Reviewer’s report

Title: Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial

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Reviewer: John Myburgh

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Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial.
Maitland et al.

1. Is the question posed by the authors new and well defined?

The FEAST study conducted by the authors of this subsidiary analysis and published in the New England Journal of Medicine in 2011 is a landmark trial has and will have a substantive impact on clinical practice, not only in low and middle-income countries, but the findings are applicable to high-income countries. The results of the trial challenge of the long-held concepts of fluid resuscitation in critically ill patients which have generated substantial debate in editorials and commentaries. Much of this discussion has focussed on the potential mechanisms of the increased mortality associated with bolus resuscitation, so the additional, and in depth, analyses presented in this manuscript have been keenly awaited. Given the clinical impact of the primary results and the need to provide insights into mechanisms, there is an imperative to publish these analyses in a broad medical journal.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

Central to understanding and interpreting these results requires recognition of the context in which the FEAST trial was conducted – ie in extreme low-income conditions. The authors have expended considerable space in defining the criteria for both Presenting Syndrome (PS) and Terminal Clinical Event (TCE). This is novel work and the authors have defined these using pragmatic and clinically relevant criteria. This is central to the internal validity of this substudy and needs to be emphasised.

In this context, the methods are sound and the methods are conducted in accordance with measures to minimise bias, which for a non-blinded trial is important – in particular blinded adjudication of PS and TCE, intention to treat analysis and no imputation for missing data. In a trial of this size, with the impressive completion rates, the study methods are sound.

This analysis focuses on FEAST Stratum A, ie patients who were randomised to
receive either bolus or control. The reference to FEAST Stratum B in the methods is complete and refers primarily to the flow diagram from the primary trial is somewhat redundant.

3. Are the data sound and well controlled?

There is a very large amount of data in the paper, most of which is explanatory to the primary outcomes. In addition, there is substantive data in the ESM, which is more explanatory.

The data presented in the main manuscript can be reduced to concentrate on the key findings – of these, Fig 1 (perhaps with the removal of Statum B), Fig 3a and Fig 4 are key.

Fig 4 could also be redrawn to present the KM graphs for each PS as 4 graphs. The rest should go to the ESM.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

The Venn diagram describing the proportions of PS is somewhat non-standard, but a useful graphical presentation. However, this could be presented in the ESM. Similarly, the definitions of the PS and TCE could be presented as a table, rather than in the text.

Accordingly, the reporting of the results in the main paper should concentrate on the data above, with reduced commentary on the component analyses for the PS and TCE categories.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

This is written well, but should be slightly re-structured to focus on the positive findings that relate to potential causality - viz cardiogenic mechanisms. This is a fundamental and critical observation and goes to the centre of challenging conventional dogma, and as such needs to be emphasised and relatively "undiluted".

The section on potential electrolyte changes is speculative without substantive data to support the suggested theories – this should be substantially shortened or deleted and left to subsequent editorial commentary. It simply detracts from the robust observations cited above.

6. Do the title and abstract accurately convey what has been found?

Yes – no comment

7. Is the writing acceptable?

Some statements of primacy and hyperbole can be removed – such as “largest”, remarkable, important. The results speak for themselves.
Professor John Myburgh

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests:
As stated above, I reviewed the FEAST study and wrote an accompanying editorial for the NEJM
I have previously reviewed this manuscript.