

**Reviewer Response-** *Pilot Study of a Novel Serum mRNA Gene Panel for Diagnosis of Acute Septic Arthritis*

**Reviewer #1**

*Blake J Schultz et al (Manuscript Number: 50870) describe and evaluate the “Serum mRNA Diagnostic for Septic Arthritis”. Their finding is interesting. Acute septic arthritis is an orthopedic emergency. Compared with conventional diagnostic methods, ‘Sepsis MetaScore’ (SMS) based on an mRNA signature has higher diagnostic accuracy. However, there are several weaknesses in this work, which should be corrected:*

- 1. On the section of Results, Please delete the redundancy sentences when the tables or figures have clearly showed the same information.**

The legend for Figure 2 was edited to eliminated redundant information (line 231-234)

Table 2- description of 6 observations being removed was move out of the table description and into the body of the text (line 211-212).

- 2. Please give a high definition image. For example, Figure 1 (A, B, C, D, E, and F) must larger than 300 dpi.**

A 300 dpi resolution image was used in the revised manuscript and we also included both a powerpoint and JPEG of the figure for any future editing needs.

- 2. On the section of Discussion, the main findings and its implications, limitations, and authors’ recommendations should be present more clearly and refining.**

This section was edited for clarity, if there are specific lines or points that the reviewer would like addressed, the authors are happy to do so.

- 4. The Table, Figure, Reference, and special symbols must fit the journal's requirements or format.**

See comment #1 regarding redundant information being deleted.

Tables were reformatted to include lines under titles, columns

References are in the Vancouver format as requested in the author guidelines.

First authors were bolded throughout the reference section

**Reviewer #2**

*This is an interesting manuscript about the “Sepsis MetaScore (SMS)” for diagnosis of acute septic arthritis. SMS showed a high level of diagnostic accuracy in predicting septic joints compared to other diagnostic biomarker such as ESR, CRP, and WBC. In addition, SMS was the only significant predictor of infection status in multivariate analysis. This manuscript is nicely structured and well written. However, I have a few minor comments about this manuscript. Please consider the following comments. (Comment)*

- 1. Page 2, Abstract, Results, line 1 Why is the total number 19 not 20? Sorry if I have got it wrong.**

The authors apologize for the discrepancy. One additional patient had been added during the manuscript preparation, and the abstract was not appropriately updated to reflect the most recent data. 20 is the correct number of patients and this has been changes in the abstract (line 70)

- 2. Page 2, Abstract, Results, lines 2-4 (AUROCs for SMS, ESR, CRP, and WBC are 0.86, 0.56, 0.59, and 0.58.) Page 9, Figure1 (AUROCs for SMS, ESR, CRP, and WBC are 0.87, 0.58, 0.6, and 0.59.) Is the one or the other correct?**

The authors apologize for the discrepancy. The values in the text are the most up to date numbers. The values in the abstract were updated accordingly. (Line 70-72)

### **Reviewer #3**

*The study is very relevant as there is no early diagnostic tool for septic arthritis now. However, in such cases, the therapeutic decision must be taken in a timely manner, and even urgently. The authors proposed a highly sensitive test (SMS) as a rule-out test for acute septic arthritis in native joints that is ideal for the clinical urgency. It is important that SMS may be useful in other inflammatory arthropathies such RA, and in patients with immunosuppression with falsely lowered inflammatory markers. I have no special comments or remarks on manuscript. The main limitations of the study were detailed by the authors. The manuscript is certainly recommended for publication; however, a minor revision is required.*

- 1. In my opinion, there are not enough latest references (2017–2019). There are only 2 links for 2017, 1 reference for 2018, and 1 – for 2019. It is advisable to add recent sources, ex.gr. PMID 30989408. Perhaps recent epidemiological studies should be added to emphasize the importance of the research topic, ex.gr. PMID 28809954, or PMID 28464432, PMID 30855548.**

The authors appreciated this feedback. The recommended updated references were added to the introduction. (highlighted in

30989408- Line 120-123

28809954, 28464432- Line 93-95

Additionally, recent references from, specifically regarding pro-calcitonin were added, including:

PMID:28623003 (line 121) -2017

PMID: 28343826 (line 296)-2017

PMID: 30846314 (line 296) - 2019

- 2. In addition, there is a slight discrepancy between the values of area under the ROC curve (round-off error?) in the abstract and in the text ('Results' Section).**

The authors apologize for the discrepancy. The values in the text are the most up to date numbers. The values in the abstract were updated accordingly. (Line 70-72)