**Reviewer’s report**

**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

**Version:** 0  **Date:** 08 Mar 2019

**Reviewer:** Brian Hobbs

**Reviewer's report:**

**Summary:**

The authors report results from a large, retrospective, multi-hospital association study of hemoglobin (Hb) levels and in-hospital mortality in COPD patients with and without CKD. The primary conclusion is that high Hb levels (compared to the hemoglobin group with the lowest mortality) are associated with a higher risk of in-hospital death in COPD patients with comorbid CKD. The study has major limitations related to the definition of COPD (unclear if spirometric or based on diagnostic coding) and the lack of available data to adjust for severity of COPD in multivariable regression. That said, the authors present intriguing preliminary data that should be replicated and validated, preferably in data sets with cause-specific mortality, spirometry, supplemental oxygen utilization, and medications.

**Major:**

1) The title and the running title are misleading with regards to the conclusions one can make from the reported investigation. High hemoglobin was not shown to "increase" in-hospital death as no causal-modeling or functional studies were done to prove that hemoglobin itself is the reason for the observed increases in mortality. High hemoglobin is merely "associated" with in-hospital deaths, and may be a marker for another process contributing to the observed increase in mortality, as the authors state as a limitation in the discussion. Throughout the manuscript, the authors need to adjust language that says Hb "increases" the risk of death to make it clear they are reporting an association, not a causation.

2) How was COPD defined in this study? There are details on classification and stratification of CKD, but no details are given for COPD determination.

3) The covariates in the regression model are quite limited. Were any data available regarding COPD severity (such as supplemental oxygen use or FEV1 level)? It seems that if COPD is defined by ICD diagnostic coding, then supplemental oxygen use should also be available.
4) The authors missed an opportunity to compare hemoglobin cutoffs for persons with and without COPD in the CCS-AKI study, thus it is unclear if any of the observations are specific to COPD or are representative of patient with CKD overall. This is a major limitation of the investigation, particularly since elevated hemoglobin levels are already known to be associated with increased mortality in CKD. The authors note that the KDIGO group recommends that Hb levels should not exceed 13 g/dL. Thus, one question from the reported investigation would be whether this upper bound for Hb levels should be more liberal in COPD, where the current manuscript suggests threshold of >14 in advanced CKD and >17 in all CKD. It do not think that is an appropriate interpretation of the current study, but it is hard to definitively draw another conclusion without a comparison of the association of in-hospital mortality with Hb levels in persons with CKD, stratified by COPD status (and severity).

Minor:

5) Introduction, pg 4, line 87, grammatical error: "…comorbid polycythemia is low, which contributes to the…” should read, "…comorbid polycythemia is low, which is attributed to the…”

6) The p value threshold of P <0.05 does not properly account for the multiple testing performed for analysis of each bin of mean hemoglobin level to a reference hemoglobin. The authors should consider more strict adjustment for multiple testing.

7) Results, all: The mortality rate throughout the results should have accompanying statistics when two groups are compared. For example, in lines 197-198, "the death rate showed an increasing tendency, which reached 3.8% and 4.0% within the 16-17 g/dL and higher than 17 g/dL groups, respectively" should be clarified to state if 3.8% and 4.0% are significantly different. I suspect they are not different and "increasing tendency" may be misleading.

8) Results, pg 8, line 192: "With an increase in Hb levels, the death rate decreased gradually." These are cross-sectional data and "gradually" may imply a longitudinal aspect to the investigation. It would be better to say, "Hb levels and mortality rate were inversely proportional."

9) Results, pg 8, lines 195-200: A lot of this text is extraneous and could more concisely describe the U-shaped relationship of Hb level and mortality, which is best visualized in Figure 3.

10) Results, pg 9, line 201: The authors talk about "correlation" between Hb and death rate, though no correlation statistics are given. I suggest either a correlation analysis be performed and plotted, or a choice of different words.

11) Results, pg 9, line 208: "independent correlation" is not the correct wording and I suggest the authors refer to this analysis as "independent association."
12) Results, pg 9, line 210: "correction factors" should be "covariates"

13) Results, pg 9, line 215: p value missing for the OR

14) Results, pg 9, line 219: ">7" should be ">17"

15) Results, pg 9, line 215: p value missing for the second OR

16) Figure 3: These lines are an inaccurate representation of the data, which is discussed according to hemoglobin bins in the main text. Additionally, the data as currently plotted do not allow the visualization of the error about the mortality percent at each level of hemoglobin. Since the data were binned according to mean hemoglobin, these data would be more accurately represented by three set of box plots in each hemoglobin bin.

17) Figure 4: The Y axis scale should for OR should be log, not linear, such that 0.5 and 2 are equally spaced around 1. This explains the upward skew of the 95% CI around the OR.

18) Given the large 95% CI around the OR at the tails of the hemoglobin distributions, a table showing the number of deaths per hemoglobin bin in each CKD stratum would be helpful.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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