

Peer Review File

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Reviewer A

This overall well-written review could be more balanced. Including the following points and references should be considered.

Comment 1: The authors specifically mention neonatal sepsis. They should include that pediatric sepsis definitions and guidelines are not applicable to neonates. In fact, there is no commonly agreed consensus definition for neonatal sepsis (PMID: 29019470, PMID: 24751791 and PMID: 31394566).

Reply 1: We thank the Reviewer for this point. We have added the following for neonatal sepsis. (Page 11 line 13)

Changes in the text: Under Neonatal Sepsis: “Unlike pediatric and adult sepsis, there is still no commonly agreed definition for neonatal sepsis (58-60).”

Comment 2: Another point to make is that fetal HRV testing has not been shown to decrease cerebral palsy in term infants but is clinically used to decide when to deliver a baby. It has resulted in a steep increase in C-section with increased maternal morbidity and mortality, and questionable benefit (PMID: 15906211).

Reply 2: The Reviewer makes an important point that the application of HRV has resulted in some undesirable implications on health services. (See Page 14, line 6)

Changes in the text: Under Discussion – Limitations of HRV, we have added: “The use of HRV in different settings can also result in undesirable effects on health services with an overall increase in interventions, hence impact on the wider healthcare setting must be evaluated before translation into practice (72).”

Comment 3: Specific limitations for neonatal HRV monitoring include the fact that medications (e.g. sedation) and/or physiological factors (persistent ductus arteriosus) may result in decreased HRV potentially causing unnecessary testing for sepsis or antibiotic exposure (PMID: 26518312).

Reply 3: HRV can be affected by different underlying conditions. We have added this to the limitations. (See Page 13 line 25)

Changes in the text: Under Limitations of HRV, we have added: “In neonates, abnormal HRV can be affected by factors other than sepsis, such as gestational age and underlying medical conditions (71), and as such needs to be interpreted accordingly.”

Reviewer B

Comment 1: Authors complete a review of heart rate variability, however, they select studies using a very narrow search term, i.e. "heart rate variability". Therefore a number of critical recent articles are missing from the review.

I suggest the authors expand their search terms to include articles that analyze 'physiomarkers' e.g. sample entropy, energy, etc. of heart rate.

These are some select articles that should be included in this review:

Shashikumar, S.P., Stanley, M.D., Sadiq, I., Li, Q., Holder, A., Clifford, G.D. and Nemati, S., 2017. Early sepsis detection in critical care patients using multiscale blood pressure and heart rate dynamics. *Journal of electrocardiology*, 50(6), pp.739-743.

van Wyk, F., Khojandi, A., Mohammed, A., Begoli, E., Davis, R.L. and Kamaleswaran, R., 2019. A minimal set of physiomarkers in continuous high frequency data streams predict adult sepsis onset earlier. *International journal of medical informatics*, 122, pp.55-62.

Ruminski, C.M., Clark, M.T., Lake, D.E., Kitzmiller, R.R., Keim-Malpass, J., Robertson, M.P., Simons, T.R., Moorman, J.R. and Calland, J.F., 2019. Impact of predictive analytics based on continuous cardiorespiratory monitoring in a surgical and trauma intensive care unit. *Journal of clinical monitoring and computing*, 33(4), pp.703-711.

Roussel, B., Behar, J. and Oster, J., 2019, September. A Recurrent Neural Network for the Prediction of Vital Sign Evolution and Sepsis in ICU. In *2019 Computing in Cardiology (CinC)* (pp. Page-1). IEEE.

Kamaleswaran, R., Akbilgic, O., Hallman, M.A., West, A.N., Davis, R.L. and Shah, S.H., 2018. Applying artificial intelligence to identify physiomarkers predicting severe sepsis in the PICU. *Pediatric Critical Care Medicine*, 19(10), pp.e495-e503.

van Wyk, F., Khojandi, A., Kamaleswaran, R., Akbilgic, O., Nemati, S. and Davis, R.L., 2017, November. How much data should we collect? A case study in sepsis detection using deep learning. In *2017 IEEE Healthcare Innovations and Point of Care Technologies (HI-POCT)* (pp. 109-112). IEEE.

Reply 1: We thank the Reviewer for this important comment and for the additional recent references. Although we did not use the word ‘physiomarker’ in our search strategy, we did go through these suggested references in detail and have acted on this. We have incorporated these important references into the manuscript.

Changes in the text: We included the fourth, fifth and sixth reference under Adult Sepsis (See Page 10, line 23): “In the adult intensive care units (ICU), the use of artificial intelligence has allowed HRV parameters to be incorporated into systems and scores that detect sepsis and severe sepsis (49-51).

We included the first, second and third reference under Adult Sepsis (See Page 11, line 1): Continuous HRV monitoring reduced the gap between the onset of sepsis and its clinical recognition by up to five hours, allowing clinicians to direct early intervention efforts in sepsis treatment (52-54)."

Reviewer C

Comment 1: The authors clearly state the aim of their manuscript – to review the role of heart rate in paediatric early warning scores, and to introduce the concept of heart rate variability. It seems that the authors are suggesting that heart rate on its own is a poor tool in discriminating between critical and non-critical illness, and that heart rate variability may hold more promise than heart rate, either alone or as part of a score. It may help the reader if the authors are explicit about this. This would improve the justification of the manuscript's importance to the reader.

Reply 1: We thank the Reviewer for encouraging us to highlight this message. (See Page 7, line 4, line 21 and Page 8, line 4)

Changes in the text: We provided in detail the role of traditional vital signs including heart rate in the section under Heart rate as a predictor for critical illness including sepsis, and stated: "Although heart rate is a convenient and easily accessed physiological parameter, there is a lack of consensus among warning scores on what constitutes significant, out-of-proportion tachycardia in a sick child..." "Tachycardia out of proportion to age and height of fever has also been proven not to have good discriminatory value in the prediction for infants with sepsis (24)." And concluded "The clinical value of traditional heart rate as a predictive tool is thus limited, and this has led to the exploration of novel methods such as HRV analysis."

Comment 2: The search strategy and search terms are clearly stated by the authors, which makes the search results reproducible to the degree demanded by a narrative rather than systematic review. Although unconventional, it may help the reader to state when the search was carried out given that this is a field that is being constantly updated, especially in the era of big data and electronic health records.

Reply 2: We have added the following to the Abstract, under Data sources: (See Page 3, line 11)

Changes in the text: "We conducted a literature search for papers published up to December 2019 on the utility of heart rate and HRV analysis in the diagnosis and management of sepsis."

Comment 3: The manuscript is appropriately referenced. The layout is logical and well sign

posted. However, I would suggest that the author consider further the following papers, some of which may have been published since the authors' search:

Arbo JE, Lessing JK, Ford WJH, et al. Heart rate variability measures for prediction of severity of illness and poor outcome in ED patients with sepsis [published online ahead of print, 2020 Jan 7]. *Am J Emerg Med*. 2020;S0735-6757(20)30012-7. doi:10.1016/j.ajem.2020.01.012

Amiri P, Derakhshan A, Gharib B, Liu YH, Mirzaaghayan M. Identifying Optimal Features from Heart Rate Variability for Early Detection of Sepsis in Pediatric Intensive Care. *Conf Proc IEEE Eng Med Biol Soc*. 2019;2019:1425–1428. doi:10.1109/EMBC.2019.8856346

Nguyen N, Vandenbroucke L, Hernández A, Pham T, Beuchée A, Pladys P. Early-onset neonatal sepsis is associated with a high heart rate during automatically selected stationary periods. *Acta Paediatr*. 2017;106(5):749–754. doi:10.1111/apa.13782

Joshi R, Kommers D, Oosterwijk L, Feijs L, Van Pul C, Andriessen P. Predicting Neonatal Sepsis Using Features of Heart Rate Variability, Respiratory Characteristics and ECG-Derived Estimates of Infant Motion [published online ahead of print, 2019 Jul 9]. *IEEE J Biomed Health Inform*. 2019;10.1109/JBHI.2019.2927463. doi:10.1109/JBHI.2019.2927463

Reply 3: We thank the Reviewer for these important references and have included them in our manuscript.

Changes in the text:

We have included the first reference under Adult Sepsis (See Page 11, line 6): “Short-term HRV analysis is a potential game-changer in better diagnostic accuracy for adult sepsis in the ED and ICUs and should be integrated with other vital signs for better performance (55,56).”

We included the second reference under Pediatric Sepsis (See Page 12, line 18): “In another study of 22 children with known cardiovascular diseases, HRV changes may precede clinical diagnosis of sepsis by up to 24 hours (69).”

We included the third reference under Neonatal sepsis (See Page 12, line 3): “However, another study showed that specific HRV parameters were not significantly modified following sepsis (67).”

We included the fourth reference under Neonatal Sepsis (See Page 11, line 16): “Heart rate characteristic (HRC) index measures the degree of reduced variability and decelerations to determine the fold-increase in the risk of developing neonatal sepsis (61,62)”

Comment 4: In addition, the following systematic review may also help, particularly to aid completeness of the review:

de Castilho FM, Ribeiro ALP, Nobre V, Barros G, de Sousa MR. Heart rate variability as

predictor of mortality in sepsis: A systematic review. PLoS One. 2018;13(9):e0203487.
Published 2018 Sep 11. Doi:10.1371/journal.pone.0203487

Reply 4: We thank the Reviewer for the additional references and have included it as part of our manuscript (see page 11, line 6).

Changes in the text: Under Adult Sepsis, we have added: Short-term HRV analysis is a potential game-changer in better diagnostic accuracy for adult sepsis in the ED and intensive care units and should be integrated with other vital signs for better performance (55,56).

Comment 5: Also, it may help the authors to help sign-post to future developments in the field such as this prospective study:

Quinten VM, van Meurs M, Renes MH, Ligtenberg JJM, Ter Maaten JC. Protocol of the sepsivit study: a prospective observational study to determine whether continuous heart rate variability measurement during the first 48 hours of hospitalisation provides an early warning for deterioration in patients presenting with infection or sepsis to the emergency department of a Dutch academic teaching hospital. BMJ Open. 2017;7(11):e018259. Published 2017 Nov 17. doi:10.1136/bmjopen-2017-018259

Reply 5: We thank the Reviewer for highlighting the importance of future development in this field and have included the reference (see Page 11, line 9).

Changes in the text: Under Adult Sepsis, we have added: HRV remains a promising research field and there are ongoing studies that evaluate its utility as part of scoring systems (57).

Comment 6: The authors largely present the scientific reasoning for their statements and the structure is logical. However, the manuscript can be improved by the consideration of the quality of evidence. Although this is not required to the degree of a systematic review in a narrative review, it is important to consider this, particularly in Tables 2 and 3. In particular, explicitly stating the design of the study and, if possible, effect size would be useful additions for the reader to understand the landscape of the knowledge that already exists. I note that many of the studies on heart rate variability use different parameters: If the authors could show how the parameters relate to the outcomes studied, this would vastly improve the ability of the reader to synthesise the information.

Reply 6:

We have worked to improve the description of each study in both Tables 2 and 3 by specifically adding in the effect sizes and the relationship between HRV parameters and outcomes.

Changes made in the text: Please refer to detailed changes in Tables 2 and 3

Comment 7: Finally, I dispute the authors' assertion in the Introduction that 'Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), some clinicians utilise the systemic inflammatory response syndrome (SIRS) criteria to identify a critically ill child with sepsis.' Sepsis-3 criteria were defined for sepsis in adults. Paediatric definitions have not embraced these yet (despite Schlapbach LJ, Straney L, Bellomo R, MacLaren G, Pilcher D. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. *Intensive Care Med.* 2018;44(2):179–188. doi:10.1007/s00134-017-5021-8). SIRS criteria were used to define sepsis by Goldstein in 2005 (Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2–8. doi:10.1097/01.PCC.0000149131.72248.E6) and this definition is still widely used despite its lack of validity and accuracy. I wish for the authors to correct this.

Reply 7: We thank the Reviewer for this point. We have included this important reference and revised the text as advised (see Page 5, line 15)

Changes in the text: Under Introduction, we have added: “Many clinicians define pediatric sepsis based on the systemic inflammatory response syndrome (SIRS) criteria established by Goldstein in 2005 to identify a critically ill child with sepsis (7).”