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Title	**Using the Clinical Chemistry Score in the emergency department to detect adverse cardiac events: a diagnostic accuracy study**
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Reviewer 1	Dr. Keerat Grewal
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Reviewer comments and author response	Thank you to the authors for this submitting this manuscript. It is a well-designed and written study. In this study the authors assess the Clinical Chemical Score (CCS), a score that incorporates a high-sensitivity troponin, and compare the the diagnostic performance of the score using two different high sensitivity cardiac TnI assays. The two assays examined were 1) the Ortho Clinical Diagnostics assay, and 2) the Abbott Architect assay. Below are some of the comments I had for the authors to consider: 1) Introduction, page 4: consider describing the CCS score in the introduction when it is first mentioned (i.e., what are the components of the score) and perhaps describe the previous test characteristics you found. Response: We have revised the text incorporating this request: “We have previously demonstrated in over 4000 patients enrolled in clinical studies assessing hs-cTn in patients with suspected ACS that a simple clinical chemistry score (CCS) which includes measurements of glucose, creatinine (for estimated glomerular filtration rate, eGFR) and hs-cTn provided superior sensitivity (i.e., ≥99.9%) for 30-day MI or death over the first two hs-cTn assays approved by Health Canada, namely Roche hs-cTnT (sensitivity=98.2%) and Abbott hs-cTnI (sensitivity=96.6%).10” 2) Introduction, page 5: the authors comment that there is no standardization between different hs-cTnI assays, "so the same sample tested with different assays may give very different results". Is there any information/literature that the authors can add about how large the difference in results between assays may be? Response: We have added the following text to highlight this difference. “For example, the same patient lithium heparin plasma material measured on the Abbott ARCHITECTi1000 (hs-cTnI), Siemens Dimension EXL (hs-cTnI) and Roche Cobas (hs-cTnT) instruments yielded mean hs-cTn results of 4.4 ng/L, 7.2 ng/L, and 26.8 ng/L, respectively.16” 3) Methods, page 4-5: when describing the two cohorts included in this study, it would be useful to add the timing of the troponin that were used here. Were tests performed on the first troponin drawn, repeat troponins, etc. If patients had multiple blood draws with troponins, which troponin blood test was used?

	Response: We have added the following text to indicate that the earliest/first blood sample was used for the analyses: "The earliest blood draw in the ED that included all laboratory measurements was used in both studies." 4) Methods, page 8: consider adding the formula for the CKD-EPI equation to the text for the reader. Response: We have added the CKD-EPI equation in the methods section as requested. 5) Methods, page 8: as above, consider adding the sens/spec of the CCS score that was previously derived. Response: We have added the previously derived estimates on clinical sensitivity and specificity in the introduction (see response to comment 1). 6) Discussion: how commonly used are the two hs-cTnI assays that were examined used in hospitals right now? Are these the main assays being currently used in hospitals? This would help the reader know how applicable the results would be. Response: We have provided these information in our response to comments raised by the Editors. We would prefer not to discuss market share and location of testing as we wish to avoid any commercial bias to our findings. Furthermore, market share today does not predict market share in the future. The focus on the manuscript is on the clinical performance of the CCS. 7) Discussion: suggest adding what future studies may need to look at - i.e., do the assays need to be run on the SAME blood sample to compare the performance of the CCS with the troponin. Do we need to look at the other assays that have been approved by Health Canada for hs-cTnI? Response: We have added the following text to address these comments: "Future studies will need to assess performance of the CCS with different blood sample types and if different combinations of point-of-care testing with the core chemistry analyzers can achieve acceptable clinical performance." 8) Conclusion, page 12: I would suggest narrowing the conclusion so that it is more apparent that there were two different assays that were examined in this study. Response: As requested, we have added "two" to indicate the number of hs-cTnI assays used in the overall study.
Reviewer 2	Mrs. Fatoumata Korika Tounkara
Institution	Research Chair in Emergency Medicine, Université Laval CHAU-Hôtel-Dieu de Lévis
Reviewer comments and author response	For Cohort 2, page 6 line 29, It would be important to include a minimum age for inclusion. Response: We have provided the age range of the patients in cohort 2 (see text

	under “Study Design and Participants”). Table1. page 21 line 22. We note that the proportion of patients with a history of stroke is higher in cohort 1 than in cohort 2. Will this affect outcomes in this cohort? Response: Thank you for pointing out this difference. We reviewed the datasets and in Cohort 1 the outcome was Stroke or TIA whereas in Cohort 2 the outcome was Stroke only. Accordingly, we have removed this row to improve the clarity of the group descriptions. Tables 2 and 3. It would be important to indicate the number of positive and negative patients found per test. In other words, the values that you used to calculate the sensitivity and specificity. These values allow us to assess the proportion of false positives and false negatives. Response: We have now provided the number of positive and negative patients for both tables 2 and 3.