Author's response to reviews

Title: A simple statistical model for prediction of acute coronary syndrome in chest pain patients in the emergency department

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Replies to the Reviewers’ comments

Reviewer 1. Ludbrook

Compulsory revisions

1. As the reviewer suggests, we have changed the beginning of Introduction to include a definition of ACS and to briefly indicate its clinical significance in the ED.

2. We agree that calculation the % risk (probability) of ACS would be helpful to the clinician who must decide on a course of action. This can be done based on the odds ratios reported in table 3, which we also show for two hypothetical patients in the 3rd paragraph of Results. Reporting the estimated regressions coefficients, as the reviewer suggests is redundant since $\text{log(Odds ratio)} = \text{Regression coefficient}$, where log is the natural logarithm

Minor essential revisions

1. The spelling in Acknowledgement has been corrected.

2. Reference #27 has been updated to the latest edition

Reviewer 2. McManus

Compulsory revisions

1. We agree. The sentence has now been changed to “This large overadmission implies an unsatisfactory quality of care for the patients….”

2. A new heading, “Reference standard” has been inserted, and the typo on line 2 has been corrected.

   All discharge diagnoses were reviewed for accuracy. However, we believe it is retrospectively very difficult, and often impossible, to disprove a discharge diagnosis of “not ACS” from the ED. To get this right would require prospective testing of all patients the day after discharge with an ECG and blood samples for cardiac markers. After looking at our data again, we have changed the text in Methods, Reference Standard to “For cases discharged from the ED, available data from the patient records indicated that the rate of missed diagnosis of ACS was low (not more than 2%)”. We have also added in Limitations of the study, second sentence: “Because of the retrospective nature of the study, there may of course be errors despite a careful collection of all data. For example, the diagnoses of the patients discharged from the ED were not tested with routine post-discharge ECG or blood samples for cardiac markers.”

3. As suggested, an introductory sentence has been inserted: “Two methods of ECG analysis were used, machine reading and expert reading”, as well as subheadings in the text.

4. This has been corrected; Citations are now after punctuation.

5. The main idea behind the cross-validation procedure was to repeated times estimate the regression parameters based on a randomly chosen training set, comprising approximately 80% of all patients, and then evaluate the obtained model among the remaining 20% patients
in a validation set kept completely isolated from the training set. We have tried to clarify this in the end of Methods.

6. We do not understand this objection. We are unable to find evidence in the literature that ECG is of no value in ED patients with other symptoms of ACS than chest pain, or even with no symptoms. See e.g. Canto et al. JAMA 2000; 283:3223-9. To support the view that the ECG is, overall, the most important variable in the ED prediction of ACS, we have inserted two references (Goldman & Kirtane, Ann Intern Med 2003; 139:987-95 and Lee & Goldman, N Engl J Med 2000; 342:1187-1195.)

7. We believe we have dealt with these comments in the revised version of the text. In Discussion, 3rd paragraph, the text now reads: “Thus, our model did not seem to perform any better than the average physician, and will therefore likely not be useful for the expert physician in the ED”. 2 rows down, the sentence now reads “…in healthcare settings with an ACS prevalence below 21% among chest pain patients, NPV may increase”. As the Reviewer kindly suggests, we have also added “…or to assist inexperienced junior staff in the ED, as a means to improve quality of care.”

Minor essential revisions

8. The references have been checked and corrected.

Discretionary revisions

9. The two ROC curves are now plotted in the same figure.

Reviewer 3. Kelly

Compulsory revisions

1. We agree that “acceptable clinical sensitivity” may be misleading, and that 95% identification is not acceptable in most countries. The only truly acceptable sensitivity is of course 100%. We have therefore made changes in several places.
   - The last sentence in Results in Abstract now reads: “At an ACS prevalence of 21% and a set sensitivity of 95%, the negative…..”,
   - At the end of Methods, Statistical analyses, we have added: “For calculation of specificity and predictive values, the sensitivity was set to 95%. This somewhat arbitrary level was chosen because with current standard evaluation, some 2-5% of the ACS patients are erroneously discharged from the ED, which implies a sensitivity of at least 95 % for the routine ED work-up”.
   - In Results, second paragraph we have changed to: “For this model, hospitalizing all patients with a probability of ACS of at least 8.66%, corresponding to 65% of all patients, would yield a sensitivity of 95% and a specificity of 43%”.
   - In Results, ECG assessment by experts, we have rewritten the sentence to “For this model, a sensitivity of 95% would yield a specificity of 50%, which at an ACS-prevalence of 21%…..”
   - In Conclusions: “At the set sensitivity of 95% and an ACS prevalence of 21%, the NPV was 96%”.
   “ACS” is now defined in Introduction, first sentence.
2. For the cross-validation results, 2.5 and 97.5 percentiles, ie, 95% reference intervals, are now added for NPV and PPV.

3. We are afraid we do not understand this comment. In the current manuscript, we describe the patient material in Methods, Reference standard, first sentence: "......and among these a discharge diagnosis of ACS was assigned in only 130 (31%), of which 28 (22%) had Q-wave AMI, 53 (41%) had non-Q-wave AMI and 49 (38%) unstable angina." There were thus 81 patients with AMI and 130 with ACS, and those with AMI were included in the group with ACS.

4. In Results, 2nd, we have now added the admission rate (65%) implied by using the statistical model. This admission rate is close to actual admission rate for these patients, which we now comment in the 3rd paragraph of the Discussion. We have no data on the number of bed days but it is unlikely that it would change significantly, given that the admission rates are similar.

**Minor essential revisions**

**Discretionary revisions**

**Manuscript formatting checklist**

Figure legends are now placed before the table legends in the document.

Figure and table titles are now provided in bold.