Author’s response to reviews

Title: Association between the Charlson Comorbidity Index and the risk of 30-day unplanned readmission in patients receiving maintenance dialysis

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Dear Dr. Smyth and Dr. Bhatt,

Thank you very much for your constructive comments and suggestions which have been most useful in helping us to improve the paper. We have carefully considered and incorporated your points in the revised manuscript. Our point-by-point answers to the comments are below in a format similar to that
of the review letter we received. The revisions in our manuscript are highlighted in red.

1. Your title and abstract are a little unclear - is it hemodialysis, peritoneal dialysis, both? This issue continues throughout the introduction. I don't think you should use the term 'dialysis' patients - it would be better if you referred to them as 'patients receiving dialysis' or 'patients with ESKD' including the clarification as to whether this is HD, PD etc. The first mention of dialysis modality is in the 1st paragraph of the results. This is ambiguous and should be clarified.

Thank you very much for your suggestions. As you suggested, we have modified the ambiguous description of patients receiving dialysis in both Abstract and Introduction sections. We used “Patients receiving maintenance hemodialysis (HD) and peritoneal dialysis (PD)” or “patients on HD and PD therapy” to replace the term “dialysis patients” in the revised manuscript. The revisions can be found in Abstract and Introduction sections on Page 3-6.

2. How well is the CCI validated in a population with ESKD? The fact that all patients will score for kidney disease means the overall score is systematically deviated towards a higher score. Did you consider using a modified CCI without counting kidney disease?

(1) How well is the CCI validated in a population with ESKD?

As for patients with ESKD, several studies [1, 2] have proved that the CCI was an effective tool for comorbidity assessment and it could be used for survival prediction. We’ve added this point into the revised manuscript in Line 61-63 on Page 4-5.


(2) The fact that all patients will score for kidney disease means the overall score is systematically deviated towards a higher score. Did you consider using a modified CCI without counting kidney disease?

Yes, it’s true that the overall score is systematically deviated towards a higher score as kidney disease is scored for patients receiving dialysis. However, the deviated overall CCI score of patients on dialysis would not affect the relationship between CCI and unplanned readmission in our study. Because we transformed a numerical CCI score to a categorical one by classifying patients into four different groups. The four CCI score categories include: 2 (scored by ESKD per se), 3-4, 5-6, and >6. So, we did not consider using a modified CCI without counting kidney disease in our study.

In addition, some studies [1, 3, 4] have developed modified CCIs for mortality analysis of dialysis patients, but the performance of a modified CCI is almost identical to the original CCI in terms of c-statistics. The original CCI was widely used in the field of nephrology to predict mortality of patients with acute kidney injury [5], diabetic kidney disease [6] and ESKD [2]. Therefore, we preferred to use original CCI in this study.

We have added a brief discussion about this point in the revised manuscript in Line 222-229 on Page 12.
3. **How well to administrative codes (ICD) highlight patients requiring dialysis? Can you separate out the HD and PD codes? Can you separate acute from chronic dialysis.**

(1) **How well to administrative codes (ICD) highlight patients requiring dialysis?**

The ICD codes used to extract patients receiving dialysis in this study include diagnosis and procedure codes related to dialysis. We gave patients a tag when any of their recorded diagnosis or procedure codes matched the dialysis code. A previous study of HQMS [7] has shown that ICD codes in the database had relatively low sensitivity and high specificity. According to the results, the non-dialysis patients were less likely to be misclassified as dialysis patients, and this helped to ensure the homogeneity of our study population. Discussions about this point were in the Discussion section in Line 257-259 on Page 13.

(2) **Can you separate out the HD and PD codes?**

Yes, we can separate out the HD and PD codes. There are specific diagnosis and procedure codes for PD and HD respectively, and thus patients receiving HD and PD can be identified in the HQMS database using specific ICD codes. In our study, all those ICD codes used to identify patients receiving dialysis were determined by nephrology physicians. In the revised manuscript, we have added description about this in Line 92-95, Page 6, and we have listed those ICD codes for identifying HD and PD in Table S1 in the Appendix.

(3) **Can you separate acute from chronic dialysis?**

Yes, we can separate acute from chronic dialysis. There are specific ICD codes for acute kidney injury (AKI). Patients with diagnoses of AKI can be identified in the HQMS database using corresponding ICD codes. In the revised manuscript, we have added descriptions about this in Line 92-95 on Page 6, and we have listed the specific ICD codes related to AKI in Table S2 in the Appendix.

4. **Why exclude those who died during the index hospitalisation?**
Thank you very much for pointing out this important issue. We excluded those patients died during the index hospitalization because death is a competing risk for rehospitalization. Those patients who died during the index hospitalization could not have rehospitalization and would increase the number of non-readmission patients, which might affect the result of our study. In the literature, some studies [8, 9] focusing on the 30-day readmission in patients receiving hemodialysis also excluded death during the index hospitalization.

In the revised manuscript, we have added a brief explanation about this point in Line 91-92 on Page 6.


5. Why randomly select one hospitalisation for those with multiple readmissions - why not the first?

Generally speaking, compared with the first hospitalization, patients would have worse conditions in the later hospitalizations. To randomize the severity of patients’ illness, randomly selecting one hospitalization is a common approach to ensure the uniform distribution of the severity of patients’ conditions [8, 9]. We have now added explanations of this point to the revised manuscript in Line 114-117 on Page 7.


6. Why is ICU stay a confounder of this association? CCI is based on predominantly chronic conditions calculated at entry into the study; how does an acute hospitalisation associate with CCI (other than the argument that hospitalisation risk depends on comorbidities which are in CCI, at which point you wonder why CCI was used at all).

(1) Why is ICU stay a confounder of this association?

Thank you for pointing this out. The confounders included in our analysis are clinically important variables. We think that patients with ICU stay during their index hospitalizations may have severe conditions, and thus we consider ICU admission during hospitalization as a risk factor of hospital readmission. A study [10] in the literature holds the same viewpoint about the relationship between ICU stay and hospital readmission as ours. A brief explanation of this has been added to the revised manuscript in Line 144-148 on Page 8.

(2) How does an acute hospitalisation associate with CCI?

We think that there is no relationship between an acute hospitalization (whether it is an ICU admission or a hospitalization through the emergency department) and CCI. Because CCI is an index of comorbidities while an acute hospitalization is a clinically important indicator of a patient’s illness. However, both CCI and acute hospitalization might be independently associated with the 30-day unplanned readmission. So we consider the acute hospitalization as a confounder of 30-day readmission.

7. Similarly, why does emergency department admission confound this association?

Similarly, we think that emergency department admission can tell us the severity of a patient’s illness at hospital admission, and we consider it as a risk factor of hospital readmission. In the literature, a study [11] included the “Index admission was urgent” as the covariate as well. We have added a brief explanation of this in the revised manuscript in Line 144-148 on Page 8.


8. The following phrase in the result is unclear "tended to have a higher percentage of 5<=CCI<=6" - what does it mean?

Thank you very much for pointing this out. In the revised manuscript, we have revised the phrase “tended to have a higher percentage of 5<=CCI<=6” to “Compared with patients without readmission, a larger proportion of patients readmitted within 30-day were with higher CCI score, and the contrast was 28.5% vs. 27.9% (readmitted vs. non-readmitted, 5<=CCI<=6) and 14.6% vs. 13.8% (readmitted vs. non-readmitted, CCI>6), respectively.”

The revision can be found in Line 164-167 on Page 9 in the revised manuscript.

9. Did you consider the reason for readmission to hospital rather than just any reason for hospitalisation? Does a 'renal' cause for hospitalisation count? Considering the large numbers you report, the results are essentially described over just one page (and 2 more lines) and seem too brief.

Thank you for this suggestion. We have now included the reasons for readmission in our analysis. We identified the reasons for readmission using the medical procedure codes recorded during the rehospitalization first. The procedure codes were given the highest priority because the most important treatments for hospitalized patients can be identified through procedure codes. For those patients without recorded medical procedures during the rehospitalizations, we then used the first diagnosis as the causes of readmission. The recorded procedure and diagnosis codes of all included patients were classified into three categories: building dialysis access, dialysis comorbidity and other reasons, among which the first two are main causes of readmission with frequency >10% respectively, and the third one consists of all those readmission reasons with respective frequency lower than 10%. We have listed the ICD codes of those readmission reasons in Appendix Table S3 in the revised manuscript.

In Statistical Analyses, we classified patients into different groups according to the causes of
rehospitalization and described the distribution of readmission reasons among patients in different CCI score categories.

In Results section, we used Table 3 to show the distribution of readmission reasons among patients in different CCI score groups. We found that most patients (68.8%) were readmitted for other reasons instead of causes related to dialysis. For those patients readmitted because of dialysis related reasons, dialysis comorbidity is a more frequent cause than building dialysis access (20.1% vs. 11.1%). The distribution of readmission reasons among patients in different CCI score groups has no significant difference (P>0.05).

All the above mentioned analysis results and descriptions can be found in Line 102-112, 136-138, 175-180 on Page 6-10 in the revised manuscript.

10. Is your point that the CCI increases the risk of re-admission or any admission to hospital? Would the CCI be 'useful' at the time of starting dialysis, or is it after you have started and are established on dialysis, and then have your first admission to hospital that the CCI may be useful in risk stratifying a patient's chance of re-admission?

(1) Is your point that the CCI increases the risk of re-admission or any admission to hospital?

Yes, our study shows that the risk of readmission would be higher with the increase of CCI score in patients receiving dialysis.

(2) Would the CCI be 'useful' at the time of starting dialysis, or is it after you have started and are established on dialysis, and then have your first admission to hospital that the CCI may be useful in risk stratifying a patient's chance of re-admission?

Thank you for raising this good question. We think that CCI would be useful during any stage of dialysis for patients receiving dialysis. In our study, as the time of starting dialysis was not able to be identified in the HQMS database, we mainly focused on analysis of patients receiving maintenance dialysis instead of incident dialysis.

We randomly selected one hospitalization as the index hospitalization, and the CCI score of patients in the index hospitalization could be useful to stratify a patient's risk of readmission according to our result. Although the “first” hospitalization is a randomly selected one from the HQMS database, we think that the CCI score could be useful to stratify the risk of readmission during the “first” hospitalization. Because dialysis patients may have uniform distribution of illness severity in their randomly selected first hospitalizations and CCI score can play as an important predictor for readmission.

We have added discussions about this point to the revised manuscript in Line 195-200 on Page 10-11.

11. How about length of stay and complexity of the readmission to hospital - surely that is also important?

Thank you for this question. The complexity of the readmission to hospital might be related to CCI score and some other factors that can represent the severity of disease such as length of stay. Just as a study [12] suggested that the long length of stay would increase the risk of readmission among heart disease patients, we considered the length of stay as one indicator of illness severity during
hospitalization, and we included the length of stay in our analysis as a covariate. We have added a brief explanation of this in the revised manuscript in Line 144-148 on Page 8.


Sincerely,
Luxia Zhang and Guilan Kong on behalf of all co-authors