Author's response to reviews

Title: Comprehensive Geriatric Assessment predicts mortality and adverse outcomes in hospitalized older adults.

Authors:

Thiago J Avelino-Silva (thiago.junqueira@hc.fm.usp.br)
Jose M Farfel (farfel@usp.br)
Jose Antonio E Curiati (jaec@terra.com.br)
Jose Renato G Amaral (jose_amaral@uol.com.br)
Flavia Campora (flacampora@uol.com.br)
Wilson Jacob-Filho (wiljac@usp.br)

Version: 2 Date: 4 November 2014

Author's response to reviews: see over
Response to Reviewers

Dear Professor Volpato,

Firstly, thank you for giving us the opportunity to revise our manuscript "Comprehensive Geriatric Assessment predicts mortality and adverse outcomes in hospitalized older adults" by Avelino-Silva et al. for possible publication as a Research Article in BMC Geriatrics. We are grateful to the referees and the Editor for pointing out critical issues that needed to be addressed in the manuscript. The description of what we have improved in response to the reviewers’ concerns is detailed below.

Editorial comment:

“(…) We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. (…)”

As requested, we have resubmitted the paper to a professional language editing service. A certificate regarding this revision is available and will be uploaded along with this letter.

Reviewers’ Comments

Referee: Davide Liborio Vetrano

Major Issues

1. “(…) LOS presents often a right skewed distribution, due to the phenomenon of the bed blockers patients, particularly frequent within geriatric populations, as
that here examined. Specifically, the authors reported in the results section quite different values of mean and median LOS (...) authors should provide clear evidence that assumptions of normality have been covered in such analysis. Otherwise, the study of predictors of increased LOS should be addressed according another methodology (short and long LOS according to the median LOS in logistic regression analysis?).

We are grateful for this important observation, having verified that the reviewer is correct and LOS did not have a normal distribution. We have therefore done as suggested and reassessed its analysis using multivariate logistic regression and selecting the median as a cut-off for shorter vs. longer LOS. According to this new analysis IADL dependency, malnutrition and history of falls were found to be related to longer hospital stays (please see subsection Outcome variables and CGA components; subsection Statistical analysis; Results section, paragraph 5, page 11; and table 3).

2. “Among the study limitations, the authors should mention how the experience of a single-center study cannot be generalizable to the whole population.”

As requested we have added the restricted generalizability as a limitation of this study (please see Discussion section, paragraph 6, page 15).

Minor Issues

1. “… Due to the nature of the outcomes here investigated and their seasonal dependency, as well as the changes in policies occurring on the long period and potentially affecting the observations, I think that an adequate correction for a time variable (semester?) should be introduced in the analysis.”
This is a valid concern that we have addressed by comparing outcome frequencies throughout the 6 semesters of the study. Using Chi-square test, we have verified that neither in-hospital mortality \((p=.58)\), nor the frequency of nosocomial infection \((p=.11)\), delirium \((p=.32)\) or longer hospital stays \((p=.11)\) significantly varied during the study extent. We also inform that there were no changes in admission or referral criteria during this period. Allusion to this matter was added to the subsection Statistical analysis and Results section, paragraph 3, page 10.

2. “The secondary outcomes studied in the present study were: delirium, nosocomial infections, functional decline and length of stay. (…) I suggest to report such results in a table, to make them more accessible to the reader. We have revised the results related to the secondary outcomes and reformatted their presentation in order to make them clearer and more accessible to readers as requested (please see Results section and table 3).

3. “In table 1 diseases are listed among the demographic characteristics, I suggest to include a specific section for diseases in this table.” As suggested we have included the header “Comorbidities” for the said section in table 1.

**Discretionary revisions**

1. “(…) I believe worthy, using a MNA cut-off of 23, to assess also the impact of the risk of malnutrition on the outcomes. This is not a mandatory observation (…).”
Because this was a very interesting proposal, we felt compelled to explore our data to investigate the impact of the risk of malnutrition (MNA scores from 17-23.5) on the outcomes. Unfortunately we were unable to detect significant associations between this specific group and the main outcomes. Since this was not a mandatory revision and the additional analysis didn’t provide noteworthy data, it is our opinion that it should not be added to the bulk of the text.

Referee: Nicolás Martínez-Velilla

Major issues

1. “(...) In populations with short-life expectancy, mortality is not the most important issue. It has been 5 years since their study started but the primary outcome was in-hospital mortality. Furthermore it could be interesting to assess long-term mortality.”

We agree that hospitalized older patients often have limited health expectancy and that various factors besides life prolongation are relevant to their care, including quality of life, functional independence and social support. We have included the analysis of the secondary outcomes length of stay, delirium, nosocomial infections and functionality, hoping to broaden the understanding of these patients. However, it is even because of such short life expectancy that we consider it important to identify who is at higher risk of in-hospital death and use the information in the clinical management and decision-making processes.

Though the patients included in this study were not followed after discharge, we concur that long-term outcomes should be better assessed and
we have studies underway that address them. Considerations regarding the subject can be found in the Discussion section, paragraph 7, page 15, where limitations are discussed.

2. “I think that the statistical analysis should be reviewed.”

   As the reviewer stated “I do not feel adequately qualified to assess the statistics”, we have reexamined our statistical analysis according to Referee Vetrano’s comments (please see responses in the section above).

3. “Perhaps the authors should have used an international accepted index like Barthel index in order to compare with other previous studies.”

   The Barthel Index of Activities of Daily Living is a very interesting instrument that is regarded as reliable and has high inter-rater reliability and test-retest reliability. Unfortunately we do not have data at this point to change from the functionality scores that were originally selected.

   However, the Katz Index of Activities of Daily Living and Lawton’s Instrumental Activities of Daily Living are widely employed instruments that also have been reported as reliable and used in the hospital setting, justifying their use in the present study. Additional supporting references were included in the text (please see references 18-23, 25).

4. “Have the authors evaluated the inter- and intra-observer variability of the comorbidity indices and other variables?”

   We did evaluate validity and reliability results when selecting the instruments for the proposed CGA model. References regarding this concern
have been added when previously absent (please see references: 18, 27, 29, 31, 34, 36, 39, 42, 44).

5. “There should be a better presentation of the results in the tables with explanation of the tests used in each of them (univariate and multivariate).”

   As requested we have made it more explicit as to which statistical analysis was performed in each table.

6. “It’s strange that there is no significant change of functional status during hospital stay, with a mean length of stay of 16.7 days: could the authors explain this issue”.

   We believe that multiple factors might have contributed to this result. One aspect centers in the fact that the studied ward follows Acute Care for Elders recommendations and promotes early rehabilitation strategies to prevent functional decline. On the other hand, a floor effect in the functional measurements that were employed associated to the high frequency of totally dependent and cognitively impaired patients might have hindered the possibility of detecting further functional decline in these individuals. We have now addressed this topic in the Discussion section, paragraphs 3 and 6, pages 13-15.

Minor issues

1. “(…) there is no mention about frailty that could enrich the discussion and conclusions. However they can apply the concept of accumulated factors (like frailty index) to the number of impaired CGA components Hospitals provide a
fundamental location in which to study frailty, due to their crucial turning-point role in patient decline."

We were very interested in the reviewer’s suggestion of applying the concept of proportion of deficits to the number of impaired CGA components and so improve the understanding of frailty in hospitals. Nonetheless, we believe that a future study, specifically designed to address this question, is necessary. Despite hospitals providing a fascinating setting to study the subject, they also entail highly complex and multifaceted patients, and detailed information regarding clinical conditions and symptoms would be essential to discern the rolls of acute illness and frailty in older adults’ outcomes. We have added remarks on this topic in the Discussion section, paragraph 5, page 14.

2. “Some data that appear in the abstract (logistic regression analysis i.e.) are not expressed in the text (results).”

We have rephrased the description of the results so Abstract and Results section are in accordance.

3. “Mortality is the main end-point and perhaps more data can be added like mean days until death, etiology, table / figure. Perhaps they could have performed a Cox regression and adjusted for the main confounders?”

Results informing on mean days until death can be found in table 1 (Hospital stay). Data on etiology of death are described in the Results section, paragraph 3, page 10. Tables 1-3 provide additional information according to mortality. Regarding the multivariate analysis, both logistic regression and Cox proportional hazards models are frequently used in longitudinal epidemiologic
studies for analyzing the association between several risk factors and a time-related dichotomous event. As the two models typically yield similar estimates of regression coefficients in studies with short follow-up and survival analysis is generally more pertinent to long-term outcomes, we feel that adding the Cox regression analysis might confuse readers without significantly refining the results. To further support this view, please see that the Cox regression results below would not change the overall interpretation of the data:

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADL dependency</td>
<td>5.04</td>
<td>2.19-11.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADL dependency</td>
<td>2.06</td>
<td>1.28-3.32</td>
<td>.003</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>3.08</td>
<td>1.88-4.79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Poor social support</td>
<td>4.35</td>
<td>2.86-6.64</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2.17</td>
<td>1.44-3.29</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presence of pressure ulcer</td>
<td>2.04</td>
<td>1.18-3.52</td>
<td>.011</td>
</tr>
</tbody>
</table>

4. “There are sparse data about readmissions though it is supposed to be a secondary outcome”.

Readmissions, though admittedly an important variable, was not included in this study as an outcome (please see subsection Outcome variables and CGA components, page 8; and Discussion section, paragraph 7, page 15). It is however one of the long-term measures that we are presently looking into (please see response to Major issues, comment 1).
5. “It's very strange that pressure ulcers were in the final logistic regression analysis of in-hospital death but not dementia/cognitive impairment. It happens the same with the binomial dementia-delirium.”

As described in the subsection Statistical analysis (page 9), all the variables that yielded $p$ values of 0.1 or lower in the initial univariate analysis were included in the multivariate logistic regression model. That is to say, both dementia and delirium took part in the final analysis (please see table 2 for respective $p$ values), but did not stand out in the final results. This does not eliminate the importance of the association of these conditions to in-hospital death, but indicates that in this population they do not independently predict mortality. We have now mentioned this in the Discussion section, paragraph 4, page 14.

6. “Falls, urinary incontinence and depression have been assessed but I don’t see any results related with this points (…)”.

As indicated in the subsection Outcome variables and CGA components (page 8), these variables were analyzed as components of the proposed CGA model and results regarding their frequencies can be found in table 2.

7. “BISEP and CIRS are useful scales in geriatric hospitalized patients instead of the frequently used Charlson index; these results confirm previous studies.”

We thank the reviewer for the comment and have entered the remark in the Discussions section, paragraph 3, page 14.
8. “Polypharmacy was defined as the regular use of 5 medications but in table 2 the mean number of medications is very low for this type of population.”

We are grateful that this was pointed out and apologize, as there were previously undetected typing errors in the line presenting the results of Number of medications in Table 2. The correct mean numbers in each column were respectively: $5.4 \pm 3.5$ (not $4.4 \pm 2.5$); $5.2 \pm 3.2$ (not $4.2 \pm 3.2$); and $6.9 \pm 3.5$ (not $5.9 \pm 3.5$). We have included in the Results section the information that 62.1% of the patients were using 5 or more medications at admission, which is compatible to literature findings.

9. “There are more recent references that could be included in the study about CGA (…).”

We appreciate the significant contribution that was offered by indicating these very recent and pertinent papers. Mention to them was included in the Discussion section.

10. “The authors affirm that their model improves the quality of care; please discuss further this point. Do they think that the model improve the quality of life of the patients?”

The data reported in this study does not permit definite conclusions regarding the impact of CGA on the quality of in-hospital care. Future clinical trials comparing this model of care to traditional strategies are needed to provide answers on the subject. We have rephrased the discussion to better conform to our results, which rather indicated an improvement in the in-hospital detection of cognitive alterations (please see Discussion section, paragraph 4,
11. “There are several mistakes in the references that should be assessed. Reference number 49 is not reflected in the text.”

Reference 49 (now 46) was originally located in the footnote of table 1, but we have transferred it to the subsection Comprehensive Geriatric Assessment, paragraph 5, page 8. As requested we have reassessed the References section for possible errors and formatted the segment using the BMC Geriatrics output style available in the software EndNote X7.0.1, Thomson Reuters.

We hope to have addressed all the comments satisfactorily, and that the manuscript is now acceptable for publication in BMC Geriatrics.

Looking forward to hearing from you soon.

Sincerely yours,

Thiago J. Avelino-Silva on behalf of the authors