Author's response to reviews

Title: Frailty And Falls Among Adult Patients Undergoing Chronic Hemodialysis: A Prospective Cohort Study

Authors:

Mara A McAdams-DeMarco (mmcadams@jhsph.edu)
Sunitha Suresh (sunitha.c.suresh@gmail.com)
Andrew Law (alaw@jhsph.edu)
Megan L Salter (megansalter@gmail.com)
Luis F Gimenez (lgimene@mail.jhmi.edu)
Bernard G Jaar (bjaar@aol.com)
Dorry L Segev (dorry@jhmi.edu)

Version: 2 Date: 12 September 2013

Author's response to reviews: see over
Dear Editors and Reviewers,

We are delighted to resubmit our manuscript, “Frailty And Falls Among Adult Patients Undergoing Chronic Hemodialysis: A Prospective Cohort Study” to *BMC Nephrology*. We have addressed the reviewers’ concerns to the best of our abilities, and we hope that it is now acceptable for publication in the *BMC Nephrology*. Below we have reproduced the comments, following each with a response indicating what changes have been made to the manuscript.

Mara A. McAdams-DeMarco, Sunitha Suresh, Andrew Law, Megan L. Salter, Luis F. Gimenez, Bernard G. Jaar, Jeremy D. Walston, and Dorry L. Segev

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**Reviewer:**
vanita Jassal

**Reviewer's report:**
McAdams-DdeMarco et al have conducted a small, prospective cohort study in a prevalent hemodialysis population to show that frailty and falls are associated. Their hypothesis as stated is a little unclear (“insights into falls ... might inform prediction), but I believe they were trying to suggest that as frailty and falls are associated in the non-renal population they may be associated in the HD population.

We thank the reviewer for this comment and have clarified the hypothesis in the introduction.

The use of the Fried criteria to establish frailty is fair, though I personally question if it is valid in the dialysis population where all patients almost invariably report yes on self-reported exhaustion and have low activity. This is particularly true in this study as more than 70% of their population were either frail or intermediate frailty phenotype. I wonder if perhaps the nephrology community will shift to the use of a more robust frailty score such as that validated by Rockwood or perhaps one of the others.

We acknowledge that there are different measures of frailty, including the *Accumulation of Deficits* (Rockwood). However, we are using a validated measure of frailty that is not based on the number and severity of diseases, but rather a phenotype that Linda Fried has shown is actually independent from comorbidity; given the burden
of comorbidity in ESRD patients, it seems important to quantify this aspect of decline in physiologic reserve. While we think it is important to understand the role of the various concepts of frailty in patients with ESRD, this was not the focus of this research.

To the reviewer's concern, we actually did not observe that nearly all participants reported exhaustion or low physical activity (Prevalence of Exhaustion=37% and Prevalence of Physical activity=40%). Furthermore, as these are only two of the five components of frailty, participants would not be classified as frail if they experienced exhaustion and low physical activity.

I have a few concerns:
1. Is it statistically valid to build Poisson regression models with 8 explanatory variables and one interaction term when only 26 people fell? I appreciate the Poisson model uses a rate. What is the model fit? Is a negative binomial or zero inflated neg binomial model a better fit?

We fit and presented multiple models (including a parsimonious model driven by AIC which penalizes added degrees of freedom, i.e. added variables) to account for the fact that the sample was small and the distribution of falls. As part of exploratory data analysis, we explored other models. In all models, the magnitude of the association of frailty and falls was similar regardless of the model used (Negative Binomial: RR=3.95, 95% CI: 1.07-14.53, P=0.04). The assumptions of zero inflated negative binomial regression were not appropriate as all participants were at risk of falling and thus there are no excess 0s and the sample size was small.

We have added a sentence to the results to state that our findings were robust to the methods analytic methods used.

2. The authors do not actually tell us the total number of falls recorded

We apologize for this omission and have included the total number of falls.

3. The methods section has a phrase “the follow up visit” – does this mean only one follow up visit was done? How were data on falls collected then? How can we ensure all falls were identified?

Only one follow-up visit was conducted. Falls were self-reported at follow-up as they were at baseline. Falls are major events in the lives of those on hemodialysis and are unlikely to be underreported by participants. Regardless, it is unlikely that the reporting of falls was differential by frailty status, so risk of bias specific to this study design was low.

4. The authors may want to include a comment in their discussion that their population may differ from many populations across N America or even Europe. The observation
that their population were predominantly African Americans may suggest a socioeconomically deprived population and a population in whom corrective glasses, suitable footwear, restorative physio or gait aids may not be accessible.

We have adjusted for a measure of socioeconomic status in our model and have clarified the reviewer's important points in our discussion.

5. There is no info re the deaths on the people excluded. The observation that patients with falls have been on dialysis for a shorter time suggests a survival bias and therefore to some extent invalidates the comparison with patients who did not fall..... this needs to be addressed in the results section and added to the discussion.

7 participants died without a follow-up visit in one year. They were no more likely to be frail than those who were included in the study (p=0.47).

Although there was a trend in fewer years on dialysis for those who experienced a fall, there was not a statistically significant difference. Additionally, frailty was not associated with time on dialysis (P=0.7), and thus it is unlikely that the results that frailty was associated with falls was the result of survival bias. We have added a sentence on survival bias to the Conclusion section.

6. Please add information re use of gait aids, cognitive function, simple measures of vision. These may be more predictive of falls rather than a history of COPD, angina, myocardial infarction etc and are notable by their absence.

We additionally adjusted for cognitive function as measured by the 3MS instrument. There was no statistically significant association between low cognitive function and falls (RR=1.32, 95% CI: 0.73-2.39, P=0.37). More importantly, the association between frailty and falls was not impacted by the adjustment for cognitive function (RR=3.02, 95% CI: 1.34-6.79, P=0.007).

Additionally, there were 12 participants that reported limitations in their ability to walk. When we excluded the participants, the association between frailty and the number of falls remained similar (RR=4.00, 95% CI: 1.75-9.12, P=0.001).

7. Please include information about whether patients had previously had a fall or not

74% of participants reported no falls in the 6 months prior to baseline. However, when we adjusted for the number of falls at baseline, frailty was still associated with future falls (RR=2.40, 95% CI: 1.05-5.49, P=0.03).

8. The text on page 8 “number of years on chronic HD (6.0 vs 4.0) “ etc... needs to be improved. When reading only the text it is unclear if those with falls were longer on HD
or not. This is true for all three comparisons. While the data are shown in the table, I needed to look to understand it.

We have clarified this paragraph.

9. The main finding – of higher risk of falls in those found to be frail 6 months previously – is intuitive and I think fair and not surprising. However I found myself wondering what I needed to do with the information. It almost seems backwards to me. Would it not have been easier to ask the patient if they had had a fall and perhaps then recognize they were more likely to meet frailty criteria? It’s a one minute question while the frailty assessment is likely 30 minutes ...? Please address and consider a comment in the discussion highlighting that asking about falls may be a simpler assessment tool....

The frailty assessment described in this manuscript takes less than 10 minutes to administer, the assessment has been widely used and validated in other populations, and it has been demonstrated that frailty can be measured as part of clinical practice. Although it would be easier to ask whether a patient has experienced a fall, we feel that this would be "too late" -- at this point there would be no way of preventing or reducing the risk of falls. We have expanded the Conclusion to explain that the onset of frailty is a precursor to disability and falls.

10. In a similar vein, but perhaps more philosophical: assuming I really had the staff to do a frailty assessment on everyone routinely: how would I use these data? Only 26 patients fell. Although we are not told if all 26 patients were frail or intermediately frail, that means that only one third of those who were frail or intermediate were going to fall. 2/3 were not. I think this really means we can only say that if a patient is not frail they are unlikely to fall.... Rather than the other way around.

The risk of falls increased for those participants who were frail: 16.7% of non-frail, 22.2% of those who were intermediately frail, and 36.4% of those who were frail. This suggests that patients who are frail are more likely to fall than those who are not frail even if not all patients fall. This adds to the evidence that frail patients undergoing hemodialysis are at risk of poor outcomes including mortality, hospitalization, and disability. Frail patients should be identified as being at higher risk of poor outcomes, including falls.

Reviewer:
Paul Bennett

Reviewer's report:
Major Compulsory Revisions
Nil

Minor Essential Revisions
Nil

Discretionary Revisions
Title: Maybe the use of 'novel' in the title unnecessary given that frailty has already been associated with morbidity and mortality in this group. Recommend removing 'novel' from the title. Introduction. Par 2 Line 1. There are over 500,000 patients... Can the authors specifically state that this is the US number of patients (not the global number).

We are confused by these comments, as they do not pertain to the manuscript that was submitted (for example, the word "novel" is actually not in the title of the manuscript that was submitted), but rather to the supplemental document that was supplied (an in-press paper that is cited in the manuscript that was submitted). We apologize for any confusion that might have been caused on our part by providing the supplemental document.

Study population
Can the authors comment on the site that the patients were dialysing. Were they in a hospital or community setting. If they were in just one of these settings (which it appears to be the case) then the results may be limited to the study context/setting and this may have to be added to limitation the limitation referring to the single-center study (p.11)

Although this comment pertains to the supplemental material, we have clarified in the submitted manuscript that patients were undergoing hemodialysis at a hospital-based outpatient dialysis unit.

Reviewer:
Emaad Abdel-Rahman

Reviewer's report:
1. The study is timely focusing on a major problem. With the numbers of ESRD patients undergoing hemodialysis exceeding 500,000 patients and the increased prevalence of falls, this kind of research trying to understand the factors associated with falls are very crucial. The authors had 2 questions; is frailty an independent risk for falls in the hemodialysis population, and if there is an association, is it across all ages.

We thank the Reviewer for the kind comments regarding the novelty and significance of our study.

2. To adjust for comorbidities, the authors listed several factors that may contribute to falls. However, there are so many other factors that may contribute to falls related to
the hemodialysis process itself that the authors ignored; hypotension, bone metabolic
diseases, anemia, arrhythmias, access-related infections, metabolic acidosis, etc.

We thank the reviewers for these interesting thoughts. Frailty had been demonstrated
to be a marker of physiologic decline that is not disease-based. While these factors may
contribute to falls, they are unlikely related to frailty and thus, would not meet the
definition of confounding the association of frailty and number of falls (i.e. associated
with both exposure and outcome). Our study focused on adjusting for the previously
published comorbidity definition that is known to overlap with frailty in older adults and
hence meets the definition of confounding.

That said, we did have access to information on anemia and arrhythmias; confirming the
robustness of our findings, the association between frailty and falls did not change after
adjusting for these conditions (RR: 2.62 95% CI: 1.15-5.93, p-value=0.02). We have
added a section to the manuscript accordingly.

3. The authors recognized the small cohort sample limitation, but also the short
duration of the study is another limitation.

We agree and have added this limitation to the Conclusion.

4. Another major problem with the manuscript is the lack of a thorough discussion,
moving from results to conclusion without analyzing their data.

We have expanded the Conclusion section.

5. I do not think that this manuscript is acceptable in its current format. I will be happy
to review if a significant changes are done on the design and a thorough discussion of
the findings are supplied.

We feel that the manuscript has been greatly strengthened by the reviewer comments
and hope that it is now acceptable for publication.