Author's response to reviews

Title: suPAR as a prognostic biomarker in sepsis

Authors:

Katia Donadello (katia_doc@yahoo.it)
Sabino Scolletta (sabino.scolletta@unisi.it)
Cecilia Covajes (cec.cov@libero.it)
Jean-Louis Vincent (jlvincen@ulb.ac.be)

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Author's response to reviews: see over
Dear Editor,

We have revised our manuscript according to the reviewers’ comments and your editorial suggestions and attach a marked-up revised version together with a point-by-point response to the reviewers’ concerns.

We believe the text has improved as a result of this process and hope it will now be acceptable for publication.

Yours sincerely,

Dr Katia Donadello
Prof Jean-Louis Vincent
Reviewer 1.

1. In the abstract, the last sentence states that suPAR may be useful for assessment of response to therapy. This is not consistent with what authors state in the body of the manuscript.

Author’s response: We thank the reviewer for noticing this and have altered the text accordingly.

2. Regarding the data supporting suPAR as a stratification biomarker: it would be useful to know when the levels were drawn in the various studies. This information is not consistently provided in the text. If available, this information is important to include as « timing » is important in judging the performance of a stratification biomarker. A stratification biomarker that is robust during the first days of admission is probably more useful than one that provides a prediction later in the course of ICU course.

Author’s response: We thank the reviewer for this important comment. We have now added sampling time data to Table 2 and a comment in the text (Page 9).

3. The Authors allude to the fact that suPAR plasma/serum levels are affected by renal function. Do they have a sense of how well this confounding factor was analyzed in the various studies?

Author’s response: We agree with the reviewer that this is an important point. Only one study (Koch et al. Critical Care 2011) analyzed this confounding factor and we have now added their results in the text, Page 7.

4. The studies reviewed regarding suPAR and stratification are relatively small, individually, and there does not appear to be any evidence of validation. As such, are the data amenable to some sort of formal meta-analysis to derive a suPAR « range » for prognostication?

Author’s response: We agree with the reviewer that the available studies do not furnish strong evidence of validation for a « consensus range ». However, because of the heterogeneity of the available studies, a meta-analysis would be difficult to conduct in terms of deriving any reference values for prognostication.

Reviewer 2.

1. In the abstract I would make it clearer that the paper address the diagnostic and prognostic value. After the sentence of low value of suPAR compared to CRP and PCT, the next sentence could start with: On the other hand, suPAR levels have been….or in contrast or something like that.

Author’s response: We thank the reviewer for this suggestion and have changed the sentence accordingly.

2. I miss a section or discussion on advantages and disadvantages of suPAR compared to the more commonly used biomarkers in sepsis, CRP and PCT. A good diagnostic biomarker is likely to have low value as a prognostic biomarker and visa versa. E.g. CRP and PCT (which I consider good diagnostic markers for bacterial infections). The fact that they are good markers for bacterial infections makes them less suited for prognostic use. E.g. a viral meningitis patients with high risk of mortality may have low CRP and PCT despite high risk of mortality. On the other hand, suPAR (which I consider a good prognostic marker), seems to be a very poor diagnostic marker. I would therefore use less review time on suPAR as a diagnostic marker in sepsis and use the free space to discuss suPAR in contrast to CRP and
PCT with regard to stability (both in vivo and in vitro), kinetics (acute vs non acute e.g. injection with LPS into healthy volunteers hardly affect suPAR (Ostrowski et al), source of production, and last, but not least, the combined knowledge of knowing the values of all 3 markers.

Author’s response: The present article was written as a mini-review to introduce suPAR as a potential biomarker in sepsis and not to compare suPAR with other available biomarkers, although we do this where data are available. Moreover, data are conflicting regarding the diagnostic and prognostic roles of CRP and PCT. Nevertheless, we have added a few sentences related to CRP and PCT in the text. We agree with the reviewer that biological markers should not be used in isolation to identify infection and have suggested the possibility of combining suPAR with other biomarkers in the conclusion (Page 10).

3. I suggest to remove the comment in table 1 to the paper of Kofoed et al in which suPAR had a diagnostic AUC of 0.50 ( !), and the comment states the « Possible use in combination with other biomarkers in the diagnosis of sepsis. It is true that combination of biomarkers may add in diagnosing, but suPAR with an AUC of 0.50 adds no value. ….

Author’s response: We agree with the reviewer and have altered the text accordingly.

4. In the middle of the section termed suPAR as a diagnostic marker of sepsis (table 1) it is stated that However, because of relatively low prognostic sensitivity and specificity, the routine….Do the authors not mean : However, because of the relatively low diagnostic sensitivity and specificity.

Author’s response: We thank the reviewer for noticing this typographical slip and have corrected it in the revised text.

5. I find a bit premature to state that currently available data do not support the sequential suPAR measurements. There are simply not enough studies that have addressed the issue to justify that statement.

Author’s response: Indeed, this sentence did not transmit our meaning well and we have rewritten it.

Reviewer 3.

Sepsis constitutes the subject of intensive research since it represents the leading cause of death among critically ill patients. Markers pointing towards early diagnosis, facilitation of prognosis and monitoring of treatment course are of great importance. The authors have conducted an interesting review regarding the potential use of a biomarker (suPAR) in the prognosis of sepsis. As referred the use of this specific biomarker seems to be useful for the severity stratification and assessment of response to therapy in the critically ill patient.

1. The authors deal with the challenging topic of sepsis and with the potential use of biomarkers for the diagnosis and prognosis in particular. The use of suPAR is relatively novel and the authors have defined its clinical assessment adequately.

2. The authors do not include in the manuscript the « methods » section. They should provide information regarding the manner they performed the search of the literature i.e. the key words and the inclusion/exclusion criteria they used for the existing studies. Besides there must be an evaluation of the effect of different study designs (double blind, observational, prospective, retrospective studies) before a final assessment could be concluded.
Author’s comment: This was written as a narrative review and, as such, we do not believe that a methods section is necessary. We have, however, specified in the abstract and text (Page 3) that this is a narrative review.

3. The data seem to be well controlled.

4. The manuscript adheres to the relevant standards for report and data deposition.

5. The conclusions are well balanced and the authors provide adequate supporting evidence.

6. The title and abstract are concise and accurately convey what was found.

7. The manuscript is well written and needs no substantial linguistic review.

Author’s comment: We thank the reviewer for these positive remarks.

Editor’s comments.

1. Abstract: The referees have suggested modifying the abstract to make it more clear what the article focuses us. In addition, I have requested that you include a more general sentence of introduction.

   Author’s response: We have modified the abstract as suggested, adding a more general introduction to sepsis and clarifying the article’s focus.

2. Introduction: This is well written, but very brief. I have suggested that you expand this a little, giving a more general introduction to sepsis, and the suitability of suPAR as biomarker. As well, I have suggested finishing off with a clear statement of the aims of the article in order to more easily transition to the later sections.

   Author’s response: We have expanded this section, providing an introduction to sepsis and a statement of the aims of the article.

3. Main text: This is primarily well written. The referees have indicated a number of points where they felt you should clarify the point you were trying to make. In addition, I have asked for some general introduction for some of the sections and that you clarify your conclusions for each section in order to give the article better structure and flow.

   Author’s response: We have modified the text according to your suggestions and the comments of the reviewers.

4. Conclusions: This is mainly well written. I have made one request for you to clarify the last sentence in order to give it further weight and finish the article off on a strong point.

   Author’s response: We have modified the text as suggested.

5. Tables/Figures: I have noticed that you have not directly referred to Table 1 in the text, nor have you referred to Table 2 at all. Please refer to both of these at the appropriate place in the main text. In addition, I have suggested including a schematic in the introduction. The tables should be removed as supplementary files and appended to the end of the main text document.
Author’s response: We have now referred to the Tables in the article and apologize for this oversight. We have also added a schematic as suggested.

6. References: Please check the references carefully to ensure they are complete? no missing dates, journal titles or page ranges etc.
Author’s response: We have checked the references and completed/corrected when necessary.