Author's response to reviews

Title: Association between ratio of measured extracellular volume to expected body fluid volume and renal outcomes in patients with chronic kidney disease: a retrospective single-center cohort study

Authors:
- Reibin Tai (rebin_1027@med.toho-u.ac.jp)
- Yasushi Ohashi (ohashiy@med.toho-u.ac.jp)
- Sonoo Mizuiiri (sm210@med.toho-u.ac.jp)
- Yoshihide Tanaka (jin-t-1972-0124@med.toho-u.ac.jp)
- Ken Sakai (kensakai@med.toho-u.ac.jp)

Version: 3
Date: 28 July 2014

Author's response to reviews: see over
Dr. Hayley Henderson  
Executive Editor  
*BMC Nephrology*  

28 July 2014  

Re: MS: 9600796221302336  

Dear Dr. Henderson,  

Enclosed please find a revised version of our manuscript (MS: 9600796221302336) retitled “Association between ratio of measured extracellular volume to expected body fluid volume and renal outcomes in patients with chronic kidney disease: a retrospective single-center cohort study” by Tai et al. We thank the reviewers and editor for their careful analysis of our work. Their comments have led to alterations that have significantly enhanced the quality of our manuscript. A point-by-point response to each comment is outlined below.  

**Responses to editor’s comments:**  

In accordance with Reviewer 2’s recommendation, we analyzed our data using the estimated ECW as calculated by Peters’ formula (PMID: 22076428) (ECW$_{Peters}$). However, we would like to emphasize that the ECW$_{Peters}$ was strongly correlated with TBW$_{Watson}$ (Supplementary Figure 1). We found a wide difference in sex between the measured ECW$_{BIA}$ and the estimated ECW$_{Peters}$; this difference was also observed in the %ECW$_{BIA}$/TBW$_{Watson}$ (Supplementary Figure 2). Therefore, we have resorted the tertile values by sex in the %ECW$_{BIA}$ in body weight, ratio of ECW$_{BIA}$/ECW$_{Peters}$, and %ECW$_{BIA}$/TBW$_{Watson}$ and have recreated the Kaplan–Meier survival curves for adverse renal outcomes according to the tertiles of all
three parameters. As shown in Supplementary Figure 3, patients in the second-lowest tertile were at lower risk of disease progression (4.1 per 100.0 patient years) than were those in the lowest (9.5 per 100.0 patient years) and highest tertiles (17.5 per 100.0 patient years) ($P < 0.001$). The discrepancy between these parameters may have been caused by a decreased ECW$_{BIA}$ with age. Intriguingly, Peters et al. reported that age was not associated with a decreased ECW in their healthy donor population. Thus, their formula did not include age as a coefficient. The ECW$_{BIA}$/ECW$_{Peters}$ ratio therefore decreased with age in our population, and patients in the lowest tertiles of the ECW$_{BIA}$/ECW$_{Peters}$ ratio tended to be slightly older (67.4 ± 14.8 years in the lowest tertile vs. 61.3 ± 15.5 years in the second-lowest tertile and 62.2 ± 17.6 years in the highest tertiles, $P = 0.120$). Otherwise, Supplementary Figure 3 may suggest the presence of a $J$ curve for adverse renal outcomes with respect to the fluid volume status. However, there was no significant difference in the adverse outcomes between the lowest tertile and the second-lowest tertile in the ECW$_{BIA}$/ECW$_{Peters}$ ratio (9.5 patients per 100.0 patient years vs. 4.1 per 100.0 patient years, respectively; $P = 0.12$). Eventually, patients in the highest ECW$_{BIA}$/ECW$_{Peters}$ and the %ECW$_{BIA}$/TBW$_{Watson}$ tertiles exhibited the worst adverse renal outcomes.

The ECW$_{BIA}$/ECW$_{Peters}$ ratio was positively correlated with a higher prevalence of resistant hypertension and furosemide use, lower serum albumin level, and higher
proteinuria level; it was also highly dependent upon height because height was included in the equation described by Peters et al. The \( \% \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) ratio was significantly correlated with more demographic factors than was the \( \text{ECW}_{\text{BIA}/\text{ECW}_{\text{Peters}}} \) ratio. For the above-mentioned reasons, we used the \( \% \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) ratio as the main parameter of the extracellular volume status. Accordingly, we changed the title of our manuscript to “Association between ratio of measured extracellular volume to expected body fluid volume and renal outcomes in patients with chronic kidney disease: a retrospective single-center cohort study.”

1. Regarding the relationship between the \( \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) ratio and age-related ICW changes: We believe that the ICW and ECW naturally decrease with age in both healthy and unhealthy subjects. We could not assess the extracellular volume by absolute quantity and percentage of body weight because the ECW content is influenced by age, sex, body size, fat content, and other parameters. The \( \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) ratio indicated that the relative increase in the extracellular volume to the expected fluid status comprised a good balance between the ICW and ECW that was appropriate for age.

2. Regarding the relationship between the \( \% \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) and BMI: We agree that the relationship between the \( \% \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) and BMI may not be correct because both parameters are influenced by height and weight. We have amended the text accordingly.

Responses to Reviewer 2’s comments:

1. Regarding the rationale for using the \( \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) ratio as a parameter of volume overload: We really appreciate your suggestion to use the Peters formula. Please refer to our answers provided to the editor. We have described our use of the \( \text{ECW}_{\text{BIA}/\text{ECW}_{\text{Peters}}} \) ratio and the \( \% \text{ECW}_{\text{BIA}/\text{TBW}_{\text{Watson}}} \) ratio as parameters of the extracellular volume status.

2. Regarding the quotation of reference 6 in introduction: Thank you for pointing this out. We have omitted Reference 6.

3. Regarding the measured \( \text{ECW}_{\text{BIA}/\text{TBW}_{\text{BIA}}} \) ratio: In accordance with Reviewer 2’s comment, we have stated in the revised manuscript that the ECW/TBW ratio may not be an
ideal measurement of volume overload.

4. Regarding the ratio of ECW$_{BIA}$/ICW$_{BIA}$: The ECW$_{BIA}$/ICW$_{BIA}$ ratio is a very interesting marker of fluid imbalance. We believe that fluid imbalance in patients with CKD is primarily characterized by excess ECW associated with sodium retention and decreased cell volume associated with malnutrition. We would like to submit this thesis in the near future and thus must preliminarily elucidate the parameters associated with the extracellular volume status.

5. Regarding the relationship between the \( \%ECW_{BIA}/TBW_{Watson} \) and BMI: As mentioned above, we agree with Reviewer 2 that the relationship between the \( \%ECW_{BIA}/TBW_{Watson} \) and BMI may not be correct because both parameters are influenced by height and weight. Please refer to our answers provided to the editor.

The manuscript has been carefully reviewed by an experienced editor of Edanz whose first language is English and who specializes in editing papers written by scientists whose native language is not English.

Thank you very much for considering publishing our work in *BMC Nephrology*. We look forward to your response.

Sincerely,

Yasushi Ohashi, MD