

Peer Review File

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Reviewer Comments

This is an important article that adds to the growing body of literature addressing the effect of the change in definitions of sepsis from a SIRS based to SOFA-based classification. An important factor in this validation study is the evaluation of bacteremic patients in the ICU, a crucial population for both clinicians and researchers. The authors note that patients meeting both the previous and newer sep-3 definitions of sepsis had a higher severity of illness and mortality compared to those who only met the previous criteria.

I have listed some of my concerns about this manuscript below in order of importance:

Critical

- There appears to be some conflict in the definition of this cohort. Page 4, line 80-83 states that the authors studied a “cohort of bacteremic patients admitted to the intensive care unit.” However, the protocol excluded patients without suspected infections. While low, this population may have included patients with positive blood cultures. I would recommend describing the characteristics of the excluded populations or note in the manuscript that only the subset of patients with suspected infection and known blood cultures were included (and describe how infection was suspected) or acknowledge this in the limitations.

Response: We thank the reviewer for this astute observation. We completely agree with the comment, and in response, we have included more information about the reason for excluding a certain group of patients under the study patients section “*We focused on patients requiring ICU admission, critically ill, with features of sepsis or septic shock. Patients who had a lower probability of an infection (based on the history and clinical course) as a cause of Critical illness or shock, were excluded.*”. As the review has suggested that there is a small possibility that some of these patients might have culture positivity, but the probability remains small. We have also included it under limitations sections.

- The authors changed the comparator group to include patients who met both criteria of shock and not just sep-3 (due to the low number of patients in the sep-3 group). As such they should clearly discuss that this study compared the hospital outcomes of patients who met sep-3 and sep-1 definitions of shock (including elevated lactate) to those who just met the old sep-1 shock definition. It would also read better to refer to this new group as “combined” criteria (or similar), than refer to them just as “new” as that may be misleading

Response: We thank the reviewer for this great suggestion. Based on the recommendation from the reviewer, we have updated this throughout the manuscript. The “new definition,” which is in true sense, means the combined (old and new definition) has been replaced with the “combined definition.”

Major

- Page 4, line 72 – SOFA is not “new”. I would revise to say patients/organ dysfunction is evaluated using SOFA and worsening of SOFA scores. qSOFA is new and can be discussed as such

Response: We agree with the suggestion of the reviewer. The word “new” has been deleted the sentenced has been reworded on page 4 line 71-72

- Page 4, line 75 – the 40% mortality is not for “meeting” SOFA criteria. That relates to the subset of patients in the new definition with shock. I would revise to reflect that as that is the population of interest in this manuscript.

Response: We agree with the suggestion of the reviewer. This has been revised in the introduction section on page 4, lines 73-77.

- Page 5, line 103 and 106 – there are two definitions of septic shock. I would clarify which ones you are referring to (eg. Sep-3 vs 1991 definition). Additionally, since the old definitions are important for this manuscript, I would define them instead of just referring to them

Response: As per the suggestion. The 2 different definitions have been referenced appropriately in the manuscript text .

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55

inger M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10

The definitions for SIRS/Sepsis (according to the 1991 definition) and Septic shock 2016 definition.

- Page 7, lines 140-144 – please do not discuss results while describing the outcomes. I would move the discussion to the appropriate results and discussion sections. Additionally, the concepts of “combined-old and new”, have not been defined yet, so moving it to a later section would be more logical

Response: We agree with the reviewer. As per the suggestion, this has been moved to the results section after an appropriate explanation of the concept of the old definition and the combined-old and new definition.

- Page 8, line 170 refers to vasopressor use but there is no mention of vasopressor in Figure 1. Please reconcile.

Response: Figure 1 has been revised

Please see new Figure 1.

- It appears that the conclusion of this study is similar to the ones used to create the new sep-3 criteria. As such, I would recommend acknowledging that in the discussion of validation of the

sep-3 definition in this particular cohort.

Response: We agree with the reviewer. Changes have been made in the manuscript under the conclusion section, page 12 line 245

Text added: This is in line with the intentions of the updated Sepsis-3 definition which offers greater consistency and ability to identify sicker patients that would require more timely and potentially aggressive management early in the course of sepsis.

Minor

- Page 7, line 138 – instead of “used”, I would say primary outcomes “were” or “primary outcomes studied were...”

Response: We agree with the reviewer. This has been changed in the revised manuscript text
Page 7 line 148

- Page 7, line 147 – I would recommend replacing “new and old..” with patients who met the “new and old criteria”

Response: We agree with the reviewer. The text has been updated in the revised manuscript.

Revised text: “Patients who met the new and old criteria for septic shock were analyzed for the outcomes mentioned above.”

- Page 7, lines 140-141 – Consider removing the line “The male gender...”. I would either report the percentages or modify the sentence structure to make it more readable.

Response: As per the suggestion, this has been changed in the revised manuscript.
Page 9 line 188-189

Revised text: “Both the groups were similar in terms of gender distribution and age”

- Page 11, lines 193-196 – please revise the sentence structure to remove the semi colon in the middle of the sentence

Response: As per the suggestion, this sentence has been revised to make it easier to read. Page 11 lines 211-214.

Revised text: “Studies on which the new third international consensus definitions for sepsis and septic Shock (Sepsis-3)(9) were based only had a small proportion of patients with bacteremia., This makes the generalizability of its results in bacteremic sepsis patients difficult.”