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: Derek Wheeler

Reviewer's report:

Thank you for the kind invitation to review the manuscript by Alves and colleagues. Briefly, Alves and colleagues present the findings of a small, prospective cohort study in which serum angiopoietin-1 (angpt-1), angiopoietin-2 (angpt-2) were measured in patients presenting with fever and neutropenia. The early recognition and diagnosis of sepsis remains a challenge for even the most experienced healthcare providers. As such, there is great interest in validating biomarkers that can predict the onset of sepsis prior to more traditional clinical markers of sepsis.

There are now several studies that suggest that angpt-1 and angpt-2 may be important biomarkers for predicting increased severity of illness, and in some studies, mortality in critically ill patients with septic shock. The current study is the first to apply these biomarkers to patients with febrile neutropenia. As such, I think this study would be of great interest and would be an important addition to the literature. Unfortunately, I have several concerns as outlined below.

Major Compulsory Concerns:

1. The sample size (n=41 patients with fever and neutropenia) is small and therefore the findings of the study are in question. Indeed, only 10 patients with fever and neutropenia developed septic shock. In order to properly validate the use of a biomarker, a much larger sample size is necessary. I don't think the current study has adequate power to detect differences between patients with septic shock vs sepsis.

2. Similarly, only 8 patients died in this particular study. The authors need to provide additional discussion of the significant weaknesses inherent in such a small sample size. Again, I don't believe that the study was adequately powered to detect differences in these biomarkers in patients who died versus those who survived.

3. The ideal biomarker for this particular patient population would reliably distinguish between patients who ultimately develop septic shock versus those who develop sepsis. Similarly, the ideal biomarker would reliably predict survival. Based on the findings in this particular study, neither angpt-1 or angpt-2 appear to distinguish between patients who developed septic shock versus those who developed sepsis until at least 48 h after the onset of fever. I suspect that the small sample size may have led to a type II error here. Rather than outright
rejecting the utility of angpt-1 and angpt-2, I believe that a larger sample size is necessary.

4. It is interesting to note that the ratio of angpt-2 to angpt-1 did appear to differentiate between patients who developed septic shock versus those with sepsis at the time of the onset of fever. Again, given the small sample size, is this a type I error?

5. The authors mention that they analyzed vWF levels as well - where are these data? The authors need to include this data or refrain from mentioning it in the Methods, Results, or Discussion.

6. The authors state in the Discussion that "the main finding of our study is that the relative concentration of Angpt-1 and Angpt-2 are different in subgroups of patients with FN that evolve to non-complicated sepsis compared to patients that develop septic shock, and that early evaluation of these two proteins in patients with febrile neutropenia is a promising tool to discriminate high risk patients with FN." However, these differences are not apparent until 48 h into the disease course (and then only for angpt-2 and the ratio of angpt-2 to angpt-1). With this in mind, the authors need to temper their conclusions a bit and change the wording of this particular sentence to more accurately portray their study findings.

Minor Essential Revisions:

1. There are several misspelled words throughout the manuscript that need to be corrected. In addition, the authors should carefully proof the manuscript for English word usage and grammar.

2. How did the authors decide how many patients to include in the study? Was this a convenience sample or did they determine the sample size before the study, taking into account the power necessary to detect differences in these biomarkers?

**Level of interest:** An article of importance in its field

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.