1/1/2019
Jia-Ping Yan
Science Editor
World Journal of Nephrology

Re: Manuscript No: 45003; Static pressures, intra-access blood flow and dynamic Kt/V profiles in the prediction of dialysis access function.

Dear Dr. Yan,

Please find our point-by-point response to the reviewers' queries in the following sections. We hope that the modifications now make our manuscript suitable for publication in the World Journal of Nephrology.

Thank you.

Sincerely,

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Query: I have only two comments that, in my opinion, require a minor revision of the manuscript. 1. Legends to Figures 1 and 2 are too minimalistic. Legend to Figure 1. should have at least a brief description of this "screenshot". Figure 2 Legend should have a brief explanation of what exactly is shown (what do the curves represent and how were they obtained).

Response: Thank you for the suggestions. We have now modified the legend to read as follows:

"Figure 1. Depiction of continuous display of adequacy of dialysis throughout therapy (Kt/V profile) as seen on a hemodialysis machine monitor. Optical orientation line depicts the ideal Kt/V profile. Normal Kt/V profile represents real-time values that closely mimic the optical orientation line. Abnormal Kt/V profile depicts major fluctuations from the optical orientation line."

Query: The claim of "inverse U" relationship is not really supported here. Namely, what the graphical representation tends to show is that is quadratic relationship between intra-access blood flow and arterial or venous pressure and that this is so in the full cohort, normal Kt/v and abnormal Kt/V. To make such a claim, a regression model would need to be fitted to the dependent value "intra-access blood flow" with the quadratic arterial pressure (fixed effects: arterial pressure, arterial pressure*arterial pressure) and so on - in order to test "linear fit" and "quadratic fit". Otherwise these figures may serve as a visual information, but no claims about "inverse U-shape" relationship should be made. Figure 2 - should include further subsets - all those factor for which the text states "no correlation" (in fact, you are not looking for correlation, strictly speaking, you are looking at "association" - and in fact you need regression models to include both the linear and quadratic effects) - should be included. So that one could have display of all facts that are mentioned in the text. The finding of "no association" in this setting is equally as important as "association". TABLE 2 - should show UNADJUSTES (univariate) and

ADJUSTED (multivariate) associations as ORs with 95% CI. Table footnote should explain the models.

Response: a) We thank the reviewer for the suggestion to clarify our methodology. We used correlation analysis and regression analysis as a measure of association. Although the terms *correlation* and *association* are often used interchangeably, *correlation* in a stricter sense refers to linear correlation, and *association* refers to any relationship between variables.

We have therefore replaced the word "correlation" with "association" throughout the text where applicable.

Response: b) We have provided the unadjusted odds ratio and mentioned that none of the parameters in the adjusted variables were significant in the Results section in text and therefore have not duplicated the findings in Table 2. Reported as:

"*Risks for Abnormal Kt/V profile*

In univariate analysis, age (OR 1.02, $CI_{95\%}$ 0.99-1.04, p=0.186), gender (OR 1.10, $CI_{95\%}$ 0.50-2.42, p=0.813), type of access (OR 1.78, $CI_{95\%}$ 0.76-4.16, p=0.182), PA (OR 1.00, $CI_{95\%}$ 0.90-1.00, p=0.874) and intra-access blood flow rates (OR 1.00, $CI_{95\%}$ 0.99-1.00, p=0.075) were not significant risk factors for Abnormal Kt/V profile. However, PV (OR 1.01, $CI_{95\%}$ 1.00-1.02, p=0.033) was a significant risk factor. In the multivariate regression model that included all of these variables irrespective of their statistical significance in the univariate model, none of them were significant predictors of Abnormal Kt/V profile.

Response: c) We thank the reviewer for the suggestion and have now modified the wordings regarding the relationship of static access pressures and intra-access blood flow

"Relationship of static access pressures and intra-access blood flow

No significant association could be demonstrated between PA or PV and intra-access blood flow, even when analyzed separately for AVF and AVF. When plotted against PA or PV, intra-access blood flow exhibited a quadratic relationship (Figure 2a,b). Similar patterns were revealed when plotted separately for Kt/V profiles (Figure 2c-f) and access types (figures not shown)."

Query: The topic this manuscript dealing with is nice. But there are some concerns. First use of the abbreviation. Spell it out in brackets such as PA and PV you mentioned then in the results.

Response: We thank the reviewer for pointing out this omission. We have now corrected this in the Methods section as follows:

"Vascular access dysfunction was defined as elevated static or derived venous pressures (PV), elevated negative arterial pre-pump pressures (PA) that prevent increasing to acceptable blood flow rates, or unexplained decreases in the measured amount of hemodialysis delivered (Kt/V)."

Query: The following sentence in the discussion needs to be more clear (Additionally, the UV absorbance method cannot measure urea as a single solute. It utilizes the high correlation between urea concentration and UV absorbance in spent dialysate to estimating urea parameters. While the UV-absorbance correlates well to the concentration of small solutes such as urea).

Response: We agree with the reviewer. Since this sentence does not add meaningfully to our discussion, we have removed it from the text.

Query: Lastly your references are a little old (the newest one 2011), please for some fresh references.

Response: Thank you. We have now added updated references: #3, 6 and 8.

Reviewer # 3 (Reviewer's code: 00503286)

Comment: The paper "Static pressures, intra-access blood flow and dynamic Kt/V profiles in the prediction of dialysis access function" should be published in this journal, after the minor formal corrections with the editor.

Response: Thank you for your kind comments.

Additional modifications: We erroneously omitted Girish Singhania as a co-author in our original submission. We have now added Girish Singhania as a co-author.