PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Importance and added value of functional impairment in order to predict mortality: a cohort study in swedish medical inpatients
AUTHORS	Torisson, Gustav; Stavenow, Lars; Minthon, Lennart; Londos, Elisabet

VERSION 1 - REVIEW

REVIEWER	Francisco José Tarazona-Santabalbina Hospital Universitario de la Ribera (Alzira, Valéncia, Spain)
REVIEW RETURNED	25-Oct-2016

GENERAL COMMENTS	The authors have properly presented a manuscript on the relationship between daily living funcionality and the potential risk of mortality. Nevertheless, some aspects of the paper could be improved. First of all, the hypothesis has already been confirmed by other authors. Various studies have employed different scales of basic and instrumental daily living activities to estimate the potential mortality risk. Also, as the authors comment on the discussion another authors have also compared the risk of mortality according frailty phenotype. A meta-analysis published this year (Kojima, J Epidemiol Community Health) shows as frail and pre-frail subjects against robust increased risk of hospitalization for any cause in a follow-up period of 12 months. The authors use a daily living activities scale (GBS -Gottfries Brane Steen-)similar to the Katz or Berthel indices. Perhaps authors could have compared which scale was better predictor of mortality. Regarding statistical methods, the authors report that the study is a sub-analysis and they include the bibliogrpahic reference of the main study. Nevertheless, authors should describe the sample size calculation and the power of the study. The authors should include this information as part of the STROBE rules too. According to the calculated predictive models, the heterogeneity of the main diagnoses at hospital admission can alter the predictive capability of the models. The authors should include it as a confounder variable. The authors used the Charlson comorbidity index as clinical complexity or comorbidity variable but it is not equivalent to principal diagnosis. Regarding the bibliography: On page 17 the authors included a first bibliography with 52 citations and in page 38 a new list with 22 bibliographic citations. I imagine that the 22 references on page 38 belong to the statistical appendix but the authors should avoid confusion in the reader. The author could name differently the second bibliography headland. As well as, the authors should assess the adequacy of statistical appendix extension. It is very possible that the reader profile of BMJ is more a clinician than a

	statistical.

REVIEWER	Terrence Murphy Yale School of Medicine, USA
REVIEW RETURNED	22-Nov-2016

GENERAL COMMENTS	It's beautifully written and very thorough. The authors are to be commended for an excellent written English that surpasses that of many native speakers. The statistical approaches and comparisons are appropriate and convincing. The only surprising thing to me, someone who has worked with measures of ADL for along time, is that I would have entirely expected, given the model terms, that indication of disability in ADLs would be strongly associated with death and would tend to be much stronger than the other terms. This is a very thorough evaluation of an association that is at once reasonable and expected.

REVIEWER	Peter Herbison University of Otago, New Zealand
REVIEW RETURNED	19-Dec-2016

GENERAL COMMENTS	I was really pleased to see such a detailed supplement to this paper. It made the analysis very clear, and gave confidence that it was very appropriate. I have only two small concerns. The first is that in the list of ways to impute missing values (in the supplement), multiple imputation is missing. This is often regarded as the best way to impute missing values. As there are few missing values in this data it may not make any difference, and it makes the analysis more complicated. But the discussion in the supplement sounds like a general one so multiple imputation should be in the list. There are other places in the supplement where the discussion turns from the general into something more specific to this problem. It would be good if it was clear when this happens. The second point is that there is discussion about some variables being "stronger" predictors than others. There are several ways of measuring how strong a predictor is, and the authors have specified what they use in the supplement. But this is not clear in the paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
The authors have properly presented a manuscript on the relationship between daily living funcionality and the potential risk of mortality.
Nevertheless, some aspects of the paper could be improved. First of all, the hypothesis has already been confirmed by other authors. Various studies have employed different scales of basic and instrumental daily living activities to estimate the potential mortality risk. Also, as the authors comment on the discussion another authors have also compared the risk of mortality according frailty phenotype. A meta-analysis published this year (Kojima, J Epidemiol Community Health) shows as frail and pre-frail subjects against robust increased risk of hospitalization for any cause in a follow-up period of 12 months.

REPLY: We agree, the association between ADL impairment and mortality has been previously

established, as stated in the Introduction section of the paper. However, we think that this paper adds two things to previous research: 1) a quantification of how large the added value of ADL is and 2) this in a comparison with a clinical model that in no way should be considered perfect but at least more comprehensive than previously studied, as expressed in the discussion section.

The authors use a daily living activities scale (GBS -Gottfries Brane Steen-)similar to the Katz or Berthel indices. Perhaps authors could have compared which scale was better predictor of mortality.

REPLY: Yes, we totally agree with this comment. This has been added to the discussion section.

Regarding statistical methods, the authors report that the study is a sub-analysis and they include the bibliogrpahic reference of the main study. Nevertheless, authors should describe the sample size calculation and the power of the study. The authors should include this information as part of the STROBE rules too.

REPLY: The section regarding the (lack of) power calculation has been slightly rewritten, as well as the point in the STROBE checklist. This has also been added to the limitation part of the discussion section. We preferred not to perform post-hoc power analysis as confidence intervals are consistently displayed or reported, indicating the power.

According to the calculated predictive models, the heterogeneity of the main diagnoses at hospital admission can alter the predictive capability of the models. The authors should include it as a confounder variable. The authors used the Charlson comorbidity index as clinical complexity or comorbidity variable but it is not equivalent to principal diagnosis.

REPLY: This is also a very good point. In fact we tried early on to include main ICD diagnosis in the analysis, but this proved difficult from several perspectives. The data was very heterogenous, in our 200 patients, 97 different main ICD diagnoses were represented. When trying to group these diagnoses we ended up with two larger groups (heart diseases and pulmonary diseases) representing 25-30% each and nine smaller groups, with 1 - 6% each. Even so, within these groups, there were large differences in severity of disease and no clinician would try to predict outcome from such categories. Thus, for ICD codes to be relevant, a much larger sample size would be needed. In addition, it could be difficult to establish a reference category for the analyses, would it be relevant to compare heart failure with everything that is not heart failure (including stroke, kidney failure and pneumonia)? A small part of this reasoning has been added to the discussion section.

Regarding the bibliography: On page 17 the authors included a first bibliography with 52 citations and in page 38 a new list with 22 bibliographic citations. I imagine that the 22 references on page 38 belong to the statistical appendix but the authors should avoid confusion in the reader. The author could name differently the second bibliography headland. As well as, the authors should assess the adequacy of statistical appendix extension. It is very possible that the reader profile of BMJ is more a clinician than a statistical.

REPLY: The header for the bibliography of the Appendix has been changed for clarity. Also, this will eventually be presented as separate documents, further minimising the risk of confusion. We think that the thorough statistical approach is the main strength of the paper and that a supplementary appendix describing the rationale is adequate, given the rather the complex analytical approach.

Reviewer: 2
It's beautifully written and very thorough. The authors are to be commended for an excellent written English that surpasses that of many native speakers. The statistical approaches and comparisons are appropriate and convincing.

The only surprising thing to me, someone who has worked with measures of ADL for along time, is that I would have entirely expected, given the model terms, that indication of disability in ADLs would be strongly associated with death and would tend to be much stronger than the other terms. This is a very thorough evaluation of an association that is at once reasonable and expected.

REPLY: Thank you. The association was expected but we believe it is important to evaluate. Given the increase in multimorbidity, it is unclear how disease-specific prognostic markers will interact with each other. Thus we believe that generic markers, as ADL impairment, will become more and more important in order to deliver the most appropriate care.

Reviewer: 3
I was really pleased to see such a detailed supplement to this paper. It made the analysis very clear, and gave confidence that it was very appropriate. I have only two small concerns. The first is that in the list of ways to impute missing values (in the supplement), multiple imputation is missing.

REPLY: Yes, this is a good point, it has been added to that section in the appendix.

This is often regarded as the best way to impute missing values. As there are few missing values in this data it may not make any difference, and it makes the analysis more complicated. But the discussion in the supplement sounds like a general one so multiple imputation should be in the list. There are other places in the supplement where the discussion turns from the general into something more specific to this problem. It would be good if it was clear when this happens.

REPLY: The appendix has been restructured so that each part starts with a general introduction, followed by a small header ”in the study”, that marks the transition into the part that concerns this specific analysis.

The second point is that there is discussion about some variables being "stronger" predictors than others. There are several ways of measuring how strong a predictor is, and the authors have specified what they use in the supplement. But this is not clear in the paper.

REPLY: The part regarding relative importance of predictors in the main paper has been rewritten. Also, the figure legend to figure 1 (with the ANOVAS) has been slightly clarified.

VERSION 2 – REVIEW

REVIEWER	F.J. Tarazona-Santabalbina Hospital Universitario de la Ribera. Alzira, Valéncia. Spain
REVIEW RETURNED	11-Feb-2017

GENERAL COMMENTS	The authors have presented a manuscript of great scientific interest. In fact, the authors demonstrate the importance of functional status to predict mortality. Nevertheless, the authors could explain in more detail some points: Page 5, lines 19-22 Since the sample is composed of two different groups (control group and group with multidisciplinary intervention), the authors should explain in limitations If this situation could mean a bias in the results interpretation and how it was tried to solve. Page 6 lines 25-26 the authors describe that "since no blood samples were drawn in the oiriginal trial, only clinical data could be used". However, hemoglobin, albumin, BNP and glomerular filtration were employed. Authors should state when the blood determinations were made.

	The reviewer also advises the authors to reduce the length of the discussion.

REVIEWER	Peter Herbison University of Otago, New Zealand
REVIEW RETURNED	30-Jan-2017

GENERAL COMMENTS	I have no further comments on this article.

VERSION 2 – AUTHOR RESPONSE

The title has been changed to include location:
"Importance and added value of functional impairment in order to predict mortality: a cohort study in swedish medical inpatients"

The limitations paragraph in the discussion has been clarified:
"A potentially confounding issue was the concurrent non-randomized trial, i.e. the intervention could have affected mortality rates. However, the variable “control/intervention status” was included in all statistical analyses, both bivariate and multivariate, without any sign of bias."

The paragraph regarding blood samples in the method section has been clarified:
"Since no blood samples were drawn in the original trial, only clinical data could be used. Candidate predictors were selected á priori on the basis of availability and previously established association with all-cause mortality. All data was obtained from the same hospital episode as ADL was measured. If a blood sample had not been drawn during that hospitalisation, the data point was labelled “missing”. If several blood samples were taken during the hospitalisation, the one closest to admission was used."

VERSION 3 – REVIEW

REVIEWER	F.J. Tarazona-Santabalbina Department of Geriatric Medicine. Hospital Universitario de la Ribera. Alzira, Valéncia, Spain
REVIEW RETURNED	15-Mar-2017

GENERAL COMMENTS	The authors have adequately answered the doubts and questions raised. In my opinion, the manuscript can be published.