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, Background. The sentence “We hypothesized that a relationship exists between fluid overload and [i] cardiovascular and [ii] inflammatory laboratory parameters” Could this sentence be re-worded? Does this mean that cardiovascular parameters may linked to fluid overload AND inflammatory parameters?

2) Page 2, ABSTRACT, Results. Some minor punctuation to sort out (spaces, full stops to be omitted/added). Acronyms such as FO need only be written in full once in abstract, i.e. ‘Fluid overload’ repeated several times in abstract and use of FO might help with word/character count if close to limit.

3) Page 2, ABSTRACT, Conclusions, first sentence. “Fluid overload in hemodialysis patients correlated inversely with body mass index and serum albumin, indicating that dry weight was inadequately prescribed and/or difficult to achieve in overweight patients.” Several points to clarify and possibly the main finding/message of the manuscript: Both NT-proBNP and Rel OH show the same relationship with BMI which is a consistent result. The inference is that high BMI subjects have a relatively lower dry weight (possibly in the direction of dehydration). Associated with the lower Relative fluid overload is the lower TnT in the high BMI group. Is it a problem of inadequate dry weight prescription or a consequence of other factors? If the weight of patients is reduced to the lowest tolerated weight then it may be that the high BMI patients tolerate a relatively lower hydration status. Possibly there is a tendency to dry high BMI subjects further because it may more difficult to differentiate body fat and free fluid as you have suggested in the discussion. Possibly the subjects in low to normal BMI range are either insufficiently dry (dry weight set too high) or the tolerance to fluid removal is poorer (as highlighted in your feedback) compared with high BMI subjects. The relationship between albumin and FO is as expected (presumably a dilution effect as you mention later) but possibly not sufficiently important to justify inclusion here in the abstract conclusion. Suggest the first sentence is replaced with something like: “Fluid overload in HD patients by different methods was found to be lower in patients with high body mass index, indicating a
tendency to achieve lower dry weight.”

4) Page 10, Results. It would be useful to expand Table 1 with some additional information on comorbidity distribution in each centre, particularly % of diabetic patients and a measure such as Charlson Comorbidity Index. This would help support the statement in the discussion later: “The highest rate of fluid overload was detected in the University-based dialysis unit, possibly because patients from this center comprised a collective with more comorbidities and were therefore more prone to chronic fluid overload.” Furthermore, was there a higher prevalence of comorbid conditions in those patients in the fluid overloaded group?

5) Page 12, Results. If available, relative inter-dialytic weight gain (IDWG) would be interesting to report in terms of BMI groupings. (Relative IDWG would be the absolute weight gain normalised to body weight) If relative IDWG in high BMI group is similar to low & mid BMI groups, it could be argued that better hydration status is achieved in the high BMI group. On the other hand, if relative IDWG is higher in the high BMI group, this may indicate a tendency for dehydration to be encountered. Either way this may shed further light regarding how dry weight is set/should be set, what is tolerated and how patient specific requests play out in the clinical setting.

6) Page 14, Discussion. “This interesting phenomenon might be explained…” It is not clear to which effect this sentence refers (as the previous paragraph refers to low weight malnourished patients). If I understand the meaning correctly, it might be better to start with “The observation of lower fluid overload in high weight/ high BMI subjects might be explained…”

7) Page 17, Discussion, Conclusion, last paragraph. Break the sentence into two sentences, i.e. “Fluid overload has emerged as a parameter that strongly correlates with cardiovascular biomarkers but seems to be independent of inflammation as well as elevated blood pressure in hemodialysis patients. Therefore we propose that fluid overload could be defined as an independent single entity - equivalent to a biomarker - with the potential to be introduced for intervention guidance.”

8) Arguably, the most interesting results are in supplementary Figure 1 and these to a large extent are different representations of the original Figure 1. Thus there is some duplication, so the suggestion would be to substitute the relevant x-y plots with the BMI box plots. There is no reference in the main text to the supplementary figures.

DISCRETIONARY REVISIONS

1) Page 14, Discussion. “These findings are in accordance with our results enforcing the view that underweight patients are more susceptible for fluid overload, whereas adipose patients tend to be in an underhydrated condition.” Any suggestions why underweight (presumably malnourished) are more susceptible for fluid overload? Is this additional fluid ‘normal’ for malnourished
patients, does the dry weight tend to be set too high in these patients or is there a problem with tolerance (CV instability) when attempts are made to normalise the fluid status?

2) Page 14 Discussion. The order of the two paragraphs starting “This interesting phenomenon might be explained…” and “The so-called reverse epidemiology in the hemodialysis population” respectively might be better swapped. i.e. first discuss the observations of fluid, low weight, high weight and the findings of others etc., then offer your explanation of why these effects may be the consequence of clinical practice.

3) Page 16, Discussion. Can you speculate why D-Dimer might be increased in fluid overloaded subjects?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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.