Author’s response to reviews

Title: Developing an Adapted Charlson Comorbidity Index for Ischemic Stroke Outcome Studies

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Author’s response to reviews:

Dear Dr Monique Kilkenny,

Please see below for responses to the reviewers. I have also included this as a separate document Under supplementary materials.

Sincerely, Ruth Hall

Responses to Reviewers

Reviewer 1:

- NRI has not been defined in the abstract, NRI has been spelled out.

- Remove space in the first sentence of the results in the abstract – space has been removed

- Line 72 typographical error – Line 72 was reviewed and I am not seeing the typographical error.

- The authors also examined the impact of including atrial fibrillation into the CCI given it is a highly prevalent comorbid condition for patients with ischemic stroke and its association with mortality. What about other stroke-related comorbidities such as obesity, smoking and hypertension? According to INTERSTROKE, these comorbidities have a higher population attributable risk of stroke and in other studies these have been shown to be associated with
mortality. Some further clarity around the selection of atrial fibrillation only appears to be warranted.

We appreciate this helpful suggestion and have included this into the discussion Line 259-261 and highlighted. We have also included an additional reference (#23) – Hospital 30-Day Mortality Following Acute Ischemic Stroke Hospitalization Measure Methodology Report, 2010 to reflect the rationale for not examining hypertension.

- What is ICES? (line 108) The name of the institution where the first two authors are affiliated. See corresponding author details on Line 16.

- Line 110 and 111 - remove "rd" - Removed

- Line 114 - incomplete sentence and typographical error - Corrected and highlighted on Line 115-117.

- Remove space line 116 – Removed but formatting pushed the word to the next line.

- Why was a cut-off of 1.2 for hazard ratios chosen? We followed the approach used by Quan et al 2011.

- Line 127 why was a logistic regression model used to test the weights instead of Cox PH? To replicate the approach used by Quan et al, 2011. Furthermore, risk-adjusted mortality models typically use logistic regression.

- Line 129 typographical error - Correction highlighted, line 144

- Line 131 typographical error – Correction highlighted, line 143.

- Line 143 typographical error – Thank you for pointing this out and corrections have been made. Line 144-147.

- Line 147 capitalise “table” Correction highlighted, line 150.

- Line 155 typographical error Correction highlighted, line 157.

- Line 158 typographical error Correction highlighted, line 161.

- Line 162 suggest change "0 and 5 and higher scores (~38% and ~6%, respectively)" to "scores of 0 (~38%) and 5+ (~6%)" - Change highlighted

- Line 164 typographical error - Corrections made see Lines 164-166

- Line 168 significant figures for percentages are inconsistent Corrections made and highlighted see Line 171
- Line 175 typographical error - Correction highlighted.

- Line 175 inconsistent presentation of data - I have removed the difference of 0.014 from the text if that is what this comment is referring to. Please let me know if I am misunderstanding your comment. See Lines 177-179.

- First paragraph of discussion has several typographical errors throughout, including use of 'didn't' and an abbreviation previously defined in line 200 – Please see revised first and second paragraph of discussion.

- Line 203 typographical error

- Lines 209 and 210 spacing

- Lines 217 and 218 typographical error Correction highlighted

- Line 220 typographical error Correction highlighted

- Expression for sentence lines 224-22 I have modified the sentences to remove some of the technical detail that may have made this difficult to read. This has editing has been highlighted Lines 222-228.

- Review sentence starting line 226. See above response.

- Line 246 has "We did not use the stroke registry" do you mean that OSR dataset was not used to ascertain comorbidities? Thank you for pointing this out. Yes and I have clarified this on line 259-261. I have also made the revision to use the OSR consistently in the Methods section as well.

- There is discussion about adjustment for stroke severity. While I understand that the goal is to be able to risk adjust using administrative data only, and that stroke severity would not be recorded in administrative datasets, readers may be wondering if stroke severity should be included in the risk adjustment models if available. Stroke severity is strongly associated with outcome. This warrants a discussion point.

Thank you for this helpful suggestion and we have included discussion on stroke severity in the discussion. See Lines 235-241. And a new reference added (#37).

Reviewer #2.

There are several confusing sentences throughout the paper. It will better to revise and have a proof read before submission. I have made several revisions throughout the paper. Please see the highlighted sections and Discussion in particular. I hope you find the paper is less confusing.
Line 127: What was the reason for adjusting three comorbidity indices in logistic regression to model for three outcomes. May be wording is not correct. Do you mean adding comorbidity indexes in the different model? Sorry if this was not clear. Line 128-131 states we modelled three outcomes. We compared the performance of three comorbidity adjusted models (ISCCI, ISCCI-AF and CCI).

Line 148: The most frequently reported hemi or paraplegia (17%). This is wrong since the study sample includes stroke. ICD-10 codes for hemiplegia may capture a large number of stroke patients.

I am sorry for the misunderstanding but the cohort is ischemic stroke patients based on the most responsible diagnosis codes. In addition each ischemic stroke patient record has additional diagnostic codes fields, it was in these additional fields that we captured the other diagnoses: including hemi- or paraplegia. The discussion section talks about this coding (see Lines 231-249).

Line 176: What is modified stroke score, never mentioned earlier.

Thank you for pointing this out. I have removed “modified stroke score” as it is confusing. Please see line 179.

What is the reason behind categorizing age? The continuous form will capture more granularity.

Agree modelling age continuously will provide more granularity and may improve model performance slightly but we believe the same pattern of model performance would be observed and not change our overall conclusions.

There is inconsistent use of ISCISS (Ischemic Stroke Charlson index summary score) and ISCCI (Ischemic stroke Charlson comorbidity index) throughout the paper. It is confusing.

I apologize for this and I have made ISCCI consistent throughout.

In past research in developing weights for comorbidity indexes, Beta coefficient were used to derive weights. I am not sure the Hazard ratio is the right way to calculate weights. What is the reason to use HR of 1.2 as a cutoff value?

We applied the same approach used by Quan et al Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676-682. Charlson’s original work (1987 vol 40(5):373-383, J Chron Dis ) used RR of 1.2 as a cutoff. See page 377 in the article, “(b) The number and seriousness of comorbid diseases: a weighted index.”

Why Peripheral vascular disease and Renal disease have 0 weights in Table 2, if HR is higher than 1.2.
After adding all eligible comorbidities to the model we retained conditions with hazard ratios (HR) greater or equal to 1.2 and p-value \(< 0.05\). See Line 118 and footnote below Table 2.

Title for table 2 is confusing- Author can make something easier like -- Hazard ratios and comorbidity weights compared with weights of original Charlson comorbidity index.

Thank you for this suggestion! Table 2 title has been changed to include your suggestion. I have also revised the look of the table and removed the Hazard Ratios from the table, provided the hazard ratio weight assignment as per Quan et al methodology in the footnote below the table.

Title of table 3 is also confusing - Author can make something easier like -- Comparison of Model performance among ischemic stroke patients in the validation cohort

Again, thank you for this suggestion! Table 3 title has been changed to include your suggestion.

There is no information regarding derivation of study sample (exclusion and inclusion criteria). Good to have flowchart.

Line 86 states, “details of the audit methodology have been reported previously (18).” In the interest of word count we opted to direct the reader to the material if more information was needed.

There is no information regarding case-mix/severity such as NIH stroke severity or modified Rankin Scale which is a commonly used scale for measuring the degree of disability after stroke. This is major limitation while using administrative data in the US. In the US, administrative claims data don't report NIH stroke severity or Rankin score. If Ontario Stroke Registry's provincial acute stroke audit and Discharge Abstract database (DAD) have any information regarding case-mix or functional status/disability, then please include in model.

We agree the lack of stroke severity and extent of disability this is a major limitation of using administrative databases. We mention the issue of stroke severity and have expanded on this issue in the discussion please see Lines 234-241.

Patients with ischemic stroke receiving TPA would have different outcome. Can you please add that in the model?

We do not feel tPA administration is a measure of comorbidity.