Author’s response to reviews

Title: Evaluation of peripheral perfusion index and heart rate variability as early predictors for intradialytic hypotension in critically ill patients

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Author’s response to reviews:

Dear Editor In Chief,

We would like to thank the reviewer for his valuable comments, we believe that this correction enriched the manuscript. Kindly find the following responses, hopefully we will find a chance for publication in your respectable journal.

Regards,
On behalf of authors

Major comments:

1. In Patients and Methods section: it is not described how patients were screened for inclusion (?on the basis of receiving IHD in ICU). Were there specific inclusion criteria otherwise? It is described how AKI is defined but only specifies elsewhere that critically ill patients were included - were only critically ill patients with AKI included?
We thank the reviewer for his valuable comment. All our patients were critically ill patients. The manuscript was modified accordingly to make it clear in the methodology section “36 adult critically ill patients. Written informed consent was obtained from patients or their surrogates before inclusion in the study. We included patients who were scheduled for first session intermittent hemodialysis according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines (pulmonary oedema, uremic complications, hyperkalemia not responding to other measures and intractable acidosis)”

2. Please explain further what it means that patients "were scheduled for their first session intermittent hemodialysis according to...KDIGO guidelines."
• Response: We meant that all of the patients included in the study were included during their first session. We rephrased the sentence to be: “We included patients who were scheduled for first session intermittent hemodialysis”.
We are ready for any more clarification if required.

3. Important to specify when PPI and HRV monitoring was done - immediately prior to initiation of IHD.
• Response: We thank the reviewer for his valuable comment. It is mentioned in the methodology section “All hemodynamic values were recorded at the following time points: 30 minutes before the hemodialysis session, 15 minutes before the start of hemodialysis session, every 5 minutes during the session, and 15 minutes after the conclusion of the session.”

4. More details about the patient population would be important to know: e.g. were any patients on vasopressors or inotropes? How many were getting mechanical ventilation?
• Response: We thank the reviewer for his valuable comment, these data were added in first paragraph in the text of the results.

5. The authors conclude that pulmonary oedema was associated with more IDH but could this just be related to more aggressive fluid removal in these patients? Does the target or achieved ultrafiltration rate correlate with IDH?
• Response: We thank the reviewer for his valuable comment, it is mentioned in the methodology section “the parameters of hemodialysis were standardized in all patients by the attending nephrologist with pump rate of 200-250 ml/min, session time not exceeding 3 hours, and maximum ultrafiltration rate of 1L/hour,”. Furthermore, the total filtrated volume was comparable in both study groups. Therefore, we believe that the strong association between patients with volume overload and intradialytic hypotension is due to severity of illness and profound physiological derangement and not due to excessive volume removal.

6. In Limitations section: other limitations include generalizability. The authors report 3 hr HD sessions max. - this is shorter than what is used at many centres and will lead to higher UF rates and possibly more IDH. Is there a way to account for vasopressor initiation or dose increase as another measure of IDH?
• Response: we thank the reviewer for his valuable comment. The protocol for IHD in our centre to around 3 hours; however, the volume of ultrafiltration were comparable between both groups during
the whole session 1615 ml and 1534 ml (Table 1).
• This comment was added to the limitation section the limitations section “Our findings are reported on certain filtration parameters and needed to be confirmed in future studies in patients whom ultrafiltration is performed through different rates and protocols.”
• We agree with the assumption that initiation of vasopressors is a good indicator for intradialytic hypotension. In our patient, hypotension was actually managed by either initiation (or increase the rate) of vasopressors, or administration of intravenous fluids. We clarified this in the methodology section.

7. Only 41 patients were screened for 36 were included. How were patients screened?
• Response: Thank you for the valuable response. We screened any critically ill patient who had acute kidney injury that necessitate IHD according to KDIGO guidelines: “Acute kidney injury was diagnosed if the patient showed any of the following criteria: 1- Increase in serum creatinine by at least 0.3 mg/dL within 48 hours. 2- Increase in serum creatinine to 1.5 times baseline. 3- Urine volume of less than 0.5 mL/kg per hour for 6 hours. Hemodialysis was decided by the attending nephrologist for volume overload, severe electrolyte disturbance (Acidosis, hyperkalemia) or severe uremia”

8. For the 5 patients excluded for missing data: at what point exactly where they excluded?
• Response: The five patients were excluded due to lost follow up of hemodynamic variables (either poor PPI signals or poor electrical cardiometry signals) during dialysis. We clarified this point in the first paragraph of results section.

Minor

1. More details about the dialysis parameters would be useful to know: sodium level, ***target and achieved ultrafiltration goals/rates.
• Response: We thank the reviewer for his comment, we mentioned in the methodology section “Our target for ultrafiltration according to the nephrologist attendant is not exceed 1 L/hr”. Achieved ultrafiltration was 1615 ml and 1534 ml (Table 1) in the hypotensive and stable group respectively. The sodium level is not available in our records; however, we did not encounter obvious hyponatremia or hypernatremia in our patients.

2. Abstract: line 11: "Early prediction..." - consider changing text to "could allow for prophylactic measures."
• Response: The abstract was changed accordingly (Abstract background)

3. Abstract: in methods - need to state when the HRV and PPI is measured relative to HD
• Response: Timing of measurement was clarified in the abstract methods section

4. Introduction: "Intermittent hemodialysis is the usual route..." - suggest changing 'usual route' to recognize that, although often used, other modalities are also commonly used for critically ill patients.
• Response: We thank the reviewer for his comment, changes were made in the introduction section.
5. Introduction: "Predicting intradialytic hypotension ..." - suggest add the word 'modalities' after 'continuous'.

- Response: The required change was done in the introduction section

6. Introduction: "Reduced HRV..." - this sentence and the following should be re-worded.
- Response: The sentence was re-worded in the introduction section “Furthermore, it is considered a useful marker for early risk stratification and prognosis in critically ill patients6–8”

7. Patients and Methods: section on definition of acute kidney injury definition: wouldn't all patients have KDIGO3 AKI on the basis of needing dialysis for AKI?
Response: we corrected the methodology section and clarified that the patients were at KDIGO stage 3.

8. Discussion: As above: suggest consideration of the role of ultrafiltration rate in IDH.
Response: We thank the reviewer for his valuable comment, we clarified the importance of ultrafiltration rate in paragraph 6 in the discussion.