Reviewer's report

Title: Fluid Overload in Hemodialysis Patients: A Cross-Sectional Study to Determine its Association with Cardiac Biomarkers and Nutritional Status

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Reviewer: Paul Chamney

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MAJOR COMPULSORY REVISIONS
None.

MINOR ESSENTIAL REVISIONS

(1) Page 2, Abstract, Results: The following sentence is a little difficult understand at first glance: “We detected predialysis fluid overload #15% of extracellular water (ECW) in 95 patients (39%; amount 22.9±4.8% ECW or 4.4±1.5L). Table 2, OH pre-HD [% ECW] offers a figure which appears to be related 22.9+-4.9% but not accurately transcribed to the abstract. 4.4 +/-1.5 L. is the absolute fluid overload? Could I suggest two sentences for example: “We detected predialysis fluid overload (FO) in 39% of all patients (n=95) in the cases where FO was #15% of extracellular water (ECW). In this fluid overload subgroup the absolute FO was 4.4 +/-1.5 L or 22.9±4.8% of ECW”

(2) Background, bottom of page 5: What is meant by “possibly higher intradialytic blood pressure changes” That the intradialytic blood pressure is higher, the blood pressure rises during dialysis?

(3) Background, Page 6, 3rd paragraph. “All three institutions subsequently participated in the 'BVM-Reg' study on dry-weight reduction [27], which investigated whether blood volume monitoring (BVM)-adjusted ultrafiltration rates might reduce intradialytic symptoms associated with a rapid ultrafiltration process in fluid overloaded hemodialysis patients [28, 29]? Could you explain shortly how the BVM-Reg studies link in with the current study? It appears that this manuscript focuses largely on fluid status, whereas the BVM-Reg studies are aimed at the question of how best to remove the fluid and the impact on intradialytic symptoms – no symptom data are presented in this manuscript which could be associated with the prevailing fluid overload in each patient.

(4) Figure 3. Linear correlations are problematic with these data, even if the direction of correlations are consistent with the findings elsewhere. Obviously, some parameters such as NT-proBNP have a very wide range and thus the influence of outliers can be significant. Could I suggest you try grouping the data in box plots using appropriate cut-off ranges? See for example the publication “Optimal fluid control can normalize cardiovascular risk markers and limit left ventricular hypertrophy in thrice weekly dialysis patients.” Velasco N et al.,
(5) Subjects & methods, Page 8, paragraph “Bioimpedance monitoring”. At the end of this paragraph please include a short description of the difference between absolute fluid overload (in litres) and the relative fluid overload (in %) as both quantities are used throughout the manuscript. E.g Pre-HD fluid overload may be described in terms of the absolute fluid overload (FO) in litres whereas relative fluid overload is the expansion of the extracellular water calculated as Rel FO = FO/ECW x 100 %. Also please use a different term such as “>15% Rel FO” in place of “(#15% of ECW)” in the manuscript as the later could be more difficult to interpret. Please also ensure consistency of terms, replacing OH with FO and ‘replacing ‘overhydrated’ with fluid overloaded’.

(6) Subjects & methods, Page 8 “As part of the quarterly blood draws” English: a clinician draws blood, but ‘blood draws’ might imply a selection from a random sample. Suggested sentence “As part of the quarterly blood sampling strategy/policy….”

(7) Subject and methods, Page 9, Outliers “Prior to statistical analyses, patients exceeding percental fluid overload of three standard deviations above or below the mean were excluded (n=1 patient).” If I understand correctly, you found the mean of the population (in terms of relative fluid overload (FO/ECW) and excluded patients +/- 3 SD of this mean? Any reason for excluding the one patient found to be outside this criteria – not consistent with the clinical situation, measurement error?

(8) Subjects and Methods, Page 10 Statistical analysis, 1st paragraph. “Dehydrated patients with <-10% ECW were thus included into the normohydrated group, as in a prior study [2]. How many subjects were below the dehydration criteria? If this subgroup was sufficiently large, it would have been interesting to observe the levels of NT-pro BNP, CRP, TnT and D-Dimer in this subgroup.

(9) Results, Page 11, 3rd paragraph. “These results corresponded well to percental ECW values.” Please omit this sentence as the fluid overloaded and normohydrated groups were formed on the basis of the 15% Rel FO criteria, as a good correspondence with absolute FO should be expected in any case where the same method is employed.

(10) Results, Page 11 4th paragraph. “Furthermore, no significant difference between the two groups could be observed regarding interdialytic weight gain (IDWG), represented by ultrafiltration volume on the day of the BCM measurement after a short interdialytic interval (1.31 ± 0.99 L vs. 1.59 ± 1.08 L, p=0.144). If I understand correctly, this refers to weight gain in normohydrated and fluid overloaded groups? Please re-word as this is another key result which underlines the difference between fluid overload and weight gain as you point out in the background, e.g. “When comparing short interdialytic intervals, there was no significant difference in the IDWG between the fluid overloaded and normohydrated groups (1.31…..)”
(11) Discussion, Page 13, 2nd paragraph “This state of higher morbidity was also reflected by significantly lower average body mass in patients dialyzing at the University-based hemodialysis unit.” Could you explain the link here?

(12) The association shown in Fig 2 is weak. Nevertheless to further support the observation of higher fluid overload in low BMI patients, it would be useful to see additionally the association of BMI with NT-proBNP and TnT. This might be best achieved with box plots for Rel FO, NT-proBNP and TnT and in each case generate boxes for 3 BMI ranges i.e. ‘low’, ‘normal’ and ‘high’. It would be ideal if these results could be presented allowing a stronger case to be argued in the discussion as to why this association might be observed at all.

(13) Discussion Page 15, 3rd paragraph. Blood pressure was not different between the groups, but this can be difficult to interpret appropriately. Firstly the number of antihypertensive is clearly a crude indicator and of course the dose of antihypertensive is a major influence. Secondly, chances are that there may be patients in your cohort with cardiac impairment who present normal to low blood pressure, despite the presence of fluid overload. Thirdly, in dehydrated patients a very wide range of BPs can be encountered for different clinical reasons. See reference “Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload.” Wabel P, Moissl U, Chamney P, Jirka T, Machek P, Ponce P, Taborsky P, Tetta C, Velasco N, Vlasak J, Zaluska W, Wizemann V. Nephrol Dial Transplant. 2008 Sep;23(9):2965-71. Regarding the current manuscript, it might be a good opportunity to offer some possible reasons why a volume dependent blood pressure relationship may be difficult to observe.

(14) Discussion. General comment. The reference “Optimal fluid control can normalize cardiovascular risk markers and limit left ventricular hypertrophy in thrice weekly dialysis patients.” Velasco N et al., Hemodial Int. 2012 Oct;16(4):465-72 is missing from the reference list. Similar methods were used in the Velasco study as reported in your manuscript. It would be useful to compare briefly your results with those from the Velasco et al. study.

(15) Discussion, General comment: The negative correlation of fluid overload with albumin is an interesting finding. Could you comment whether this might be an acute phase response, reflects a state of malnutrition or possibly a dilution effect due to expanded plasma volume?

DISCRETIONARY REVISIONS

(1) Background, Page 6, 2nd paragraph. “These methods allow for the important differentiation between chronic fluid overload [2, 25] and interdialytic weight gain [1, 26].” This is a key point, especially as weight gain is often used inappropriately as a surrogate marker of fluid status. It would be useful to elaborate further on the differences between fluid overload and weight gain.

(2) Results, Page 11, last paragraph. You state that that the relationship between
Rel FO and BMI is strong. I would not agree. On the contrary, the data indicate a rather weak relationship, irrespective of the statistics. At best the data ‘suggest’ that a negative relationship might be present, but certainly it would be worth proposing some possible explanations in the discussion.

(3) Discussion, Page 14, 3rd to 5th paragraph. Are underweight patients really more susceptible to fluid overload or is this in part a reflection of the limitation of clinical methods for dry weight determination? Your suggestion of clinical misclassification is likely to be on the right track and it is one of the subtle issues frequently overlooked. No doubt you have also encountered patients of low weight who do not wish to reduce their weight further, particularly when the difference between excess fluid and normally hydrated body tissue is not apparent. Is it not for such reasons (dry weight management policy) that relationships between fluid overload and BMI can be misleading? Indeed, are there any specific clinical reasons why the majority of underweight/malnourished patients cannot achieve normohydration status? You may wish to elaborate further on the issue of clinical misclassification and how this may influence the apparent observations regarding FO and BMI.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am an employee of Fresenius Medical Care, the manufacturer of the BCM device used in the study to which the manuscript relates. Otherwise I have no financial or non-financial competing interests concerned with this paper.