Author's response to reviews

Title: A systematic review protocol for measuring comorbidity in inpatient rehabilitation for non-traumatic brain injury

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Author's response to reviews: see over
Dear Drs. O’Neil and Rohling and the Systematic Reviews Editorial Board,

Thank you for your thorough review and suggestions on our revision of our protocol submission “A systematic review of comorbidity measurement methods for patients with non-traumatic brain injury in inpatient rehabilitation settings”, which have further strengthened our protocol. The encouraging positive comments were appreciated. We have indicated below how we have addressed the reviewer comments and hope that our manuscript is now suitable for publication. In the text below, the reviewer’s comments have been copied and pasted. Our response to the comments follows each comment in red font, with references to the line numbers in the revised manuscript where appropriate.

1. First, the writing is improved but still needs to be reviewed for grammar and clarity. Perhaps because of the track changes it is difficult to ensure that sentences flow well, so I would recommend that authors review a draft with all edits incorporated.

   We have reviewed a draft with all edits incorporated and further enhanced the grammar and flow of the document.

2. The purpose of the review is clarified; however, I still feel that the rationale for such a review is not strong. While comparing the validity of comorbidity assessment tools has value, it is not clear that there is a specific need to address this concern in this population, particularly given the breadth of patients included in the definition of nTBI. The rationale could be strengthened by listing more comorbidity assessment tools, highlighting their differences and similarities, and hypothesizing why one would be more or less applicable or relevant for this population. In your search strategy, you list many indices (40. (‘charlson comorbidity index’ or ‘CCI’ or ‘CMI’ or elixhauser or ‘BOD index’ or ‘cumulative index rating scale’ or ‘CIRS’ or ‘Coroni-Huntley index’ or ‘DUSOI index’ or ‘Hallstrom index’ or ‘Hurwitz index’ or ‘Incalzi index’, ‘Kaplan index’, ‘Liu index’, ‘Shwartz index’).tw.) and summarizing research on other populations which has highlighted important validity findings would be helpful yet are potentially different in this population.

   We have elaborated on the development and validation studies for commonly used comorbidity measurements, such as the Charlson Comorbidity Index and CMS Comorbidity Tiers, to demonstrate the idiosyncratic development methods, including the specific populations and outcomes for which they have been validated (which are not nTBI) [Lines 45-58]. We have also cited literature to show that the predictive validity of these measures differs in various populations [Lines 59-72].

   It is considered good practice within epidemiology to “demonstrate the appropriateness of the proposed methods for testing the stated hypotheses” (International Epidemiologic Association, 2007). This includes demonstrating that the measures used are valid and reliable within a given population. Common measures of comorbidity, such as the Charlson comorbidity index were developed and validated in specific populations for
specific outcomes – i.e., s – and some were not developed or validated in a predictive
sense (e.g., ICD codes) thus it is not appropriate to assume that the measures will show
good predictive validity for patients with nTBI [Lines 73-81]. We are not aware of any
systematic reviews specifically on nTBI populations and rehabilitation outcomes,
particularly length of stay and functional outcome. Absence of evidence is not evidence
of absence, thus we cannot assume that any of the measures demonstrate better predictive
validity compared to others.

We agree that the breadth of the patients included is an important point, and there may in
fact be differences between populations. We have provided an example of how the
validity of a comorbidity measurement method may differ between different nTBI sub
populations, and why it is important to study nTBI as a whole as well as by subtypes
[lines 82-90].

3. You need to better clarify how the data will be used to answer the questions of
interest.

To address the primary research objective, i.e., “to identify current comorbidity
measurements used for the nTBI population”, the measurement method, e.g., Charlson
comorbidity index, or Elixhauser, or number and/or type of condition based on ICD
codes, etc., will be listed in the column titled “comorbidity measurement”. In the event
that we decide to undertake a validation study ourselves, this information will provide a
starting point for comorbidity measures that we may want to compare [Lines 159-162]

A better description of face and predictive validity, and how these are addressed by
the studies you will include, is needed.

To address the secondary research objective, i.e., “to assess the validity of these
comorbidity measurements”, measures of predictive power or model fit statistics, e.g., c-
statistics for logistic regression and $R^2$ values for linear regression will be extracted if the
study used regression techniques and report these statistics. Face validity will be assessed
by the rationale or justification provided by the authors. This information will be
extracted in the column titled “comorbidity measure rationale/justification/validation”. If
two or more studies are found to compare the predictive validity of various comorbidity
measures within an nTBI population, this can be confirmed by us in a future validation
study, and then used in our predictive models in further studies [Lines 162-171].

Your data extraction sheet states, "comorbidity results," but it is unclear what type of
results you are looking for to answer your questions of interest.

To address the tertiary objective, i.e., “to catalogue the profile of comorbidities”, any
result related to the comorbidity measurement method used will be extracted. For
example, if the Charlson is used, the Charlson score will be reported as it is reported in
the included article. As stated in our previous response, this information would be useful to health care professionals that work with patients [Lines 171-175].

How does the data tell you which tool is preferable? Are you comparing the tools to some other gold standard (if so, what are the comparators that are included)?

Since the comparison of predictive validity of comorbidity measurement methods for risk adjustment is an emerging field, there has yet to be an established gold standard measurement for comorbidity in order to predict a given outcome.

Also, it is unlikely that there will be a gold standard for risk adjustment, generally, due to the diversity of variables considered, including various outcomes, such as mortality, or length of stay, cost, etc., and the idiosyncratic development and validation methods used.

As stated in the previous response to Dr. Rohling’s comment on a preference for meta-analyses, in the event that an adequate number of studies are found that present quantitative data, a novel meta-analytic technique will be employed, as was done in Sharabiani et al. (2012). This technique uses a hypergeometric test and confidence intervals for proportions to identify the comparators (i.e., various comorbidity measures) with significantly inferior/superior performance for functional outcome and rehabilitation efficiency [Lines 210-220].

These are points which need additional development in your protocol in order to strengthen the rationale for this review.

We believe that we further developed these points in the protocol and have strengthened the rationale for the review.

In your cover letter you elaborate on the purpose, noting, "The purpose is not to study the effectiveness of specific clinical or rehabilitation interventions but to inform efforts to develop a predictive multivariable model of rehabilitation outcomes (e.g., function independence measure efficiency) for health services research based on population based administrative health data." This rationale is still unclearly stated, particularly in the protocol itself.

We have now explicitly stated this within the protocol itself [Lines 97-101].

The specific ways the data will help develop such models, and how such models are related to the validity of comorbidity assessment tools, both need explanation and support.

We have explicitly linked the items in the data extraction template to our research objectives [see above regarding research objectives and the data].
4. Your current rationale still includes some circular logic. For example, you state, "Selecting the most valid comorbidity measurement method specific to the nTBI population in the rehabilitation setting can ensure that comorbidities are accurately and appropriately assessed in their influence on rehabilitation outcomes." This is basically saying that validity ensures validity. When strengthening your rationale, please attempt to remove such circular arguments.

We have attempted to remove such circular arguments

5. A major concern that remains is the exclusion of stroke patients, and this rationale, though strengthened in the revision, is still unclear and inadequately supported. You mention in your cover letter that stroke is not always included in the definition of nTBI, yet I don't believe that it is commonly excluded. This point needs much more support to be used as part of the rationale for exclusion.

In addition to the rationale that we previously provided – i.e., that we have never included stroke in our numerous peer-reviewed and published manuscripts on nTBI – the definition of nTBI that we employ is similar to the Toronto Acquired Brain Injury Network (2005) definition, which is also employed in other research programs (e.g., Evidence based review of rehabilitation of moderate to severe acquired brain injuries, 2011). This definition of nTBI includes subarachnoid hemorrhage, vascular malformations, and aneurysms, tumors, et al., but excludes stroke, intracerebral hemorrhage (which is different from intracranial hemorrhage, which we included), and cerebrovascular or vascular accidents. However, since there is no universally agreed upon definition of nTBI endorsed by a higher academic or health care authority, it remains to be debated whether stroke should be classified as an nTBI.

Beyond definitions, a more practical reason for the exclusion of stroke from our definition of nTBI reflects the structure of research and clinical rehabilitation settings. For example, within national administrative rehabilitation research databases, such as the Canadian National Rehabilitation Reporting System (NRS) and the US Center for Medicare and Medicaid Services (CMS) Inpatient Rehabilitation Facilities (IRF), stroke is classified separately from brain dysfunction, which is further stratified into non-traumatic and traumatic brain injuries(Canadian Institute for Health Information, n.d.; Centers for Medicare and Medicaid Services, 2012). Moreover, this separation is mirrored in practice, as evidence by the existence of separate stroke and acquired brain injury rehabilitation units in well-known rehabilitation facilities (e.g., Toronto Rehabilitation Institute and Rusk Rehabilitation at NYU). Thus, our exclusion of stroke reflects practice and research in the field in rehabilitation contexts and increases applicability to clinical settings [Lines 141-147].

There are also research networks for nTBI conditions other than stroke (e.g., cancer), yet this remains included in your review.
This is a valid point. Although there are cancer institutes, detailed information on brain tumours are typically not available because cancer institutes investigate many cancers – e.g., lung, breast, etc. – and brain tumors are not one of the most common conditions, whereas stroke networks primarily investigate stroke. However, we have chosen to remove the rationale of the existence of separate stroke research funding network to justify the exclusion of stroke that was previously used as it is more of an economic or political rationale. Instead, we have included a clinical and research based rationale for the exclusion of stroke from other forms of nTBI – i.e., rehabilitation centers commonly have separate stroke and ABI units, and stroke is categorized separately in national rehabilitation databases such as the CMS (USA) and NRS databases (Canada).

Additionally, you state that (1) we acknowledge that a separate systematic review on stroke rehabilitation is warranted and (2) a systematic review on measuring comorbidity in the stroke population already exists. These points seem to counter each other. If a review of comorbidity measurement in stroke already exists, then it could easily be included in your systematic review’s narrative synthesis by summarizing these results.

The systematic review cited is actually focused on measuring comorbidity in cardiovascular research, and includes stroke as one of three clinical groups (acute myocardial infarction, heart failure, or stroke). It did not find or include any studies within the rehabilitation context, which is a goal of our proposed review, thus it would not meet the criteria for inclusion. However, we have elaborated on the need to conduct a separate review for comorbidity measurement in stroke, particularly in relation to rehabilitation outcomes [Lines 253-263].

Finally, the clinical rationale for including vascular insults but excluding stroke is very unclear. I strongly suggest that you include summaries of recent reviews of stroke, when available, and include primary research on stroke for key questions when other reviews aren't available.

The rationale for including vascular insults but excluding stroke is based on the definition of nTBI summarized above. We still believe that assessing stroke is out of the definition and scope of this paper as it does not reflect research and clinical practice, thus we have not elaborated on studies on stroke.

We thank you once again for your thorough review and suggestions and look forward to your response.

Sincerely,

Wayne Khuu