

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jlpm-23-20>

### Reviewer Comments

#### Reviewer A

**Comment 1:** It would be useful to have a direct comparative analysis between traditional Troponin and high-sensitivity troponin. What would be the added benefit of the rationale for this particular blood test? Even if there is a negative Tn- would these patients undergo CTCA if there were any concerns of ischaemic chest pain? Would it be useful to consider this blood test as an adjunct to the workup? Serial troponin adds the benefit that the patient is monitored for a prolonged period, which would not be possible with single Troponin. What is the impact of utilising this strategy? What percentage of patients return for further investigations? Are there any systematic reviews with regard to the above?

**Reply 1:** These are all reasonable questions, but outside the scope of the request that was made of us to submit this manuscript by invitation; which was, 'to contribute a review article on ruling in or ruling out myocardial infarction based on a *high sensitivity* troponin measurement'. We believe that we have done this.

**Comment 2:** It would be useful to expand on the limitations of the article.

**Reply 2:** A strengths and limitations section has now been included

#### Reviewer B

**Comment 1:** Line 44 would say "acute" Myocardial injury

**Reply 1:** Corrected

**Comment 2:** line 77 you say concern about myocarditis has increased trop measurements (would add reference for that).

**Reply 2:** This paragraph has been removed as we believe it does not add to the central message of this manuscript.

**Comment 3:** At time you use MI and other times AMI. Pick one for consistency

**Reply 3:** All changed to AMI for consistency

**Comment 4:** line 113 would add findings at coronary angiography here too.

**Reply 4:** Added

**Comment 5:** line 115. Careful what you say about type 2 MI. There can be significant CAD and still have a type 2. The point is that the stress on the heart is not from plaque erosion but on another entity (normally external to the heart) like pulmonary embolism, sepsis, fast heart rate, etc

**Reply 5:** This has been amended to read "...or Type 2, characterised by an imbalance

between myocardial oxygen supply and demand, such as in sepsis or pulmonary embolism”

**Reviewer C**

**Comment 1:** After carefully checking, we find this manuscript suits a Clinical Practice Review better than a Narrative Review, as it mainly provides expert opinions and summaries of clinical issues.

**Reply 1:** This has been changed to a Clinical Practice Review, and this is now identified in the Title. Accordingly, the structure has been changed to include a structured introduction with (a) Background (b) Rationale and knowledge gap (c) Objective. The word ‘narrative’ has been deleted from lines 51 and 55.

**Comment 2:** The authors mainly summarize the clinical experience and opinion of the emergency department in managing cardiac troponin results, could the authors consider highlighting it?

**Reply 2:** The title has been changed to: “Ruling Out Acute Myocardial Infarction Based on a Single High-Sensitivity Troponin Measurement in the Emergency Department: A Clinical Practice Review”

**Comment 3:** We suggest the authors combine "Overcrowding", "Chest pain in the context of overcrowding", "Different perspectives between clinical specialties" and "Patient flow and clinician decision making in chest pain" as "Introduction".

**Reply 3:** These sections have been combined.

**Comment 4:** For a clearer article structure, we strongly suggest the authors number the subheadings. For example:

- 1. Context of the Emergency Department setting (i.e., Introduction)
- 2. Characteristics of high-sensitivity troponin assays
- 3. Use of high-sensitivity troponin assays in clinical decision making

**Reply 4:** Subheadings in the main body of the manuscript have now been numbered.

**Comment 5:** "Concern about myocarditis..." seems more appropriate in the subsection "Chest pain in the context of overcrowding", which well shows the relationship and severity of chest pain and myocarditis/myocardial infarction.

**Reply 5:** This has now been removed as it does not add to the central purpose of this manuscript.

**Comment 6:** "and takes considerable time": We suggest the authors specify the time-consuming of cardiac troponin measurements.

**Reply 6:** This sentence has been changed to read "This means that the assessment and safe decision making for the management of these patients is challenging and time-consuming" to clarify that it is the entire assessment and decision making process which

is time-consuming.

**Comment 7:** Chest pain in the context of overcrowding: We recommend that the authors report available methods for diagnosing whether ED patients presenting with chest pain have AMI (e.g., ECG, cardiac biomarkers) and clarify the advantages of troponin testing.

**Reply 7:** We apologise, we don't quite understand this comment. All guidelines recommend the use of troponin testing for the assessment of patients presenting with potential AMI. We believe that the methods for diagnosing AMI are outlined in this paragraph: "The diagnosis of acute myocardial infarction cannot be made on either cTn alone, or with a single result. Dynamic cTn concentration change is required in the clinical context of myocardial ischaemia, identified by symptoms suggestive of AMI, ECG changes, imaging or coronary angiography."

References, as cited in manuscript:

Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain. *Journal of the American College of Cardiology*. 2021 Nov;78(22):e187–285.

Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* [Internet]. 2018 Nov 13 [cited 2023 Mar 30];138(20). Available from: <https://www.ahajournals.org/doi/10.1161/CIR.0000000000000617>

**Comment 8:** Please cite the literature on the views of cardiologists and clinical biochemists on cardiac troponin.

**Reply 8:** Now cited, see examples in strengths and limitations section

**Comment 9:** Given that there are some similar reviews of ED views on cardiac troponin (PMID: 33279982, 32232671): How does this review differ from previous reviews? What does this review add to existing knowledge? Please cite similar reviews for comparison and clearly state this. Also, please specify the objective and significance of this review, accordingly.

**Reply 9:** The new "Strengths and Limitations" section now outlines the the principle strength of this review is that it is written predominantly by emergency physicians, to give the ED perspective, and does reference the two reviews about which were written by cardiologists.

**Comment 10:** "and so require assays with precision at low concentrations": Please specify what indicator (or broadly, "cardiac biomarkers") concentrations.

**Reply 10:** This statement has been clarified and now reads "Single test rule out strategies involve decision making at very low troponin concentration thresholds, and therefore emergency physicians require assays with accuracy at low cTn concentrations."

**Comment 11:** Table 1: Reference 28, made by Mahler et al, is published under the CC

BY-NC-ND license as standard. We suggest the authors delete Table 1 and only keep the description in the text due to the copyright issue and necessity.

**Reply 11:** Table 1 removed and description remains in text.

**Comment 12:** Please kindly check the copyright of Figure 1. Is the image original? Or, from an article in a journal (may require permission to use)?

**Reply 12:** This is an original figure, created for this manuscript.

**Comment 13:** "Examples of single test rule out" & "Examples of widespread implementation".

We suggest the authors combine these two subsections.

**Reply 13:** These have been combined

**Comment 14:** We suggest that the authors put the pathways and the corresponding description together. That is, "i) Emergency Department Assessment of Chest Pain Score (EDACS) pathway (64) (see Supplement S1): EDACS pathways were developed in Australasia and ... can be used for single-test and serial-test rule-out of AMI."

**Reply 14:** These have now been combined

**Comment 15:** "All of these pathways have been validated in real-life patient care and are considered safe to use. They have also been shown to be effective in facilitating earlier discharge of patients from the ED". Please cite the literature with specific data to support its safety and efficacy

**Reply 15:** These references have been added

**Comment 16:** We recommend including a separate section on the STRENGTHS and LIMITATIONS of this review to promote a more intellectual interpretation.

**Reply 16:** A "Strengths and Limitations" section has now been added which states "The principle strength of this clinical practice review is that it has been written predominantly by emergency physicians, and so provides an ED perspective on the use of single test rule out for AMI. It focusses on the experience of assessing patients with chest pain in ED, rather than from a cardiology or laboratory viewpoint."

**Comment 17:** Please ensure that abbreviations are defined with their first use, e.g., "AMI" (line 86, line 93), URL (line 224).

**Reply 17:** These have both been corrected

#### **Reviewer D**

**Comment 1:** Should there be an advocacy for reporting both NPV and sensitivity with their respective CIs for all studies. Similarly for PPV and specificity.

**Reply 1:** We agree, it is helpful for studies to report both NPV and sensitivity, we have indicated this in section 2. of the main body, along with cautioning that disease prevalence must be considered when interpreting NPV. PPV and specificity are more relevant to rule-in strategies.

**Comment 2:** Are there patient subsets to be particularly careful about; e.g. those with abnormal ECGs, women, elderly etc.

**Reply 2:** A number of clinical pathways take into account factors such as ECG, sex and age. In addition to this, many pathways use sex-specific cutoffs for the URL. From an emergency physician perspective clinical history, examination findings, and investigation results are all taken into account in risk stratification within ADPs, as discussed in both the introduction and also the section 3. in the main body of the manuscript (Development of ADPs). We have also added this sentence to section 4. “A single troponin test for rule-out of ACS should only be used within ADPs.

#### **Reviewer E**

**Comment 1:** L179 “an assumed” instead of “a assumed”

**Reply 1:** Corrected

**Comment 2:** L215 “when an hs-cTn” instead of “whenan hs-cTn”

**Reply 2:** Corrected

**Comment 3:** L223 “A number of studies” instead of "A number of Several studies”

**Reply 3:** Corrected

**Comment 4:** L226 “an hs-cTn” instead of “a hs-cTn”

**Reply 4:** Corrected

**Comment 5:** L227 “an NPV” instead of “a NPV”

**Reply 5:** Corrected

**Comment 6:** L240 and 243 “an NPV” instead of “and NPV”

**Reply 6:** Corrected

**Comment 7:** L243 “30-day” instead of “30day”

**Reply 7:** Corrected

**Comment 8:** L325-326 “does not allow for the determination of a type 1 versus type 2 AMI” this suggests that a serial troponin measurement can adequately distinguish between type 1 and 2 AMI, but this is not correct.

**Reply 8:** This has been further explained “Further testing such as angiography demonstrating critical coronary artery stenosis or imaging providing evidence of new regional wall motion abnormalities are often required to make a conclusive diagnosis of the cause for a cTn rise (**and therefore determination of a Type 1 versus Type 2 AMI**).”