Author's response to reviews

Title: Comparing frailty measures in their ability to predict adverse outcomes among older residents of assisted living.

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Author's response to reviews: see over
August 21, 2012

Dr. Stefano Volpato
Associate Editor
BMC Geriatrics

Dear Dr. Volpato:

Please find attached our revised manuscript entitled, “Comparing frailty measures in their ability to predict adverse outcomes among older residents of assisted living” submitted for further consideration to BMC Geriatrics. We found the reviewers’ comments very helpful and we have provided a point-by-point response to each comment below. We have highlighted the changes to our manuscript in yellow.

All co-authors fulfill each of the three criteria required for authorship (i.e., 1) have made substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have contributed to drafting or revising the manuscript for important intellectual content; and, 3) have provided final approval of the version submitted for review and publication). All authors declare that they have no competing interests.

As noted previously, this manuscript represents original work and has not been submitted for consideration elsewhere.

The following section details our Acknowledgements and Funding sources:

Special thanks are given to Deanna Wanless, Anna Charlton, Cheri Komar (Study Coordinators), Dr. Misha Eliasziw (Study Advisor), our research staff, and the facilities, residents and their family members who participated in ACCES.

This study was funded by the Alberta Heritage Foundation for Medical Research (#200400893), the Canadian Institutes of Health Research (CIHR) (MOP81216) and CIHR-Institute of Aging Northern and Rural Health Research Initiative (HAS-63179).

Please do not hesitate to contact me if you have any concerns or questions regarding our re-submission. We thank you for your continued consideration,

Sincerely,

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Response to Reviewers

MS: 9154236857189015, BMC Geriatrics
Hogan DB et al.
Comparing frailty measures in their ability to predict adverse outcomes among older residents of assisted living.

REVIEWER #1

REVIEWER #1 COMMENTS: In light of this potential conflict of interest, after summarizing the article, I will stick closely to the guidelines for reviewers, noted below. In addition, because I know this area in some detail and have given thought to how best to operationalize frailty in secondary analyses, regarding some points I have made "additional comments" for the authors' interest. These need not be responded to in relation to the paper itself, but may help move forward some of the conversation in this area by virtue of offering a "worked example" and so are made in that spirit.

REVIEWER #1 COMMENTS: 1. The question of why and how one needs to compare frailty measures is clearly spelled out. Additional comment about the objectives. Frailty here refers to "a heightened vulnerability to stressors, which leads to an increased risk for multiple adverse health-related outcomes" (P4) with which I agree. Even so, I have a slightly different take. Reflecting our systems approach to frailty, I would add "an increased risk for people of the same chronological age". The reasoning is thus: since Gompertz described his "law" of mortality in relation to age in 1825, it is well recognized that the death rate is precisely age-dependent, although in subsequent years, the precision has been increased with various amendments. Even so, this is key to both the clinical definitions (used in this paper) and the statistical definition. (Briefly, the clinical measures see this as variable factor which will change over time; the statistical measures treat it as fixed for an individual). It is recognized that there are male-female differences. Why bother with this emphasis on variable vulnerability in relation to age? The pragmatic importance is three-fold: first, it makes the point that predicting variable outcomes is key, but only in relation to age and sex, not co-morbidity, which is a second-level variable. Second, it also makes clear the need to grade frailty. There is little advance to replacing "variable vulnerability of people of the same age" with "variable vulnerability of people who are frail". (Note however that for any group, there will always be some vulnerability; even amongst the very frailest people, given differential environmental exposures, the survival curve will have the form of a radioactive decay process.[Greenwood & Irving 1939. The Biostatistics of Senility. Human Biology 11:1–23; ECONOMOS, A. C. 1983. Rate of Aging, Rate of Dying and the Mechanism of Mortality. Archives in Gerontology and Geriatrics 1:3–27.)] Clinically, the more mathematical approach to frailty that I am describing sees it as a state (this too is shared by the statistical and clinical definitions, and by the mathematical one that we use) and not a syndrome.

AUTHORS' RESPONSE: Thank you for this comment. We’ve modified the sentence on page 4 so that it now reads: “… a heightened vulnerability to stressors (for a given chronological age and sex) …”

REVIEWER #1 COMMENTS: 2. Are the methods appropriate and well described? In general yes, but two points require discretionary revision, in my view.

(a) The authors spell out how they aimed to replicate an earlier report by Armstrong et al. Using an FI derived from interRAI data (the 43-item “Armstrong FI”) with an 83-item FI that made use of all available data otherwise within the interRAI-AL tool. For the latter, they used criteria spelled out in an earlier BMC Geriatrics paper (Searle et al., 2008). I am a little puzzled by the omission of 3 variables due to missing data. Inasmuch as the interRAI-AL data were obtained by "Trained research nurses administered the Resident Assessment Instrument for Assisted Living (interRAI-AL) and additional performance-based frailty measures" it’s odd that they were not able to determine whether respondents could walk or could bathe themselves. Given that functional
impairment and impaired mobility have important prognostic value, this seems to risk losing useful information. (Elsewhere, we have proposed, in relation to performance data, coding "missing" as the lowest possible score on that item. [Rockwood et al. Failure to complete performance-based measures is associated with poor health status and an increased risk of death. Age Ageing. 2007 Mar;36(2):225-8.] This seems less important for self-rated health, inasmuch as "When people are frail, worse health attitude does not seem to increase mortality..." [Lucicesare et al., An index of self-rated health deficits in relation to frailty and adverse outcomes in older adults. Aging Clin Exp Res. 2010 Jun;22(3):255-60]

AUTHORS' RESPONSE: Thank you once again. We noted the approach suggested by the Halifax group (Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62(7):722-727) to include variables where the rate of missing values would be less than 5% per variable. Two of 43 variables (Armstrong index) and 3 of 83 (Full index) violated this practice. We felt that we should report that we did have three variables (bathing, walking, self-reported health) with more than 5% missing data. Although we did report that 3 variables had more than 5% missing data, they were still included in both indices. We added a sentence to our Methods on page 7 to clarify that these variables when present were retained in the indices. We would like to point out that "locomotion" is another item included in the Full Frailty Index and would be expected to overlap with "walking" while there are a number of other functional items (e.g., dealing with personal hygiene and dressing) in both indices that would be expected to overlap with "bathing." One reason we retained bathing and self-reported health is that they were part of the Armstrong index and we did not want to modify it any further (we had to modify it already as not all the items on the original Armstrong index were available on the interRAI-AL tool). Each individual variable contributes only 1.2-2.3% to the total number of potential deficits in the respective indices. The Halifax group also showed that indices are relatively robust as to the choice of variables with indices retaining any 80% of the original variables behaving similarly (Searle SD, Mitnitski A, Gahbauer EA et al. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24). We feel this justified our decision to retain the three variables with missing data rates of greater than 5%. As well we wished to examine how these indices would function in a "real world" situation using standard methods in completing the interRAI form. Any variable where there was a missing value was removed from both the numerator and denominator of the ratio used to calculate the frailty index for an individual participant (i.e., if one of our research subjects had one variable with a missing value, when calculating their Full Frailty Index the denominator was 82). We didn't explore different ways of coding the missing values such as assigning missing values the lowest possible score for that item or using other sources of information to improve on the completion rate. In summary, as the frailty index allows a certain amount of leeway with missing data, we chose to leave the data as is. In addition, we wanted to simulate a frailty index derived from a routine completion of the interRAI-AL form.

As for why information on a person's ability to bathe or walk was on occasion missing, the interRAI-AL form specifically requires the person completing the form to consider activities that had taken place in the preceding 3 days. If the activity had not taken place, the option "activity did not occur" was provided on the form. The use of this response option ("activity did not occur") for this particular assessment of the resident is the source of our missing data for these two variables. We've reworded this sentence on page 7 to hopefully make it clearer.

In response to the comment about our use of additional sources of information to minimize missing data for the CHS approach, we'd note that there are only 5 items on this scale, their determination of frailty requires complete data for an assessment to be made, and the extent of missing data was much greater for this approach.

(b) I'm not sure that I follow the rationale of adjustment for co-morbidity, when co-morbidity is part of the Armstrong and full FIs.

AUTHORS' RESPONSE: Thank you for this comment. A number of researchers see frailty as overlapping with but separate from comorbidity (and disability). They feel it should be independently associated with certain outcomes such as hospitalization and death (Fried LP, Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004
Mar;59(3):255-63). We wanted to see what if any effect adjusting for co-morbidity had on the associations seen between the two indices we examined and the outcomes of interest. As can be seen in Table 3, adjusting for co-morbidity (as well as age and sex) had a modest impact. As well, although the frailty indices examined specifically include comorbidities, the other approaches evaluated (CHS and CHESS) do not. The co-morbidity measure used (Charlson index) also differs from the approach used in the indices (a count of select conditions). We hoped that the number of other variables included in the indices prevent collinearity in the models. Based on our results with and without comorbidity, collinearity did not appear to be an issue.

REVIEWER #1 COMMENTS: Additional comment: I am sympathetic to the authors using the full FI; in the era of rapid information processing, there seems to be no merit to not using all data in secondary analyses of large datasets. The paradigm of aggregating into a single variable information from individual items that might only have small effects seems better suited than data reduction techniques that seek to eliminate variables. The consequences of this approach can be breathtaking, including in the elaboration of the idea of inter-chromosomal linkage disequilibrium, and the demonstration of heritable complex phenotypes that nevertheless appear to show non-Mendelian mechanisms of inheritance. (Kulminski et al., Inter-chromosomal level of genome organization and longevity-related phenotypes in humans. Age (Dordr). 2012 Jan 27. [Epub ahead of print] and related papers and correspondence by the same authors e.g. Exp Gerontol, 2011 Dec;46(12):979-86 and 2012 Jun;47(6):481-2.

AUTHORS’ RESPONSE: Thank you for this comment. We agree that aggregating into a single variable information from a large number of variables offers interesting possibilities, though we were thinking of it more from the standpoint of feasibility for clinical use. We do refer to this in our Discussion where we note that the calculation of a frailty index could be automated (page 14). We’ve added a sentence here to make this more explicit.

REVIEWER #1 COMMENTS: 3. Are the data sound? They are standard of care, but puzzling, as noted above in relation to whether a patient can walk. I note too that some interRAI data were substituted for CGS performance measures to reduce the burden of missing data. Discretionary revision: A recent report, commenting on the missing data issue, has suggested that the CHS definition is not well suited to studies of people who are greatest risk – Collerton et al., Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: Cross-sectional findings from the Newcastle 85+ Study. Mech Ageing Dev. 2012;133:456-466) Does this mean that the interRAI data were self-report only? Why couldn’t a trained nurse, having done an assessment, make a judgment about whether an AL resident could walk or bathe themselves?

AUTHORS’ RESPONSE: Please see the response for this under item 2a. The interRAI instrument assesses whether residents “did” something rather than whether they “could” perform these activities. A trained nurse could make a judgment about a resident’s ability to walk or bathe themselves, but that is not how the instrument is used in the field.

REVIEWER #1 COMMENTS: 5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes. Even so, as a minor essential revision, I would think it reasonable in any comparison of instruments to mention that the extent to which the instrument is feasible for us varies: here, the CHS had many fewer people with complete data, even when the initial operationalization was replaced by the interRAI-AL assessments: 927 vs. 1066 in comparison with 1066 for each of the additional measures.

AUTHORS’ RESPONSE: We agree with this comment and discussed this point extensively in our previous paper (Freiheit et al, BMC Geriatrics 2011). While we comment that obtaining the performance measures required for the CHS frailty criteria raises questions about feasibility (page 14), we feel this should be more explicitly noted and have added a comment about this to our Discussion (see pp. 16-17).
REVIEWER #2

REVIEWER #2 COMMENTS: (1) Pg 10: The top paragraph on clustering could benefit from some additional information. I was not able to determine what the authors were talking about without referring to the referenced paper. A few additional points regarding the hierarchical nature of the data and the potential impact of nesting would improve the paragraph’s clarity.

AUTHORS’ RESPONSE: Thank you for the comment. We have changed the following sentence as follows:

From:
“We previously examined the effects of clustering on the outcomes and determined that the level of clustering was minimal [14].”

To:
“We previously examined the effects of clustering (i.e., violation of the independence assumption due to nesting by AL-institution) on the outcomes and determined that the level of clustering was minimal [14].”

REVIEWER #2 COMMENTS: (2) Methods: Why was age, sex and comorbidity controlled for in the models? I would like to see some justification to why this was done.

AUTHORS’ RESPONSE: Thank you. This was also raised by the first reviewer. As noted in our response to him, a number of researchers see frailty as overlapping with but separate from comorbidity and disability. They feel it should be independently associated with certain outcomes such as hospitalization and death (Fried LP, Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004 Mar;59(3):255-63.) Although the frailty index specifically includes comorbidities, the other approaches examined (CHS and CHESS) do not. By including comorbidity in our model, we wanted to see the strength of the association between the specific approaches to detecting frailty and the outcomes of interest even with comorbidity in the model. It is hoped that the number of other variables included in the indices prevent collinearity in the models. Based on our results with and without comorbidity, collinearity did not appear to be an issue.

REVIEWER #2 COMMENTS: (3) Methods: Unless I am missing it, there is no mention of how the CHS frailty assessment was performed. Some information or reference to a previous paper is needed.

AUTHORS’ RESPONSE: Thank you. The relevant references (#9 and 14) are given in the section titled “Methods: Frailty Assessments and CHESS Score” where we discuss the CHS approach while the specific approach we used is described in detail in Appendix C.

REVIEWER #2 COMMENTS: (4) Limitations: Due to the large amount of missing CHS data, the limitations section would benefit from discussion of this.

AUTHORS’ RESPONSE: We do agree that there are limitations with using the CHS measure in a more vulnerable population of older adults (such as those in AL settings) and we have added commentary about this to our discussion (please see pp. 14, 16-17). However, this is a limitation (from a feasibility perspective) of the CHS performance items in this particular population and not a limitation of our study as we have discussed in our previous publication (noted here as ref # 14).

REVIEWER #2 COMMENTS: (5) In Appendix A, it should be made clear that COPD, emphysema, and asthma are included as a single item. As it stands, asthma is on a new line and this may confuse some readers. This may be corrected when formatted by the journal.

AUTHORS’ RESPONSE: We have extended the column width so that this item does not wrap, and will check the formatting again with the journal.