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

Authors:

Ju-Yeh Yang (yangjiuyeh@gmail.com)
Tsung-Chun Lee (johnlee0212@gmail.com)
Maria E. Montez-Rath (mmrath@stanford.edu)
Glenn M. Chertow (gchertow@stanford.edu)
Wolfgang C. Winkelmayer (wcw1@stanford.edu)

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Author's response to reviews: see over
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Hayley Henderson
Executive Editor
The BioMed Central Editorial Team

Dear Dr. Hayley:

My co-authors and I are pleased to resubmit 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”. Thank you for considering our revised manuscript. We have made additional modifications to the manuscript according to referee and editorial comments. We hope that this manuscript can be accepted soon.

With best regards,

Wolfgang C. Winkelmayer, MD, MPH, ScD
Associate Professor of Medicine
Director of Clinical Research
Reviewer: Laura Plantinga
Reviewer’s Comment:
1. The definition of prior episode of ANVUGIB is still confusing. In their responses the authors stated they had to have a year of claims prior to the index event (presumably claims due to ESRD and not due to age 65 or disability?), and that prior ANVUGIB was defined in that year. But in the paper the authors state that they searched back to 1996 for prior history. I think the latter is fine but still has the problem that those who were older or of very long dialysis vintage would be more likely to have a history by virtue of having records to search. This needs to be acknowledged.

Authors’ Response:
We ascertained all comorbidities, except for prior ANVUGIB event, from one year of inpatient and outpatient claims preceding the ANVUGIB event. We traced back to all available claims in our database (since 1996) to define prior ANVUGIB history.

Indeed, patients with prior ANVUGIB history were younger (mean age for patients with and without prior ANVUGIB: 61.4±15.0 vs. 63.7±14.5 years) and with longer vintage (median (IQR) for patients with and without prior ANVUGIB: vintage 4.3(2.6-6.8) vs. 3.6 (2.1-5.9) years). But the effect of prior ANVUGIB was independent after adjusting for age and vintage. We had already addressed the potential bias from the duration of Medicare coverage prior to the index event in page 17 (bottom), where we stated:

“However, this finding may reflect survivor bias, a special case of selection bias, or may be confounded by the duration of Medicare coverage prior to the index event.”

Reviewer’s Comment:
2. I think I was previously unclear in my question regarding death from ANVUGIB outside the hospital. I was getting at whether there would be deaths that would not be captured at all by claims (emergent bleed that leads to death outside the hospital or physician office, such that only the death certificate might have this information). It should be stated in the limitations if this is a possibility (can be presumed to be a rare event if that is the case).

Authors’ Response:
Thank you for this clarification. We now state the limitation explicitly on page 19.

“Nevertheless, severe episodes from which patients died before ANVUGIB could be diagnosed or coded may not have been captured by our data.”
Reviewer’s Comment:
3. In their response the authors state that multivariate adjustment uncovered the independent association of vintage with post-ANVUGIB mortality. This is possible, but it is also possible that this change from non-significant to significant could have occurred due to collinearity (maybe with modality?), statistical anomaly/small cell sizes (with variables like modality, where both the numbers with PD and cases with PD were probably quite low), or adjustment for a collider (less likely with mortality as the outcome, but this can cause an observed association where none exists). I think the results can be interpreted as "this is what we observed" but not as definite "truth." It may also be good to investigate which variable in the model made that result significant and report that.

Authors’ Response:
For clarification, we have added the following statement on page 16: “The association with vintage became significant mainly after adding age and prior ANVUGIB history into the model. The percentage of prior ANVUGIB increased with longer vintage (29.4%, 36.2% and 41.3% for vintage 1-3 years, 3-6 years and >6 years respectively), while age was negatively correlated with vintage (r=-0.19, p<0.001). Because prior ANVUGIB and younger age were associated with better outcomes, they confounded the association of vintage in the unadjusted model.”

Reviewer: Eric Weinhandl
Reviewer’s Comment:
I have no further comments.

Authors’ Response:
Thanks.

Editorial comments
1. Copyedit
We hope to highlight your manuscript on the BMC Nephrology homepage. Therefore, we recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service.

Authors’ Response:
We have gone through this paper one more time to ensure appropriate language and wording.

2. Appendix
Please upload your Appendix as additional files on the submission system. Please cite them accordingly as additional files within the manuscript text.
Authors’ Response:
We have cited the appendix as additional files within the manuscript text. (pages 7, 12)

3. Ethical Statement
Please can you include the ethical statement in the Methods section of your manuscript.

Authors’ Response:
We had an ethical statement already in the methods, on page 10.

4. Formatting
Please also ensure that your revised manuscript conforms to the journal style. It is important that your files are correctly formatted.

Authors’ Response:
We have revised the manuscript to fully conform with journal style.