Reply Letter

Manuscript No. 82605

Title: Intracranial Pressure Monitoring in The Perioperative Period of Patients with Acute Liver Failure Undergoing Orthotropic Liver Transplantation

London, On, March 28, 2023

Dear Jin-Lei Wang,

Company Editor-in-Chief,

Editorial Office

Baishideng Publishing Group Inc

We are pleased to resubmit our revised manuscript, *"Intracranial Pressure Monitoring in The Perioperative Period of Patients with Acute Liver Failure Undergoing Orthotropic Liver Transplantation"*, for consideration of publication in World Journal of Transplantation.

We appreciate the comments of the expert reviewers. As you will see, we have answered to the reviewer comments in a detailed manner. We are submitting a revised manuscript together with a Response to Reviewers letter. Our changes are documented in red within the text. When we were not able to properly reply to the reviewers' comments, we added a sentence in the limitation section to acknowledge their inputs.

WE ARE UPLOADING THIS REPLY LETTER AS AN ATTACHMENT WITH A BETTER LAYOUT TO FACILITATE THE READING OF IT.

All Authors have reviewed the paper and have approved its resubmission.

Sincerely,

Raffael Zamper

Corresponding Author

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: This was a review on intracranial pressure monitoring for intracranial hypertension in patients with acute liver failure. In the first part, the Authors briefly described pathophysiology of elevated ICP in ALF patients. In the second part, they summarized the ongoing indications provided by International Societies, including timing and risk factors for invasive ICP monitoring. In the last section, they described their own protocol. I congratulate the Authors for this paper. I have only few suggestions

- The title dealt with patients with ALF undergoing liver transplantation.

Is there a difference on invasive ICP measurement between patients having or not an indication to transplantation -

Response: We thank the reviewer for the suggestion. Invasive ICP monitoring is a crucial tool for discriminating the candidates for liver transplantation. Therefore, select patients with ALF will have ICP monitoring, but not all will go for a liver transplant. We have removed the words 'liver transplantation' from the title for clarification.

Page 7, line 176: the Authors said that invasive ICP monitoring has been recommended by the European Guidelines only in patients with high risk of hemorrhage. Please double check -

Response: We thank the reviewer for the recommendation. This was an error due to the use of ICH in the EASL text. In this context, ICH refers to intracranial hypertension not intracranial hemorrhage. The text has been changed accordingly.

The Authors spoke about risk of intracranial hemorrhage after device placement. What about infectious risk or risk of dislocation?

Response: We thank the reviewer for bringing up this interesting point. The incidence of infection after inserting an ICP monitor is 0-22%. The risk factors described include.

- systemic disease,
- depressed skull fracture,
- lack of tunneling of the catheter,
- site leak, and
- frequency of sampling of the CSF.

To the authors' best knowledge, there is no different incidence of infection in patients with ALF or liver disease. There are three case series describing the use of ICP

monitors in ALF patients; among them, only one series of patients describes one patient who had an ICP insertion-related infection. The incidence of dislodgement is also a significant risk factor for complications after inserting an ICP monitor; we have added this to our manuscript.

The new paragraph reads as follows: "Another potential complication associated with ICPM insertion are infection. The general risk of infection is approximately 1-20%. [40] To our knowledge, ALF patients have no associated increased in infection risk, however, data is limited. Multiple small case demonstrated a low incidence of ICPM-related infections [24, 39, 41]. Reported rates of infection ranged from 0 - 7%. A common practice to reduce infection risk is the administration of prophylactic intravenous antibiotics to cover the typical skin flora prior to ICPM placement. ".

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: I read with interest this review paper on intracranial pressure monitoring for intracranial hypertension in patients with acute liver failure. The topic is matter of debate among Experts, therefore the paper has merit. In the first part, the Authors briefly described pathophysiology of elevated ICP in ALF patients. In the second part, they summarized the ongoing indications provided by International Societies, including timing and risk factors for invasive ICP monitoring. In the last section, they described their own protocol. I congratulate the Authors for this paper. I have only few suggestions –

The title dealt with patients with ALF undergoing liver transplantation.

Is there a difference on invasive ICP measurement between patients having or not an indication to transplantation? If no, I suggest to remove the words liver transplantation from the title -

Response: We thank the reviewer for the suggestion. Invasive ICP monitoring is a crucial tool for discriminating the candidates for liver transplantation. Therefore, many

patients with ALF will have ICP monitoring, but not all will go for a liver transplant. We have removed the words 'liver transplantation' from the title.

I suggest the Authors to add a Table with recommendations of ICP monitoring provided by current guidelines (EASL, AASLD, Critical Care Medicine) -

Response: We thank the reviewer for this recommendation. We have added the following Table.

Table 1. Summary of recommendations for intracranial pressure monitor in patients with acute liver failure.

Society	Recommendation	Quality of Evidence
AASLD 2005 [1]	ICPM is mainly considered for patients who are listed for transplantation. In the absence of ICPM, frequent evaluation for signs of intracranial hypertension is needed to identify early evidence of uncal herniation.	Evidence level III
AASLD Revised 2011 [33]	The use of recombinant factor rVIIa may be considered.	n/a
ALSFG 2007 [30]	Insufficient data to recommend ICPM placement in all patients with ALF. However, most members of the ALFSG place ICPM in patients with advanced (stage III/IV) hepatic encephalopathy.	n/a
EASL 2017 [34]	ICPM should be considered in a highly selected subgroup of patients, who have progressed to grade 3 or 4 coma, are intubated and ventilated and deemed at high risk of intracranial hemorrhage, based on the presence of more than one of the following variables: a) young patients with hyperacute or acute presentations, b) ammonia level over 150–200 lmol/L that does not drop with initial	(Evidence level II-3, grade of Recommendation 1)

treatment interventions (RRT and fluids), c) renal impairment and d) vasopressor support (>0.1 lg/kg/min)

AASLD: American Association for the Study of Liver Diseases, ALSFG: U.S. Acute Liver Failure Study Group, EASL: European Association for the study of the Liver, ICPM: Intracranial pressure monitor, RRT: renal replacement therapy, ALF: acute liver failure, rFVIIa : recombinant factor VIIa.

I suggest to highlight who are the patients who may benefit from ICP monitoring according to risk factors. -

Response: We thank the reviewer for this recommendation. The occurrence of cerebral edema and ICH in ALF is related to severity of encephalopathy. Cerebral edema is occasionally observed in patients with grade I-II encephalopathy. The risk of edema increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma. A stepwise approach to management is therefore advised. We have added this to our manuscript Line 104.

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(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Transplantation, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response: We thank the Editor in Chief for this interesting suggestion. We have corrected our tables and used the RCA database to corroborate most updated citations.

When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Response: One of the authors, Dr. Sonja Payne, is a native English speaker who has thoroughly reviewed the revised version of the manuscript.