Author’s response to reviews

Title: High hemoglobin is associated with increased in-hospital death in patients with chronic obstructive pulmonary disease and chronic kidney disease: A retrospective multicenter population-based study

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Author’s response to reviews:

Dear editor,

Thank you for your message.

We have carefully read the reviewers’ comments on our manuscript and think that these comments are very constructive and have been of tremendous benefit.
In the revised manuscript, we have made some modifications/corrections in accordance with the reviewers’ feedback. We hope that these changes will help us meet the requirements for publication in your journal.

In the following section, the text shown in red corresponds to new text that has been incorporated into the revised manuscript, and all of our responses are marked in blue.

Thank you for your time and careful work.

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Reviewer reports:

Brian Hobbs (Reviewer 1): Summary:

The authors have adequately responded to my initial concerns and comments as well as those of my co-reviewer. On remaining major concern that came up in my repeat review is that the definition of CKD is not clear. That authors need to clarify that they took steps to assure that the low eGFR is indeed chronic (present for at least 3 months) and not representative of acute kidney injury (AKI). My remaining comments are mostly minor and semantic.

Major:

1) I apologize for missing this in my initial review; however, what criterion were used to separate incidence of AKI (new Cr increase either at presentation to the hospital or during hospitalization) versus CKD (kidney injury present for > 3 months as defined by KDOQI guidelines)? If the "CKD" definitions are based only on presenting eGFR at admission to the hospital and are not retrospectively determined by observation of at least three months of kidney injury, then this is a severe limitation to the assertions of the current investigation, where the presence of AKI would confound the association between COPD and concurrent "CKD." The authors need to clarify how the definition for CKD was obtained and what steps were taken to assure AKI was not misclassified as CKD. As CKD and CKD severity is the primary stratification point for the analysis, the CKD definition needs to be precise and accurate.

Response: Thank you for your concern.
The data analyzed in this study were derived from the China Collaborative Study on Acute Kidney Injury (CCS-AKI), in which CKD was distinguished from AKI in strict accordance with the current KDOQI guidelines. The eGFR threshold (60 ml/min/1.73 m2) in the serial studies of the CCS-AKI was calculated based on the serum creatinine “baseline” for AKI classification, which was defined as the lowest serum creatinine level during a 12-month period before discharge of the latest hospitalization. Such a definition method can also be found in an epidemiological study on AKI conducted by Mehta et al. (2016). To further clarify the CKD definition, we have rewritten the definition of CKD in the “Definitions and outcome” subsection. In addition, we have added a citation to support the definition. The changes are as follows:

“CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2, which was based on the lowest serum creatinine level within 12 months before discharge of the latest hospitalization, according to the KDOQI guidelines [20].”

The newly added reference:


Minor:

2) Page 8 line 199 and page 9 line 207 refers to an "independent correlation," which as was noted in my initial review should be corrected to "association" throughout the manuscript.

Response: The "correlation" has been replaced with "association" throughout the manuscript. Thank you.

3) Page 9 line 215: "independent association" can be simplified to "association".

Response: Thank you for your suggested. We have simplified the original "independent association" to "association".

4) Throughout the manuscript, the authors mention a "multivariate" analysis. I believe the authors intended to say "multivariable."

Response: We have made the suggested change throughout the manuscript. Thank you.
Spyridon Fortis (Reviewer 2): Authors have improved the manuscript substantially.

Minor comment

The last paragraph of the results should be part of the discussion as it includes only the authors' interpretation. No further comments.

Response: Thank you for your feedback. In the revised manuscript, the original last paragraph of the results section has been moved to the end of the first paragraph of the discussion section, with minor modifications:

“The results of the present study of the hospitalized COPD population are in accordance with those of other reports showing the effect of CKD on anemia [4] and the associations of anemia with increased mortality [2]. We extended these previous observations by showing the association between high Hb concentration and in-hospital death in CKD patients, which was particularly significant in the advanced CKD group. Based on the analysis of the serial Hb intervals, the upper reference interval of Hb was 17 g/dL for CKD and 14 g/dL for advanced CKD. According to these preliminary reference intervals, high Hb levels were observed in 275 patients (4.0%) with CKD and 116 patients (10.8%) with advanced CKD.”