Reviewer’s report

Title: Anemia and hemoglobin serum levels are associated with exercise capacity and quality of life in chronic obstructive pulmonary disease

Version: 2 Date: 30 December 2014

Reviewer: Afrodi Boutou

Reviewer’s report:

This study adds to the current literature on the association between hemoglobin levels, exercise capacity and HRQL in COPD patients. The novelty of this study is that authors have sought a potential association between muscle strength and hemoglobin in these patients. However, this is not properly presented. Authors should focus on the novel aspect of their study (even though no association was found), describe the gap in the current literature, describe the rationale and present their study hypothesis, since none of these is done. The association between Hb, exercise capacity and HRQL could serve as secondary aims, as this topic is not particularly novel.

Major Compulsory Revisions

Rationale-study hypothesis: as described above

Material-Methods:

1) What is the study type? It seems to be a retrospective study, since authors reviewed the medical records of COPD outpatients. Whether it is another type of study it is not clear, and authors should provide more information regarding study design.

2) exclusion criteria: How many patients were on ARBs? Such information is important as those drugs are known to be associated with anemia.

3) what was the rationale for CRP measurement? This is not a measurement which is systematically done in outpatients, so was it prospectively conducted?

4) What is the definition of polycythemia?

5) Exercise testing: Again, CPET and 6MWT are not systematically conducted on outpatient basis. Have these patients conducted these tests as part of another protocol running in the department? If so, please give more details, because then this COPD population might be a selected and not a general one.

6) Please define the timeframe within exercise testing, PFTs and lab testing were conducted.

Results

1) Previous studies have established a difference in CRP levels between anemics and non-anemics (John et al, 2005; Boutou et al, 2012). The current study however failed to establish such a difference, so authors should try to
explain why their results are different from existing literature.

2) Authors state that there is a linear relationship between hemoglobin, exercise capacity and HRQL; if this is true then polycytemic patients should have the best quality of life and exercise capacity. However, there is currently no literature data to support that polycythemia is beneficial in COPD patients, while some historical studies indicate a symptomatic relief for polycythemic patients after erythropheresis (Wedzicha JA, Rudd RM, Apps MC, Cotter FE, Newland AC, Empey DW. Erythropheresis in patients with polycythemia secondary to hypoxic lung disease. Br Med J (Clin Res Ed) 1983;286:511-514.) The equation should rather be linear up to a point and then become non-linear, and this point has to be defined. Authors should have separated Hb concentration in smaller ranges and separately test the linearity or not of its association to the outcomes of interest. Unfortunately the vast majority of patients are non-anemic with mean Hb concentration of 14.5, so the number of cases than can be used to test such associations at the very ends of Hb range is very small (so is the number of polycythemic patients). The conclusion should then be less strong and all these limitations have to be described.

Discussion
1) “When the content of arterial O2 is low, the gradient of diffusion of the gas from the blood to the mitochondria decreases rapidly, producing an early anaerobic metabolism” Do the authors have any AT data for their patients to support this theory?

2) “It is also possible that people with anemia are less active and have more sedentary lifestyles, which would lead to muscular deconditioning” Please explain why this theory is not supported by your data.

3) “However, CRP was inversely related with indices of exercise capacity and hemoglobin levels in the bivariate analysis (data not shown), but was not associated to 6MWD or VO2max in the multivariate one. These results seem to indicate the link between inflammation and reduced physical performance is not direct but mediated by its inhibiting effect on proliferation of erythrocyte progenitors [16, 40], and by the resulting anemia”

Here the authors seem to jump to a conclusion not supported by their findings on inflammation.

4) Line 278: cross sectional design or other?

Minor essential revisions

Abstract: What is the type of the study? It seems like a retrospective one-authors should add study type to the abstract.

Typing errors:
Line 92: correct to “studies”
Line 137: correct to “with”
Line 251: correct to “subjects”
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'