Reviewer's report

Title: Imbalances in serum angiopoietin concentrations are early predictors of septic shock and survival in patients with post chemotherapy febrile neutropenia

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Reviewer: Michael Darmon

Reviewer's report:

The manuscript submitted by Dr Alves and Colleagues demonstrate Serum angiopoietin concentrations to differ between neutropenic patients developing non complicated sepsis and septic shock.

The question posed by the authors is well defined, but the two objectives of the authors (describing Ang-1 and Ang-2 in neutropenic patients with fever and evaluating performance of these biomarker as predictor of poor outcome) may deserve to be more clearly stated.

As regard with the methods of this manuscript, I believe that the limited sample size that precludes any adequate adjustment for confounding factors. In addition I have concerns regarding the use of a Cox model in such a small population of patients.

In the same way, the authors should consider the use of the STARD recommendations (http://www.stard-statement.org/) when reporting performance of Ang-2 and Ang2/Ang-1 ratio.

Discussion and conclusions should be more balanced as regard to the results of the study (see comments) and the limits of this study should probably more clearly stated in the discussion section.

The manuscript is well written and interesting despite the above mentioned limitations although several methodological weaknesses should be corrected or at least acknowledge.

In my opinion, the two main limits of this study is the limited sample size that preclude any adequate adjustment for confounding factors and the huge overlap regarding angiopoietin concentrations between the studied group.

Major Comments:

1- Eight patients died and 10 patients developed a septic shock. This precludes any multivariable analysis. Indeed, to limit biases it is usually consider that a ratio of 1 variable for at least 7 to 10 events should be respected. I have concerns regarding the validity and the statistical power of the Cox model presented in this study. This model should probably be deleted from the manuscript.

2- A flowchart of the patients admitted in the authors unit during the study period,
and including the patients not included in this study would be of interest.

3- There is two parts in the authors study: The descriptive analysis in a very specific population of patients that is of interest and the search for biomarker predicting outcome and severe sepsis. Although the descriptive part of the work is well conducted, several informations are lacking to demonstrate interest of angiopoietin concentrations as predictors of septic shock or death.

a. I would recommend the authors to follow the STARD recommendations (http://www.stard-statement.org/).

b. Although angiopoietin-2 48h after onset of fever and Ang-2/Ang-1 at fever onset differs between patients with septic shock and sepsis, there is a wide overlap between the two groups of patients. This would probably translate into limited specificity, sensitivity and Area under ROC. I believe these informations to be mandatory to assess performance of angiopoietin as biomarker.

c. Authors should avoid overinterpretation of their results. For example, when stating that “after 48 hours, patients with septic shock presented an almost 25-fold higher ang-2/ang-1 ratio when compared to patients with non-complicated sepsis, the authors suggest a significant difference that is not supported by the data (P=0.06)

d. In the same way, when describing correlation between SOFA and Ang-2 or Ang-2/Ang-1 ratio, the authors describe a significant but weak correlation that is difficult to interpret.

e. Please provide P Value for every test (not only NS…)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests