Dear Editor in chief

Please find enclosed our manuscript " Comparison of the prognostic value of Charlson and Elixhauser comorbidity measures in ACS patients: a national registry database study" (Manuscript ID JCEPI-D-21-00450) for resubmission to the Journal of Clinical Epidemiology. We thank the editorial team and the reviewers for their time and their thoughtful comments on our manuscript. We have now revised the manuscript as per the reviewer's suggestion and comments. We believe they have enabled us to improve the manuscript in this revised version. We have addressed all the reviewer's comments and provide a comment-by-comment response below. We have tracked all changes in yellow in the manuscript for ease of reference. We hope that this will enable the publication of our manuscript in your esteemed journal

Sincerely Yours

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Professor Mamas A. Mamas

Comparison paper \_ Revision:

**Requests:**

According to the guidelines to authors, we request that your abstract is structured in the following format:

R1 - Each original article must have an abstract/summary not exceeding 200 words.

R2 - Abstracts must be structured with the following headings: Objective, Study Design and Setting, Results, and Conclusion.

R3 - Double-space abstracts.

Abstracts not in compliance with this format will be returned to the authors for revision.

**Answer:**

Thank you, we have implemented the aforementioned suggestions in the revised version. Below is the new abstract format.

***Objective:*** *To compare the performance of risk adjustment models using the Elixhauser and Charlson comorbidity scores in predicting in-hospital outcomes of ACS patients from a nationwide administrative database.*

***Study design and Setting:*** *All hospitalisations for ACS in the United States between 2004 and 2014 (n=7,201,900) were retrospectively analysed. We used ECS and CCI score based on ICD-9 codes to define comorbidity variables. Logistic regression models were fitted to three in-hospital outcomes including mortality, Major Acute Cardiovascular & Cerebrovascular Events (MACCE) and bleeding. The prognostic values of ECS and CCI after adjusting for known confounders, were compared using the C-statistic, Akaike information criterion (AIC) and Bayesian information criterion (BIC).*

***Results:*** *The statistical performance of models predicting all in-hospital outcomes demonstrated that the ECS had superior prognostic value compared to the CCI, with higher C-statistics and lower AIC and BIC values associated with the former.*

***Conclusion:*** *This is the first study that compared the prognostic value of the ECS and CCI scores in predicting multiple ACS outcomes, based on their scoring systems. Better discrimination and goodness of fit was achieved with the Elixhauser method across all in-hospital outcomes studied.*

R4 - The bottom of the abstract page should list six key words (index-appropriate terms) and a running title.

**Answer:**

We have also revised the keywords and running title accordingly. Both are highlighted in yellow in the manuscript.

R5 - The Journal of Clinical Epidemiology uses titles that include the 'answer' in the title.

If not already done within a limit of 15 words, please would you modify your title to incorporate the main message of the conclusion?

Please state verbs in the past tense for individual studies (whose results might be over-ruled by later studies or meta-analyses), and in the present tense for systematic reviews (whose results are less likely to be over-ruled by later studies).

**Answer:**

Thank you for the advice. We have revised the original title into a title which contains the “answer”, following:

*“Elixhauser outperforms Charlson comorbidity index in prognostic value after ACS: insights from a national registry.”*

Reviewer #1:

Interesting study about a clinically relevant topic. Improving risk stratification in high risk non selected patients with ACS (taking into account the burden of comorbidities) con contribute to improve knowledge in this clinical setting.

Some comments to the authors:

Q1 - The authors should clearly state which is the main objective of their study. Is it to improve baseline prognosis in patients with ACS? Is to improve adjustment methods when assessing outcomes in patients with ACS? This is an important point.

**Answer:**

We thank the reviewer for their thorough review of our manuscript and for their comments. Indeed, our main objective was to *improve adjustment methods when assessing outcomes in patients with ACS, through the comparison of prognostic value of ECS and CCI.*

We have further clarified this in our “Introduction” section (highlighted in yellow in the manuscript) and quoted below.

*“The primary objective of this analysis was to compare the prognostic value of the CCI and ECS in predicting clinical outcomes using their scoring systems in a national cohort of patients admitted with an ACS, to improve the risk-adjustment methods in assessing ACS outcomes.”*

Q2 - Related to the first comment: I am not sure that including interventions in the model is correct, especially if you want to apply these findings to baseline risk prediction. In a significant proportion of cases clinical management (angiography, revascularization, treatments) is closely related to the burden of comorbidities (a more conservative management in comorbid patients). In this sense, interventions might be a confounder in the association between comorbidity (both measured by the Charlson and the Elixhauser index) and outcomes. The authors should describe the C statistic of models including demographic characteristics, clinical factors and the comorbidity scores without including interventions.

**Answer:**

Thank you very much for your comment.

We thank the reviewer for raising the point that *“a significant proportion of cases clinical management is closely related to the burden of comorbidities (a more conservative management in comorbid patients), those interventions might be a confounder in the association between comorbidity”*. Randomised trials have shown that an invasive approach is associated with favourable outcomes post ACS and represents the standard of care in contemporary practice. Not including interventions is likely to act as a significant confounder to our findings and change the relationships between comorbidity burden and outcomes.

However, given reviewer’s suggestions, we have undertaken an analysis in which we have not included interventions. We obtained 12 C-statistics; as expected it was found these C-statistics for all in-hospital outcomes were lower than the C-statistics in the models that included intervention. For example, all C-statistics for MACCE in this analysis were around 0.71, which were lower than the C-statistics for Model 3-7 including interventions (over 0.75). Meanwhile, we see the same trend as seen in the models including interventions, that Elixhauser score outperforms Charlson score. These extra results were listed in supplementary table 4 alongside the other models.

Q3 - On the other hand, as stated by the authors the Elixhauser index has a significantly higher number of comorbidities as compared to Charlson index. This is an important point, since model with a higher number of covariates have usually higher C statistics values. This should be discussed.

**Answer:**

Thank you very much for your comment.

We agree with the reviewer's point: *“ This is an important point since a model with a higher number of covariates have usually higher C statistics values. ”.*

This issue was found in all previous ECS/CCI comparative studies, which we discussed as one of the potential reasons why previous papers presented ECS might outperform CCI (in the "Discussion" section).

We have added the following text:

*“ It is possible that modelling the ECS and CCI in this way could lead to the models using Elixhauser comorbidities having a higher C-statistic or being ​overfitted compared to the ones using Charlson comorbidities as Elixhauser contains nearly twice the number of conditions, potentially leading to bias. ”*

Q4 - On the other hand, the sample size is very large, and, despite the C statistic is significantly higher with Elixhauser index, the differences are mild (probably not clinically relevant when using theses scores for predicting baseline prognosis from a clinician perspective).What I mean is that Elixhauser is probably useful tool for predicting prognosis in patients with ACS (at least as useful as CCI), but I am not sure about the fact that these differences are clinically meaningful for predicting prognosis with theses scores. Therefore I suggest to reduce the strength of conclusions.

**Answer:**

Thank you very much for your comment.

Yes, we agree with the reviewer that is difficult to quantify the difference between very similar C-statistics.

We also considered this question before framing our conclusion. Given that the dataset is large and the differences in C-statistic appeared small, the clinical importance of the difference in performance becomes of interest. For example, does a difference of 0.01 in C-statistic matter? If the model is good enough or can well explain the difference in outcomes (but our main objective is not to develop a perfect prediction model), I would say a tiny difference in C-statistic still make sense in view of the big dataset, we can identify more patients in high risk or patients in low risk (because C-statistic is the proportion of correctly classified individuals, we have a huge dataset, so even 1% more patients correctly classified is probably a huge number of patients in the data, so perhaps this can indicate an important difference). At the population level this may be clinically meaningful although we agree with the reviewer that at the individual patient level perhaps less so.

Given it is difficult to quantify the difference and further research could look to explore other measures such as net benefit. In this study, we chose not to examine measures of clinical benefit like this, and focus on statistical performance measures. This is because the aim of the study is not to develop a new risk prediction model for use in practice, and rather to examine the prognostic value of ECS and CCI specifically. This is why we have not considered other important measures associated with a risk prediction model such as measures of calibration, and why we have not concerned ourselves with model parsimony.

In our paper, it may note that while there are minor differences in how much ECS and CCI add to the prediction of different in-hospital adverse outcomes given that they both add something to demographic, clinical risk factors, and processes of care predictors, but one measure of comorbidity still should be included in models predicting in-hospital adverse outcomes, and ECS may be preferable.

However, we still have revised the conclusion to further reduce the strength of the conclusion according to the comment. Following:

*“ In conclusion, based on analyses of nationally representative US data from 2004-2014, the Elixhauser measure outperforms the Charlson method in predicting several important in-hospital outcomes, and should therefore be preferred for risk adjustment in future work to investigate whether their performance improves and whether they optimise patient centred approaches in ACS management. ”*

Reviewer #2:

Article "Comparison of the prognostic value of Charlson and Elixhauser comorbidity measures in ACS patients: a national registry database study" compared the prognostic value of the ECS and CCI scores in predicting multiple ACS outcomes, based on their scoring systems. The paper shows that based on analyses of nationally representative US data from 2004-2014, the Elixhauser measure outperforms the Charlson method in predicting several important in hospital outcomes. Overall the paper is well written and reviewer doesn’t have any major comments.

Q1 - Perhaps the main weakness of the paper as the authors highlight very well in their limitations is lack of post discharge follow up. perhaps authors can comment on clinical applicability of the findings.

**Answer:**

Thank you very much for your comment.

We have amended the discussion to address this point (highlighted in yellow in the manuscript and quoted below).

*“ Furthermore, our analysis was limited to clinical outcomes during the hospital stay because data for post discharge outcomes are not captured in the NIS database, which limits our ability to conduct comparisons of comorbidity measures when investigating longer-term outcomes. Nevertheless our findings are still clinically relevant, particularly when related to in-hospital outcomes, for example when risk adjusting and benchmarking of in-hospital clinical outcomes. However, we cannot speculate whether ECS still outperforms CCI in long-term ACS outcomes. However, a previous study reported that the performance of ECS was better than CCI in predicting long-term (1-year) mortality in patients with acute MI, which was consistent with our findings in the in-hospital outcomes. Even so, this previous study still had the limitations highlighted previously (did not use scores), therefore, our findings should drive further research into the performance of ECS and CCI relating to post-discharge outcomes.”*

Q2 - Was information on LVEF available?

**Answer:**

LVEF is not captured in the NIS database. However, patients with pre-existing (systolic and diastolic) heart failure are identified using ICD-9 codes. Both comorbidity indices include congestive heart failure as one of their components.