Peer Review File
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Reviewer A

Thank you for asking me to review this paper which is a review of clinical phenotypes in sepsis. It provides a narrative review of a variety of papers and attempts to classify them by infection site, type etc

1. I'm afraid that I'm not really sure what this paper is trying to achieve. Sepsis is a clinical diagnosis and although the paper mentions the use of AI modelling in the introduction, it stops there and doesn't take us any further forward. I find the style quite waffley and am concerned that ChatGPT may have contributed to the opening Background section. The first section is too long (pages 2-3) and repeats itself.
Response: Thank you for your suggestion.we have modified our text according to your suggestions (see Page 4, line 72-87)", thank you very much.

2. It is not really until line 202 that the paper realises some of its potential by talking about ML / AI phenotyping but then goes on talk about the phenotypic responses to sepsis rather than diagnosis.
Response: Thank you for your suggestion. It has been deleted. (see Page 4, line 87)".

3. The authors say that there are over 100 subtypes of sepsis proposed - it would be better that this review offered the best ones to target rather than talking around the possibilities.
Response: Thank you for your suggestion. This article summarizes the commonly used clinical phenotypes in order to emphasize that the classification of sepsis holds immense significance in improving clinical cure rates, reducing mortality, and alleviating the economic burden associated with this condition.

Reviewer B

The authors attempted to review the phenotypes in sepsis. The paper is well written, but very imbalanced. The content could be significantly improved

General comments:
1. The important studies are 'buried' among many secondary, much less interesting studies which are described in detail. The important studies are those from the MARS group, from Scicluna et al, from Sweeney et al, and from Seymour et al. (ref 10 - 14), and these ones should be discussed more.
Response: we have modified our text according to your suggestion (see Page 13, line 462-466) (see Page 14, line 496-500), thank you very much.

2. The references 15 to 27 can be deleted as they do not bring much to the review.
Response: Thank you, but we still keep these references because the content in the article cited these references.

3. There should be some qualitative assessment: is it important to differentiate between the various sources, the types of microorganisms, etc?
Response: Thank you for your advice. A prospective study suggests that the site of infection may be one of the reasons for the heterogeneity of sepsis. In future research on sepsis classification, the site of infection may be an important factor that cannot be ignored. The type, quantity, and distribution of microorganisms are important factors leading to heterogeneity in sepsis

4. There should be more emphasis on the implications of these subphenotypes (or even more the treatable traits)): fluids, corticosteroids, … Otherwise it remains an intellectual exercise.
Response: Thank you for your advice. Page 15,line 516-528 is about corticosteroids.
Other comments:
1. the phenotyping of hemodynamic patterns is quite poor: 'hyperkinetic' (formerly called 'warm') vs. hypokinetic (formerly called 'cold') would be more appropriate, but it may be deleted altogether.
Response: We agree with you, therefore we didn't include the patterns of'hyperkinetic' (formerly called 'warm') vs. hypokinetic (formerly called 'cold').

2. Sepsis can be categorized into two subtypes based on the nature of the infectious disease: internal and surgical.': I suppose the authors refer to medical and surgical patients. Is this distinction important?
Response: Thank you for your advice. The "internal and surgical sepsis" has been changed to "medical and surgical sepsis".There are differences in the types of sepsis among different departments, and understanding the heterogeneity of department distribution can help clinical doctors identify and make judgement on sepsis earlier.
3. The paper would benefit from some illustrations.
Response: Thank you for your advice. We added a table about the methods.

4. A comparison with cancer (and the recent suggestion to abandon the classification based on the primary organ involved) would be welcome.
Response: Thank you for your suggestion, in our paper the classification of sepsis was based on factors such as infectious diseases, infection sites, pathogens, body temperature changes, hemodynamics, conventional clinical data and molecular omics, which may supply helpful information in improving clinical cure rates, reducing mortality, and alleviating the economic burden associated with this condition.

Reviewer C

Thank you to the author for this manuscript. It is a comprehensive review, but there are some issues that need to be addressed. Below are detailed comments regarding this study.

1. The author mentioned that "Their findings suggested that sepsis patients with hypothermia and normal BMI might face a higher mortality risk compared to those with low or high BMI." Can the authors provide more information on how hypothermia and normal BMI contribute to the higher risk of mortality, in contrast to low or high BMI?
Response: Thank you for your good question. In that study, patients with body temperature < 36 °C (hypothermia) had a higher in-hospital mortality rate than that had by those without hypothermia in the normal BMI group (25/63, 39.7% vs. 107/549, 19.5%); however, this was not true for patients in the low or high BMI groups, which I think caused by sample size bias.

2. In the introductory section, the authors highlighted the Rationale and Knowledge Gap. To help guide future research on exploring the phenotype of sepsis, it would be helpful to provide a summary of the knowledge gap for each issue. This will enable other researchers to design further studies aimed at resolving the knowledge gap
Response: Thank you, but I didn't understand the "knowledge gap". We want to emphasize the personalized patient care according to the clinical phenotypes of sepsis, which would be helpful for improving survival rate.

Reviewer D

Thank you for the opportunity to review this manuscript. This is a well-written and thoughtful overview of different proposed schema for sepsis subtyping. I have some small comments that I hope will be of use to the authors and editors:

Specific comments:
1. Page 5, lines 96-97 - the terminology "surgical "and "internal" to describe sepsis is non-standard and in fact is not used in the three references cited in the following three paragraphs. I would suggest reconsidering the use of this terminology, although the underlying concept is valuable. (This may be a problem with translation…perhaps "medical" and "surgical" would be acceptable.)
Response: Thank you for your advice .we have modified our text as advised (see Page 6, line 192、198)

2. Page 7, line 135 – "Sepsis is a form of infectious poisoning" is an inaccurate phrasing. I would either delete the expression entirely, stating simply that "Bacterial infection is the most common cause of sepsis", or just refer back to the opening sentence of the paper (sepsis is "a dysregulated immune response to infection resulting in acute organ dysfunction").

Response: Thank you for your helpful suggestion, we have modified our text as advised (see Page 8, line 266-267).

3. Page 7, lines 140-141 – It is likely premature to say that viruses cause only 1% of sepsis. On some level, this is a limitation of diagnostics and will also vary enormously by time and place. (During some phases of the H1N1 and COVID-19 pandemics, viruses were the dominant causes of sepsis.) Similarly, parasitic disease is a major cause of sepsis in malaria-endemic regions.
Response: You are right, thanks a lot. We have modified our text as advised (see Page 8, line 272-273).

4. Page 7, line 148 – Lymphopenia and immune exhaustion is a common feature of both bacterial and viral sepsis, not specifically viral sepsis. I would include a reference to this sentence, or at least clarify that it is referring to COVID-19 specifically (if it is).
Response: We have modified our text as advised(see Page 9, line 309), thank you very much.

5. Page 8, line 171 – Say “Hemodynamics constitute”, not “constitutes”. (The word is usually considered to be plural.)
Response: Exactly, we have modified our text as advised (see Page 10, line 349), thanks again.

6. Page 8, line 173 – Clarify this sentence. As written, it implies that you use vasopressors to maintain a lactate >2 mmol/L.
Response: We have modified our text as advised (see Page 10, line 352), Thank you.

Reviewer E

Major points:
1. The authors only introduced the prior studies in section 4. Please show the strong and weak points of each phenotyping method. Please also show what kind of phenotyping methods are needed in the future, including the variables and statistical methods. In addition, please state how the physician should use many phenotypes in the clinical setting.
Response: In our review, we introduced the classification of sepsis based on factors such as infectious diseases, infection sites, pathogens, body temperature changes, hemodynamics, conventional clinical data and molecular omics, which may supply helpful information in improving clinical cure rates, reducing mortality, and alleviating the economic burden associated with this condition. However, there is still a lack of precise and effective classification methods for sepsis, and further research is needed.

2. The authors explained only about machine learning in the section "3. Research methods for sepsis classification". However, many articles in section 4 did not use machine learning. How does it work in the whole article?
Response: It was misunderstand. Only a few articles are based on machine learning, which is a method for dealing with large amounts of data in large databases, but not all studies adopt this approach.

Minor points
1. Please cite the original articles (ref. 1, 2, 4, 5, 7). For example, reference number 1 did not report the pathophysiology of sepsis; it only stated the pathophysiology, citing the article about the pathophysiology.
Response: Thank you for your advice. It was done, thank you for your suggestion.

2. (P. 8) “between body temperature trajectory and persistent cytokine subtypes, facilitating personalized immunomodulatory therapy for sepsis based on bedside immunophenotypic." The paper did not facilitate personalized immunomodulatory therapy, but facilitating personalized immunomodulatory therapy is expected by the result of the study.
Response: Thank you for your advice. You are right, we changed “facilitating personalized immunomodulatory therapy for sepsis based on bedside immunophenotypic” to “these subphenotypes could play a role in the bedside identification of cytokine profiles in patients with sepsis” (see page 9, line 321-323). Thank you for your good suggestion.
3. The second and third paragraphs on page 10 are not about sepsis classification based on hemodynamics. Please rename the section.
Response: Thank you for your advice. We have modified our text as advised, the third paragraph in P.10.had deleted. And adjust the order of the second paragraphs. (see Page 11-13, line 393-474)

4. The citation is needed for a retrospective study by Zhang et al. (P. 10).

Response: Thank you for your advice. This paragraph has been deleted， Zhang's research described at Page 12, line 437-443)

5. The first paragraph in section 4.7 iscoverlapped with the third paragraph in P.10.
Response: Thank you for your advice. We have modified our text as advised, the third paragraph in P.11.had deleted. (see Page 11).

Reviewer F

In this review, the authors discuss a new age of AI and ML to assist with clinical phenotypes. They use the terms internal and surgical infections, which are not commonly used terms in the sepsis field. The review is a summary however what is

largely unclear is how this review provides new insights into the field? Many reviews have already been published to summarize known data in sepsis and this review fails to provide a new approach or utilization of AI/ML to reorganize new clinical phenotypes. How does this review differ from others? What are the key takeaways that are insightful to the use of AI/ML? These questions would need to be answered to differentiate this from others.

Response: Thank you for your advice. After searching for recent studies on sepsis related phenotypes, I has summarized the following subtypes to assist the physicians have a better understanding of various phenotypic characteristics and provide a better basis for the classification. Only a few articles are based on machine learning, which is a practical method for dealing with large amounts of data in large databases, but not all studies adopt this approach.