Author's response to reviews

Title: Risk Factors of Short-term Mortality after Acute Nonvariceal Upper Gastrointestinal Bleeding in Patients on Dialysis: A Population-Based Study

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Author's response to reviews: see over
January 15, 2013

Hayley Henderson  
Executive Editor 
The BioMed Central Editorial Team

Dear Dr. Hayley:

My co-authors and I are pleased to submit to BMC Nephrology our revised manuscript entitled “Risk Factors of Short-term Mortality after Acute Nonvariceal Upper Gastrointestinal Bleeding in Patients on Dialysis: A Population-Based Study.” We were grateful for the detailed editorial and reviewer comments. Our revision incorporates these suggestions and we feel that the manuscript has been substantially improved and the message clarified as a result.

We are submitting two versions of our revised manuscript, one with tracked changes, the other a clean version with all changes incorporated.

Thank you for considering our revised manuscript. We look forward to your reactions.

With best regards,

Wolfgang C. Winkelmayer, MD, MPH, ScD  
Associate Professor of Medicine  
Director of Clinical Research
Itemized Responses to the Reviewers’ Comments:

**Referee: Eric Weinhandl**

**Reviewer’s Comment:**

**Abstract**
It would be reasonable in the Methods to explicitly declare that this study is restricted to the subset of patients in the USRDS with Medicare coverage. “The joint ability of all factors captures to predict mortality was modest (c=0.68).” Two notes: (1) Consider replacing "captures" with "captured". (2) Consider replacing "predict" with "discriminate", as the c-statistic is properly a measure of discrimination.

**Authors’ Response:**
We have made these suggested changes.

**Reviewer’s Comment:**

**Introduction**
This section is lengthy and much of the content in the second paragraph is better suited for the Discussion, in my opinion.

**Authors’ Response:**
We have shortened this section per your suggestion.

**Reviewer’s Comment:**

**Methods: Data Source**
The USRDS does NOT contain claims for "almost all patients." This is an overstatement.

**Authors’ Response:**
We have modified the statement.

**Reviewer’s Comment:**

**Methods: Identification of ANVUGIB episodes**
Please list all diagnosis codes used to ascertain events, even if only in an online appendix. It is not clear to me that the text currently includes all codes used by Targownik et al and the reader should not be expected to refer to that study for full details of the methods used here.

**Authors’ Response:**
We have added an appendix to list all diagnosis codes used (Appendix 1).

**Reviewer’s Comment:**
I think that the audience would benefit from a clear description of types of claims searched (inpatient, outpatient, home health, hospice, skilled nursing facility, physician/supplier) and which types to which the label "outpatient" refers here.
**Authors’ Response:**
We searched for all institutional claims and physician/supplier claims. For institutional claims, those sources of the bill valued “inpatient” or “PMMIS inpat stay” were labeled as “inpatient”. For physician/supplier claims, “inpatient” referred to those places of service valued “inpatient hospital”. Otherwise, the claims were labeled as “outpatient”. This is now also stated in Appendix 1.

**Reviewer’s Comment:**
Regarding esophagogastroduodenoscopy, did the authors search outpatient facility claims for the diagnosis code and physician/supplier claims for the procedure code? Or did the authors merely search physician/supplier claims for the inclusion of both applicable diagnosis and procedure codes? (The latter may be a sufficient approach, so please do not overinterpret my use of the word "merely".)

**Authors’ Response:**
We searched both institutional claims and physician/supplier claims for the procedure codes. This is now also stated in Appendix 1.

**Reviewer’s Comment:**
Please, at some point, clarify that in the cases of two outpatient claims or two events in a 30-day period, that the latter claim or event was used as the index date marking the beginning of follow-up.

**Authors’ Response:**
We used the prior event as the index date marking the beginning of follow-up. (p. 9)

**Reviewer’s Comment:**
**Methods: Candidate predictors**
Regarding prior ANVUGIB episodes, I am not religiously opposed to the approach here, but the authors should alert the reader (in the Discussion) to the fact that the accuracy of this covariate is, by construction, confounded by the duration of Medicare coverage prior prior to the index event. Later, I see that no history of ANVUGIB is a risk factor for death. Is it truly? Or are incident patients, without historical claims indicating ANVUGIB, at increased risk of death?

**Authors’ Response:**
To avoid this concern, we limited only those patients continuously covered by Medicare at least for one year before the ANVUGIB episode were included to ensure adequate and uniform ascertainment of comorbidities. As for prior ANVUGIB history, we had added the statement in the discussion.
Reviewer’s Comment:
Methods: Statistical Analysis
I am unclear about which interaction were assessed, without surmising the approach from the results in Appendix 1. I will remain agnostic about Whether this is a problem.

Authors’ Response:
We were a priori interested in the interactions of age, sex, race, and dialysis modality with other risk factors. (p. 10) The appendix only presented significant interactions in the derivation sample. Only one interaction (sex and CAD) satisfied the validation criteria (declined AIC value).

Reviewer’s Comment:
Results
The reported prevalence of hypertension is dubious. Consider whether this comorbidity possesses sufficient face validity so as not to detract from the quality of the study.

Authors’ Response:
Since the status of the comorbidities derived from only claims within one year before the indexed date of ANVUGIB, the prevalence of the comorbidities might be lower than other surveys (e.g. Medical Evidence Report). For example, patients might became normotensive after the they started regular dialysis.

Reviewer’s Comment:
"The most common cause of bleeding..." A strong statement, in my opinion. A truer interpretation of the data is this: "The diagnoses most commonly identifying ANVUGIB episodes were..."

Authors’ Response:
We have modified the statement as suggested.

Reviewer’s Comment:
In addition to reporting c, the authors might also consider reporting a pseudo R^2 statistic, as many exist for logistic regression. Discrimination is one piece of the puzzle, but it is only piece. Also, it would be interesting to see if c itself is greater simply when age is parameterized as continuous factor rather than categorical factor. The presented model have modest discrimination, but the measured covariates themselves may have been discriminatory capability than has been surmised to this point.

Authors’ Response:
The statement has now been expanded: “The full model exhibited only modest discrimination with a c statistic of 0.68 and a r-square of .04. The
death rate in the lowest decile of predicted probabilities of death was 2.3 per cent, as compared to 21.9 per cent in the highest decile.”

Reviewer’s Comment:
The authors do not clearly identify whether "other" race is a risk factor. It’s clear to me that white race is a risk factor with respect to black race, but the same cannot be said for white race vis a vis other race.

Authors’ Response:
“Other” race versus white race is not a significant risk factor. (Table 3)

Reviewer’s Comment:
I think that vintage should be more granular than what has been constructed. Patients with vintage < 3 yr are not a homogeneous group. Vintage < 1 yr is substantially different than vintage between 1 and 3 yr.

Authors’ Response:
Since we limited only those patients continuously covered by Medicare at least for one year before the ANVUGIB episode, there was no patient with vintage < 1 yr. We had noted this on Table 1 and Table 3.

Reviewer’s Comment:
Regarding "Bleeding likely peptic ulcer related"; is this covariate defined by the presence of a diagnosis code for peptic ulcer with hemorrhage, as displayed in Table 2?

Authors’ Response:
This covariate defined by the presence of a diagnosis code for gastric, duodenal, peptic, gastrojejunal ulcer with hemorrhage.

Reviewer’s Comment:
Regarding hospitalized episodes, it would be helpful to see a sensitivity analysis that delineates whether this risk factor is primarily a function of in-hospital death or whether the risk persists in those who are discharged alive. Also, it would be interesting to see this analysis repeated in the mutually exclusive subsets of patients who were hospitalized and who were NOT hospitalized on the index, so as to see whether risk factors are similar.

Authors’ Response:
We analyzed interaction between hospitalization and other risk factors. Only heart failure and peptic ulcer disease fit declining AIC criteria in validating set. Heart failure had a stronger effect among non-hospitalized episodes (OR: 1.9099 (95% CI: 1.3718-2.6592)) compared with hospitalized episodes (OR: 1.1768 (95% CI:1.0755-1.2876)). Peptic ulcer disease was associated with better outcome only among hospitalized episodes (OR: 0.9088 (95% CI
0.8357 - 0.9882). The effects of other covariates on the 30-day mortality were not modified by hospitalization or not.

**Reviewer’s Comment:**
**Discussion:**
The authors note that the liver disease was the most prominent comorbidity, on the basis of adjusted ORs (I would surmise). However, cancer is virtually indistinguishable on the basis of OR magnitude. The authors might consider some discussion of this aspect.

**Authors’ Response:**
As the reviewer’s suggestion, we had addressed this part in discussion (p 16).

**Reviewer’s Comment:**
The discussion of CAD and ischemic heart disease is wandering and could be reasonably shortened. I think that the adjusted OR for CAD here may be attenuated because of complex causal pathways among histories of CV events (e.g., MI causes HF, so simultaneous adjustment for history of MI and history of HF blocks the effect of CAD). I suppose it's fair to say that I have a difficult time interpreting this risk factor too rigorously.

**Authors’ Response:**
We had shortened the discussion of CAD (p 16).

**Reviewer’s Comment:**
This PD vs HD issue is exactly the sort of contrast that I'd like to see replicated in the subset of patients who are hospitalized and who are not hospitalized on the index date.

**Authors’ Response:**
There was no interaction between dialysis modality and hospitalization or not.

**Reviewer’s Comment:**
I think that the discussion of prior ANVUGIB is great, but if the authors want to devote this much attention to the topic, then I think that the case of refining the definition of history of ANVUGIB is even stronger. I wonder about how much of this effect may be driven by "history of" is a marker for readmission following survival from the previous episode (which, as the authors note, is survivor bias). I am increasingly uncomfortable with searching claims back to 1996, when patients do not all have the same duration of claims history.

**Authors’ Response:**
Since the median vintage was 3.8 years (IQR 2.2-6.2 years), we could ascertained ideally most complete “prior” ANVUGIB episodes of all “dialysis”
patients by searching claims back to 1996. 40.6% (7,164) of previous episodes (17,645) occurred before 2003. Without tracing back claims before 2003, we would incorrectly label these patients as “no prior ANVUGIB”.

Reviewer’s Comment:
The limitation about applicability to patients dialyzing for less than 1 year now has been wondering about the cohort definition in a new way. Did the authors exclude patients with < 1 yr of dialysis at the time of ANVUGIB? While it's true that non-elderly patients would often be implicitly excluded by requiring 1 year of Medicare coverage, elderly patients with Medicare prior to ESRD would not necessarily be excluded. On this note, the decision to require an entire year of claims to ascertained comorbidity ---- in my humble opinion ---- is up for some debate. I suspect that conclusions would be very similar (and N would be larger) if the authors had simply required 6 months of prior Medicare. The authors might still consider such a revision, depending on appetite for further analysis.

Authors’ Response:
We did not search for claims of those elderly patients with Medicare prior to ESRD, thus all patients with < 1yr dialysis at time of ANVUGIB were be excluded.

Reviewer’s Comment:
Given the data source, it's curious to me that in a study about bleeding, that the authors made no attempt to ascertain data about anemia management, including EPO doses, Hb concentrations, and transfusion events.?

Authors’ Response:
We had evaluated transfusion events (The percentage of patients receiving blood component therapy during the hospitalization was 35.3%, increasing from 24.5% in 1999 to 41.3% in 2008. Page ). We did not analyse Hct and EPO dosage due to too many missing data and we believed they were not missing at random.

Referee: Shang-Jyh Hwang

Reviewer’s Comment:
- Major Compulsory Revisions
1. This study included prevalent dialysis patients from 2003 to 2007, but they defined prior ANVUGIB history with tracing back to all available claims in database since 1996. Is this the reason why those patients with prior history of ANVUGIB had less mortality due to competing death and lead time bias? If you study the incident ANVUGIB in incident dialysis patients, what the results you would expect compared to this prevalent case study.
**Authors’ Response:**
Since we used logistic regression to evaluate a short-term outcome (expired or not within 30 days), the concern of competing death and lead time bias should be minimal. If we only studied incident ANVUGIB in incident dialysis patients, we could not test the effect of prior ANVUGIB.

**Reviewer’s Comment:**
2. In the results, the factors associated with short term mortality were mostly similar to the causes of mortality in dialysis patients, and compared to the report of ANVUGIB mortality in general population, the mortality in dialysis patients was 10 times higher. Does it mean that ANVUGIB is a condition secondary to, or coincident with those dialysis complications, thus it has a higher mortality than in general population, which might not be existed in cases from general population? Would you give some comments on discussion part?

**Authors’ Response:**
We are not sure that we fully understand this comment. Trying to satisfy this comment, we have added a statement that the identified risk factors are also risk factors for mortality in ESRD patients in general, even in the absence of ANVUGIB.

**Reviewer’s Comment:**
3. Since the case numbers in HD are much greater than those of PD, is there any difference in vintage, mean age, etc, that might cause a longer exposure time and risk compared to HD? The possibility of statistical bias due to great difference in case numbers should be addressed.

**Authors’ Response:**
As stated in the manuscript, there was no significant interaction between dialysis modality and other covariates.

**Reviewer’s Comment:**
- Minor Essential Revisions
1. Despite that the authors states that “the algorithm used to identify ANVUGIB episodes had been validated by Cooper et al. [32] and modified by Targowinik et al. [10]”, for a better understanding I would suggest draw a flow-chart to describe the selection of studying population that will make the readers easily catch up the process of study with logic thinking.

**Authors’ Response:**
We had added appendix 1 to describe the selection criteria of ANVUGIB.
Reviewer’s Comment:
2. Please label the page number.

Authors’ Response:
We have inserted page numbers.

Referee: 3

Reviewer’s Comment:
- Major Compulsory Revisions
1. The research question appears to be determining the predictors of 30-day mortality after an ANVUGIB episode. However, later in the Methods, the authors discuss the use of a development and validation cohort, the Appendix lists all the AIC information, and in the Discussion they note that they were not able to develop a risk prediction tool (“Hence, the c-statistic of the fully-adjusted model was only 0.68, which precluded us from developing a robust prediction scoring system”). Was this part of the research question as well? If the authors want to include this information they should make this part of the research question to make the information seem less tangential to the reader. Alternatively, they could remove these references and report only on the predictors in overall cohort, which is still interesting and worthwhile.

Authors’ Response:
We have added the hypothesis of interactions in the background. (p. 6) We removed the statement about wanting to develop a scoring system. Thanks for catching this.

Reviewer’s Comment:
2. In the methods it seems the definition of ANVUGIB episodes is based on outpatient claims. But later on, the authors have defined “hospitalized” vs. “not hospitalized” events. When the authors discuss ICD-9 codes, they should make sure to note that they are using both types of claims.

Authors’ Response:
We searched both outpatient and inpatient claims, while eligible outpatient claims need to fit more criteria to avoid lack of specificity. This is now stated in the detailed description of the event definition in Appendix 1.

Reviewer’s Comment:
3. Do people die of ANVUGIB episodes without ever being hospitalized? If there are any data on this I might include it in the limitations; or, if this is a highly unlikely event, this should be stated as well, so that the reader can be assured that any such bias is minimal.
The mortality rates among hospitalized and non-hospitalized ANVUGIB episodes were 5.5% (298/5120) and 11.4% (5115/39964) respectively.

4. The authors define history of ANVUGIB back to 1996 in the records. However, if a patient is <65 and not yet receiving treatment for ESRD, they would not have any records of previous episodes. How was this handled? This potential ascertainment bias is a big concern since the authors found that having an ANVUGIB history was associated with decreased risk of mortality, which seems a bit counterintuitive.

Since the target population is patients with ESRD on dialysis, those ANVUGIB episodes occurred before initiation of dialysis (e.g. not be covered under Medicare) would not be eligible as prior ANVUGIB. In other words, each patient had to have at least 1 year of Medicare claims prior to an eligible event, to establish a uniform minimum ascertainment window for baseline variables, including prior ANVUGIB.

5. The authors used complete case analysis and state that “only 0.04% and 0.35% patients had their race and dialysis modality missing”---but what about the many other variables in the model? What was the total number of non-complete cases? And did they differ from the complete cases?

There were total 199 non-complete episodes (among 50696 episodes). Among 177 episodes with missing modality, 41 died. The average age was younger (57.6±14.3 years) and the median vintage (4.0 (IQR: 2.2-7.6) years) was longer than complete cases. Other proportion of comorbidities did not materially different. (DM 62.3%, HF 51.8%, CAD 32.7%, COPD 26.1%, CVA 20.1%, cancer 8.5%, HTN, 78.4%, Arrhythmia 47.7%, VHD 35.2%, liver disease 16.6%).

6. It seems from the methods that models were run with main effects and interactions, which is fine, but please ensure that the reported main effects are not taken from the models with interaction terms.

The main effects are not taken from the final model (p. 11).
7. The authors may want to further consider the results with dialysis vintage. It is only a significant predictor after adjustment for other factors. Thus, some caution in the interpretation of the association is warranted.

**Authors’ Response:**
Vintage was confounded by other factors, so multivariate adjustment uncovered the independent association of vintage.

**Reviewer’s Comment:**
**Minor Essential Revisions**

8. The authors state “To avoid concerns about multiple comparisons while exploring for interactions among covariates, we randomly split our data...” I am not sure how this addresses multiple comparisons, or why this is a concern. Could the authors clarify?

**Authors’ Response:**
The concern is mainly to avoid over fitting the data. We have changed the statement (p.10).

**Reviewer’s Comment:**
9. Explain the 10%, 90% range in the Methods, are these just percentiles?

**Authors’ Response:**
The 10% and 90% (in the results, p. 13) described the distribution of the number of episodes per patient.

**Reviewer’s Comment:**
10. Table 1---these are really episode characteristics rather than patient characteristics, since some patients had more than one episode. I would suggest showing patient characteristics as suggested by the title. The % with 1 episode and % with 2+ episodes could be provided. Table 2 is OK at episode level.

**Authors’ Response:**
Table 1 actually does present episodes, not patients, which is now clarified in the title.

**Reviewer’s Comment:**
11. The authors refer to “first” and “repeat” episodes---note that some may not be “first,” particularly among the younger patients. It is really the “first” episode after baseline, which may or may not be at the start of dialysis.

**Authors’ Response:**
This reviewer raises a good point. We struggled in finding a better term and ended up using “initial” instead of “first”.

Reviewer’s Comment:
12. “To our knowledge” should probably be added to “Furthermore, we tested the associations between dialysis specific parameters (such as dialysis modality and dialysis vintage) and ANVUGIB mortality for the first time.”

Authors’ Response:
We have modified the statements (p. 15).

Reviewer’s Comment:
13. The sex-/CAD-stratified results are somewhat confusing nested within Table 3. I would suggest a separate table, particularly since much of the discussion is devoted to these results.

Authors’ Response:
These results came from a single model and are therefore best presented in a single table.

Reviewer’s Comment:
Discretionary Revisions
14. The paper would benefit from a careful proofreading. In addition to typos and grammatical issues, there are several places where words are missing, e.g. “In spite [of the fact?] that the risk for mortality from ANVUGIB was 5-10 times higher among patients with kidney disease compared with patients with normal or near normal kidney function” in the introduction

Authors’ Response:
We have carefully proofread and edited the manuscript. Thank you.