Author's response to reviews

Title: The risk of upper gastrointestinal bleeding in patients treated with hemodialysis: A population-based cohort study

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Author's response to reviews: see over
Response to reviewer 1 comments:

1. 1046 patients-9 pediatrics-166 with UGIB in "baseline"-3 transplant-57 PD=811 patients. However, the authors report a final sample size of 808 patients. Please resolve this discrepancy.

Response: The number of UGIB diagnosed before or within 90 days of the date of patient initiation of dialysis was 169. 166 was a mistake. We are sorry about this.

2. Please list the caliper/criterion for a match according to age.

Response: We now mention the criterion (matched by year of birth) for a match according to age in text. (line 83)

3. I am dubious about ascertainment of hypertension. In the HD population, I highly doubt that prevalence of hypertension is only 71.1%. Hyperlipidemia is a difficult factor to address, as well, because we do not have compelling evidence that the relationship between lipid levels of CVD risk is homogeneous in ESRD and non-CKD. Do the authors have any access in the database to biochemical measures:

Response: There is no information available on biochemical measures in our dataset. We mention this point in the discussion section. This lack of information is one of limitations of this study. (lines 181-187)

4. This analysis involves a pretty serious competing risk: death. Use of Kaplan-Meier curves is entirely inappropriate. Please use proper cumulative incidence estimators.

Response: If the risk (UGIB) were higher for censored (death) than for non-censored observations (those who remained in the cohort) over time, the study population would include a progressively greater proportion of lower risk subjects; as a result, the true overall cumulative incidence would be underestimated. The assumption that the censored observations have the same probability of the event as those remaining under observation is particularly relevant when the magnitude of the absolute incidence estimate is the focus of the study. In an approximate (large sample) sense, however, the biases resulting from losses (death) are reasonably similar in the groups being compared in our study. The issue is thus less important because we are primarily interested in a relative estimate (comparing incidence in two groups). We believe that
not to re-analyze the data would not have affected the validity and the important finding of this study.

5. The authors write that they used a frailty model, but I can only assume that they included a random effect for each matched cluster. Is that true? Please make this explicit.

Response: Yes, we incorporate an unmeasured "random" effect in the hazard function to account for the heterogeneity in the subjects. (lines 122-125)

6. Upon revision, please report a log-rank test that corresponds to the correct cumulative incidence estimate comparison.

Response: See my response to Q4. We think that we analyzed the data in common with the majority of the published papers which used the same study design. We believe that not re-analyzing the data does not have affected the validity and the important finding of this study.

7. I would like for Tables 1 and 2 to have similarly order columns (i.e., HD on the left, non-CKD on the right).

Response: We now put HD patients on the left and comparison patients on the right in Table 2 according to your suggestion. (Table 2)

8. Why does the adjusted model in Table 2 not include all of the covariates listed in Table 1? (understand that the authors do not need to adjust for gender and age, as these factors have been used as matching factors.

Response: Table 2 shows the numbers of patients who experienced gastric, duodenal, peptic, or gastrojejunal bleedings during the study period for these two cohorts and also shows their corresponding HRs. These HRs are crude hazard ratios. We therefore did not include all of the variables listed in Table 1.

9. In P1 of the Discussion, the speculation about the difference in rates is unfounded. Reference 10 was a study of the DMMS Waves, which included only dialysis patients. There were no
transplant patients in that study. Moreover, the % of PD patients in that study was low, as in most US studies of all dialysis patients. So the exclusion of PD patients from the current study cannot explain the almost 2-fold difference in UGIB rates. The authors should consider other possibilities, including whether general population rates in Taiwan are higher or whether aspects of the HD population are substantially different.

Response: We now mention other possibilities that could explain the higher incidence of UGIB in Taiwanese HD patients according to your suggestion. Thank you for your comments. (lines 157-160)

10. This is not a prospective cohort study. The data were collected for claims.

Response: We have changed "prospective study" to "matched cohort study". (line 167)

11. "We found that HD patients were more likely to have..... This findings are consistent with previous studies, which reported that [a][b][c] may be risk factors for UGIB. This makes no sense at all. Establishing a difference in prevalence of comorbidity does not confirm or refute whether those conditions are risk factors for UGIB in dialysis. Moreover, if the authors want to establish these conditions as risk factors, they will need to conduct a cox model analysis in ONLY HD patients, b/c the confounder associations are predominantly informed by non-CKD control in the dialysis (as there are 4 such patients for each HD patient).

Response: We agree with your comments. We have now deleted this paragraph.

12. Why is misclassification likely to be nondifferential? I would challenge the authors not to write this, because I argue that they have no evidence to support this claim. Pure speculation.

Response: We have now deleted the sentence according to your suggestion.

13. The discussion of provider audits is interesting, but my educated guess (based on American experience) is that auditors are concerned about procedures and money, not about accuracy of diagnosis codes for comorbid conditions.

Response: We agree with your comments. We have now deleted this paragraph and just mention that regular chart-review and cross-checking mechanisms conducted by Taiwan's NHI
14. "However, there is no reason to assume that this (overestimation of medication use) would be different for case cohort and control cohort". There is plenty of reason to suspect differential inaccuracy. HD patients take many more medications than non-CKD patients and adherence to oral medication is documented to be low to very low.

Response: We agree with your opinion. We have deleted this sentence. Thank you for your comments.
Response to reviewer 2 comments:

1. Is the question posed by the authors well defined? Yes, the question is clear, however it is not quite the one that have answered. The outcome assessed is not UGI bleeding, but rather a subset of non-variceal UGI bleeding. These bleeds would be a minority of UGI bleeds in many countries.

Response: The definition of the outcome assessed in our study is similar to those published in previous studies (Ref 10, 22). These bleeds were called upper gastrointestinal bleeding in the literature (Ref 10, 22) although these bleeds would be a minority of UGI bleeds in many countries.

2. Are the methods appropriate and well described? Methods seem generally reasonable if the question is rephrased to fit them, however they are not well described. When was age measured? Is the measure of medication use the total DDDs over the period of the study? Also the statistical methods are in my opinion inadequate. The authors have assumed a linear relationship between drug dose and outcome in all cases it seems. They have also apparently assumed there is no effect modification between the groups. Given that they have failed to demonstrate that NSAIDs increased the risk of GI bleeding it seems unlikely that both these assumptions are correct. They need to rewrite the methods to allow reproduction of their results, detailing their modelling strategy as well as how and when exposure are measured. They need to examine the possibility of non-linear relationships, and of effect modification appropriately.

Response:

(a) The definition of the outcome assessed in our study is similar to those published in previous studies (Ref 10, 22). These bleeds were called upper gastrointestinal bleeding in the literature (Ref 10, 22). We therefore choose not to change the title.

(b) Age was measured at the time when patients were beginning HD (the index date) between January 1, 1999 and December 31, 2003.

(c) Yes, we determined the cumulative medication use during the follow-up period. We mention this point in the method section. (lines 101-104)

(d) The aim of this study is to determine the risk of UGIB among HD patients during a 6-year period using general population as an external comparison group. Our study does not aim to identify risk factors for UGIB (such as NSAIDs) or explore whether there is effect modification between the groups. For simplicity, we just provide the stratified Cox Proportional hazard regression results (stratified by potential confounders) to calculate the hazard ratio of each explanation variable in Table 3. The authors think that this could not have affected the study validity and results. Thank you for your comments.
3. Are the data sound? I believe so.

Response: Thank you.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? No. The Strobe guidelines are not followed in respect to title or variable definition (as stated above).

Response: The definition of the outcome assessed in our study is similar to those published in previous studies (Ref 10, 22). These bleeds were called upper gastrointestinal bleeding in the literature (Ref 10, 22). We therefore choose not to change the title. We believe that not to change the title would not have affected the validity and the important finding of this study.

5. Are the discussion and conclusions well balanced and adequately supported by the data? No. For the most part the discussion is good, however the conclusion that "our findings provide evidence that HD patients should be monitored more carefully for UGIB development and targeted with preventive intervention strategies" is not supported by the work. They present no evidence that such a strategy would be beneficial.

Response: We have now deleted this sentence according to your comments.

6. Are limitations of the work clearly stated? Yes.

Response: Thank you.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished. No. They need to reference the work which shows hypertension, diabetes, and hyperlipidemia to be risk factors for GI bleed.

Response: The aim of this study is to determine the risk of UGIB among HD patients during a 6-year period using general population as an external comparison group. Our study does not aim to identify risk factors for UGIB (We need to conduct a Cox analysis in ONLY HD patients if we want to identify these risk factors). We therefore delete the
paragraph which mentioned the risk factors for UGIB in the discussion section.

8. Do the title and abstract accurately convey what has been found? No, See above.

Response: The definition of the outcome assessed in our study is similar to those published in previous studies (Ref 10, 22). These bleeds were called upper gastrointestinal bleeding in the literature (Ref 10, 22). We therefore choose not to change the title.


Response: We have invited an academic whose mother language is English to correct the grammatical errors for the revised manuscript.