zui Zou,2 and Xue-Yin Shi2 Influence of preoperative diastolic dysfunction on hemodynamics and outcomes of patients undergoing orthotopic liver transplantation. Int J Clin Exp Med. 2013; 6(5): 351–357. PMCID: PMC3664002 ? Cristina Ripoll1, Raquel Yotti2, Javier Bermejo2, Rafael Ba?ares1, The heart in liver transplantation. J Hepatol 2011, 54 (4); 810–822. doi:10.1016/j.jhep.2010.11.003 ? Gautam Ramakrishna, MD?; Juraj Sprung, MD, PhD?; Barugur S. Ravi, MD?; Krishnaswamy Chandrasekaran, MD?; Michael D. McGoon, MD? . Impact of Pulmonary Hypertension on the Outcomes of Noncardiac SurgeryPredictors of Perioperative Morbidity and Mortality. J Am Coll Cardiol. 2005;45(10):1691-1699. doi:10.1016/j.jacc.2005.02.055 ?

We fully agree with the reviewer's assessment of impact of pulmonary hypertension on the outcome after liver transplantation. It is well documented that right heart dysfunction and the presence of pulmonary hypertension negatively affect the survival after the procedure. However, our study collective were patients with normal preoperative cardiac workup and normal pulmonary pressures. The focus of our study was the value of the intraoperative pattern of the MAP/mPAP ratio as an indicator for cardiac function/cardiac reserve. This intraoperative pressure ratio as a predictor of outcome for OLT has not been previously examined.

> *However, the strong point is that the measurements included different time points in the course of the preoperative and operative phases. The conclusion that the anhepatic phase is the valid predictor of outcome is novel. However, this is a unique study in the sense that it has related pulmonary hypertension ie decreased or stable mean arterial pressure to mean pulmonary pressure ratio in cases of OLTx.*

Thank you for your evaluation.

> *The use of vasoactive agents has to be clarified in greater detail. This does not affect the final outcome of the study. That an elevated mean AP/PP ration is a good prognostic parameter. However, it does lend weight to the fact that use of vasoactive substances in cases of OLTx may have a favorable effect on the AP/PP ratio during the anhepatic phase and therefore should be advocated .*

We agree. Unfortunately due to the retrospective nature of the study we are not able to provide more detailed information about the use of vasopressor during the surgery. We provided information about frequency and type of vasopressor support (similar between group 1 and 2). More information about cumulative dosing can not be extracted from the medical records. We are in the process of a prospective clinical trial allowing us a more detailed assessment and better control of other variables (as vasopressor therapy).

Reviewer 00049727

Thank you for your comments:

In this paper, Rebel et al. evaluated the MAP/mPAP ratio as a potential indicator for poor outcome after OLT. This paper may raise awareness to MAP/mPAP ratio. I think the following points will further improve the quality of your paper.
1. Is it possible to modulate MAP/mPAP ratio by therapeutic intervention? Please discuss this insight in more detail.

Thank you for your comment. A paragraph to address possible therapeutic interventions to modulate the MAP/mPAP ratio has been added in the discussion.

2. Figure 1: The text is too small. Please increase the letter size.

Thank you. The font size has been changed.

3. Could you perform prospective validation study? Your hospital had many OLT cases.

We are in the process of a prospective clinical trial, possibly as a multi-institutional project to validate our findings, control more variables (as vasopressor use) and provide more information about pathophysiology/usefulness of the MAP/mPAP ratio.

Reviewer 00504591

Thank you for your comments and very helpful suggestions:

Rebel et al described that the systemic to pulmonary artery pressure ratio can be a predictor of survival after liver transplantation. I have some comments.
(Major) (P7, L1) The definition of groups are unclear. The author described that MAP/mPAP ratio by >= 1 from baseline to anhepatic phase were categorized into Group 1. Please define the MAP/mPAP ratio of the baseline. Is it the MAP/mPAP ratio before the operation? Next point is as to the MAP/mPAP ratio of the anhepatic phase.

The initial data for MAP/mPAP ratio at Baseline for both groups are shown in Table 2 (group 1 3.32±0.73, group 2 4.13±1.19). A description of the measurement points are clearly defined in the method section (page 6, second paragraph): Baseline MAP/mPAP ratio was measured 30 minutes after incision, with a second measurement point 'pre-anhepatic' = 1hr before IVC cross-clamp, and the third measurement point 'anhepatic' = 15min before reperfusion. Since IVC cross-clamp times in our institution are approx. 50-55min, the MAP/mPAP ratio was measured 35-40min after IVC cross-clamp. These definitions are clearly given in the methods section.

Anhepatic phase is not a pin point time but is a term which has a duration usually more than one hour. During the duration, the MAP/mPAP ratio should be fluctuate. How do the authors define the MAP/mPAP ratio of the anhepatic phase? (P21, Table) Also please explain how the measure point of the MAP/mPAP ratio during the pre-anhepatic, neo-hepatic phases. (P15, L3 from the bottom)

As referred to in our response above, MAP/mPAP measurement points are described in the methods section (page 6, second paragraph). In our institution the anhepatic period is usually less than 60min. To account for fluctuations in this anhepatic period we chose a measurement point at 15min before reperfusion (IVC cross-clamp release) to allow sufficient equilibration time for reduction in cardiac preload caused by the IVC flow interruption.

The author refer the manuscript number 3 in which the preoperative MAP/mPAP ratio was significantly higher in survivors of the cardiac surgery. However not referring the paper on the cardiac surgery, previous paper (Bushyhead D et al. Liver Transpl. 2016 Mar;22(3):316-23) has already disclosed that the preoperative MAP/mPAP ratio was a prognostic factor of liver transplantation. The author should consider referring the paper.

The Bushyhead publication focused on the preoperative echocardiographic parameters (such as pulmonary systolic artery pressure) associated with increased postoperative complications and did not examine the MAP/mPAP ratio. However, we agree with the reviewer that the paper provides useful information that supports our findings. A paragraph examining the implications of the Bushyhead paper has been added to the discussion.

(Minor) (P22) The legend of the table is too much, which should be short or explain in the results section. (P23) The legends of x axis in Figure 1 cannot be seen which should be replaced with clearer and larger letters.

The table and figure have been changed. The table legends have been shortened. However, we did not remove information about the measurement points since a reviewer specifically requested more information about this data.

Reviewer 27958

Thank you for your comments:

Title: THE SYSTEMIC-TO-PULMONARY ARTERY PRESSURE RATIO AS A PREDICTOR OF PATIENT OUTCOME FOLLOWING LIVER TRANSPLANTATION The aim of this retrospective study was to assess the value of the MAP/mPAP ratio for predicting outcomes following OLT. The investigators used the changes MAP/MPAP ratio during the anhepatic phase relative to the pre-anhepatic as a factor that impacted the patient outcomes. The outcome criteria that they used

were: duration of ICU and hospital stay, duration of post-transplant intubation and mechanical ventilation. Here are my comments:
1- The paper needs some minor language editing and correction of some grammatical errors.

The manuscript has been revised and has been reviewed/edited by a native English speaking scientific assistant.

2- The extubation time should be changed to duration of post-operative intubation and/or mechanical ventilation; it makes more sense that than term (extubation time).

Thank you for this suggestion, the terminology has been changed.

3- Not sure why the investigators selected the anhepatic phase, it would be better if they selected the post-re-perfusion phase which is the most stressful phase during OLT. They could compare the post-reperfusion phase to the baseline and/or to the neohepatic phase.

We chose the anhepatic phase because it represents a single hemodynamic alteration (preload reduction) and for a prolonged duration (in our institution approximately 45 minutes). Therefore, all patients will undergo a similar type of cardiac stress. While we agree with the reviewer that reperfusion can cause cardiac strain, the cardiac response to reperfusion depends on multiple factors and some of them may be due to the donor organ. The duration of reperfusion is usually short and therefore changes in MAP/mPAP may be not reflecting the cardiac response to the changes in preload, cardiac contractility or afterload. We are not aware of a publication showing that reperfusion is the most stressful situation during OLT. Based on observation of the cardiac index (pulmonary artery catheter) and transesophageal echocardiography monitoring of cardiac function, the anhepatic phase creates significant cardiac stress to support our approach to focus our attention on the MAP/mPAP changes during this surgical period. We are in the process of a prospective clinical trial in order to validate our findings. In this next study we will obtain continuous pressure measurement – therefore allowing a 'stage independent' MAP/mPAP tracing.

4- It seems that the preferred surgical technique that they used is cross-clamp the IVC without veno-venous bypass and without piggy-back technique, this will lead to cut-off 50% of venous return and 50% decrease in the pre-load which explained the use of high vasopressors during this phase. The changes in the MAP/MPAP ratios may be due to use of the vasoconstrictors and not changes in the cardiac condition which is different from the patients undergoing cardiac surgery where the primary etiology is pump dysfunction. The dose and the type of the pressors they used may affect the SVR and PVR, for instance vasopressin has little or no effect on the PVR while strongly affects the SVR which will be reflected by positive changes in the MABP/MPAP. Although, I do not doubt their findings but in my

opinion during such tremendous variations in the SVR/PVR and use of pressors and IV fluid administration, it is very difficult to make such a conclusion.

We agree that the variation in vasopressor use during the anhepatic period may have affected the MAP/mPAP ratio pattern. Due to the retrospective study design we are only able to provide information about frequency, dose range and drug combination during the anhepatic period. Our data analysis did indicate that the vasopressor use was similar between both groups, and therefore should not account for the differences in MAP/mPAP ratio pattern seen between group 1 and 2. More detailed quantitative analysis of vasopressor/inotrope use will be performed during our next prospective clinical trial.

5- I am not sure that their speculation that the outcomes are truly related to the variations in the intraoperative ratios of MABP/MPAP! They did not explain what was the etiology of such post-operative courses (prolonged hospital/ICU stay, prolonged intubation), surely they cannot be due to changes in these ratios!

Based on the observational and retrospective character of our study, we are not able to speculate on the etiology of our observations. The focus of the manuscript has been to report our findings and raise awareness (as indicated by reviewer #00049727 and 02936520). We are in the process of a prospective clinical trial, possibly as a multi-institutional project to validate our findings, control more variables (as vasopressor use) and provide more information about pathophysiology/usefulness of the MAP/mPAP ratio.

6- It may be an interesting and new finding in these patients, but it requires further validation! I suggest that they should check the ratios during the ICU stay and if it correlates to post-operative course, check the ratios during the reperfusion phase and try to find the real cause of the complicated post-operative course in group-2.

Thank you for your suggestions. We are in the process of a follow up prospective study. We will obtain more data concerning the postoperative period.

7- Any consideration for the graft function, sepsis, AKI all can be the reasons for postoperative complications in group-2.

We have recorded the frequency of postoperative complications as described in the results section. Due to the retrospective character of the study we are unable to provide additional information on the etiology of the postoperative complications.

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I trust the above additions and changes in the manuscript are to your entire satisfaction. Please let me know if you require any additional information.

I look forward to hearing from you.

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Sincerely,

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