Peer Review File

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Reviewer Comments:

The study argued that inotrope dose can be used as a surrogate for lactate. although lactate is not readily available in resource-limited countries, it is important to note that inotrope dose can be influenced by many subjective factors such as the perceived target of MAP; e.g. some physician would like to maintain blood pressure higher, while other would like to maintain it lower. In this situation, the inotrope dose can be different for a given patient with the same conditions. Other factors such as amount of fluid also influence the inotrpe dose. thus, I want to argue that. inotrops cannot be used as a biomarker for disease severity.

Reply: Thank you for this comment. It is thought provoking and, in many ways, aligns with one of the underlying premises of this paper…what is a simple parameter that reflects overall patient haemodynamic/circulatory status? We were concerned about the utility of lactate as well as cost and availability and thus asked the question "does lactate offer a unique selling proposition or can we substitute something else for it that is as good, or better, and doesn't impose any extra resource allocation. The concerns with lactate are similar to the concerns raised above regarding inotrope dose: inter-individual variability. With lactate this may arise from differences in lactate response in different populations, lactate production driven by adrenaline, differences in lactate kinetics at different stages of resuscitation etc. Some of these were addressed in our previous paper on the subject (Elhouni A, De Vasconcellos K. SAMJ. The utility of hyperlactataemia in the definition of septic shock: Evaluating the Sepsis-3 definitions in a sub-Saharan African intensive care unit. 2019;109(11):880-4.). In the study ICU inotrope doses are titrated according to Surviving Sepsis Guidelines, thus reducing inter-physician variability. Where a physician chooses a higher target and thus a higher inotrope dose, however, this may still be an important summary indicator of the patient's overall haemodynamic status. Similarly, fluid therapy should also be directed using established guidelines, minimizing variability in this regard. Our hypothesis is that inotrope dose (while imperfect) is at least as good an indicator of disease severity as serum lactate and we believe that the results of this study support this hypothesis. We have however included a statement in the limitations section highlighting the potential confounding factors for inotrope dose.

Other specific comments are as follows:

1. The authors may need to compare inotrope dosage with other readily available biomarkers such as CVP, Blood pressure, heart rate and respiratory rate; if the diagnostic performance did not outperform these signs, the inotrpe dosage may not be applicable.

Reply 1: We did not specifically look to compare these parameters with lactate and inotropic dose. CVP is not used in the study unit to guide haemodynamic optimisation so was not evaluated. BP is controlled by inotrope dose so is unlikely

to reflect outcome once inotropes have been started. HR is also likely to be insensitive as it is influenced by multiple factors potentially unrelated to haemodynamic status. All but 3 patients received mechanical ventilation and RR is thus likely to have been controlled and less likely to reflect physiological status. As such these values were not included in our data collection and analyses. We did however collect quick SOFA variables prior to ICU admission and have analysed respiratory rate and systolic blood pressure as predictors of the primary study outcome: neither of which were significant at the $p<0.05$ level.

2. The method section should be subdivided by subheadings as listed in STROBE checklist.

Done

3. "As previously described the optimal cut-off point for lactate was 4.5mmol/l in the study cohort. "---add reference for this statement.

Done

4. "variables that were significant on univariate analysis,"---what is the specific threshold for this univariate filtering?

Reply 4: We used a $p<0.05$ and have included this in the manuscript.

5. You need to distinguish inotropes, vasopressors and the equivalent dose amond many vasopressor agents should be specified.

We did allude to this in the study methodology:

Reply 5: "Unless otherwise specified the terms inotropic and vasopressor support refer to the use of the "inopressors" adrenaline and noradrenaline as "pure" vasopressors or inotropes were not used in the management of septic shock in the study ICU during the study period." We have expanded on this however to read as follows:

"Unless otherwise specified the terms inotropic and vasopressor support refer to the use of the "inopressors" adrenaline and noradrenaline as "pure" vasopressors (phenylephrine or vasopressin) or inotropes (dobutamine) were not used in the management of septic shock in the study ICU during the study period. Adrenaline and noradrenaline were treated as equipotent for the purpose of calculating inotrope dose."

6. more variables should be reported for describing the baseline characteristics such as infection site, patient type (surgical vs. medical), comorbidity, CRP, PCT and other relevant lab values for septic shock.

Reply 6: We have described infection site and patient type in the text of the results section. These characteristics were not included in the presented analyses as none of them were statistically significant for the study outcome. The data collection sheet and ethics approval for the study included only data necessary for the chosen severity of illness score (SOFA) and thus did not include comorbidity data and other biomarker results as these were not deemed relevant to the primary aim of evaluating the utility of lactate in outcome prediction in septic patients requiring inotropic support.

7. It would be helpful to combine several biomarkers to improve predictive value. for example, you can build a baseline model with only vital signs and GCS; further, you

can explore whether the baseline model can be improve by adding vasopressors or lactate. Use the Net benefit, decision curve analysis as performance measures. These can be easily done in R.

Reply 7: Thank you for this input. Our intention with this study was not to create an outcome prediction model. We aimed to critique the use of lactate in the Sepsis-3 definition of septic shock and to evaluate whether a "simple" clinical summary parameter (inotrope dose in this case) would be an effective substitute, especially in in a resource limited setting. One of the study authors (KdV) does however wish to create and evaluate a predictive model in the study setting and will consider utilizing the suggested technique. Due to the focused data set included in this study we believe that creating a predictive model should not be attempted as part of this study and do not want to distract from the clear message of the study.