Author's response to reviews

Title: Chest pain in the emergency department: a risk-stratified approach

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Author's response to reviews: see over
Dear Editor,

We highly appreciate the detailed and valuable comments of the Referees on our manuscript. The suggestions were quite helpful for us and we incorporated them in the revised paper. We also addressed each of the raised concerns, as outlined below.

Referee 1:

I am a little bit puzzled by the low number of admitted patients. Only 19% of patients with chest pain were admitted, which is low compared with other studies. In addition, considering the low admission rate the proportion of patients with MACE at 6 weeks was only 9%, which also is lower than in other studies where commonly around 15% develop ACS. This does not make sense. How many patients were actually discharged from the ED with an ongoing ACS? I am concerned that there must have been a few.

Response: We thank the Reviewer for the comment. The composite endpoint of 6-week MACE comprises all-cause death, myocardial infarction or unscheduled revascularization. Patients with unstable angina that did not meet those criteria did not contribute to MACE. In fact, the proportion of patients diagnosed with ACS in our population is slightly lower than that mostly reported in the literature, but the fact that the incidence of 6-week MACE was not much higher is a reassuring finding. We added a new figure to the manuscript (figure 2), representing a flow diagram of all patients in the study, which may help the interpretation of data.

I believe the authors describe and discuss the Manchester triage system quite extensively without saying that this was one of the aims with the study. However, I believe that this information is important and interesting.

Response: We thank the Reviewer for the comment and we reformulated the background section of the manuscript, in order to clearly include the value of Manchester triage system for risk stratification as one the aims of the study (lines 54-55 and 103: “We aimed to describe the population with chest pain, to characterize the subgroup of patients with acute coronary syndrome (ACS) and to assess the prognostic value of Manchester triage system and of HEART score.”);
“(3) to determine the value of Manchester triage system and HEART score for risk stratification in acute chest pain.”

In this centre in Coimbra do they really have 4-500 visits per day. That would mean 170-190000 visits per year which I believe is a very high number. Is this really correct?

Response: The average number of patients per day in the emergency department (ED) is correct. The Coimbra Hospital and Universitary Centre is actually the largest hospital in the country (it has 1200 beds), being a tertiary universitary referral hospital located at the central region of Portugal.

One thing which concerns me is that in the definitions unstable angina is not included in the outcome MACE. Yet, the authors write that the most common diagnosis was unstable angina?

Response: Unstable angina (n= 10, 4.3% of total population) was the most common ACS subtype diagnosed in this population. In fact, a patient with an unstable angina is not included in the outcome of MACE by itself.[6] However, the patient can match the 6-week endpoint of MACE if he undergoes a percutaneous or surgical revascularization, has a myocardial infarction or dies during that period of time.

I would suggest the authors to do additional analyses in order to investigate if adding the other variables in the HEART score to ECG and troponins would add any information. This is the crucial question. If the variables do not add anything beyond what we already know from the information we get from the ECG and troponins it seems meaningless to use the HEART score in risk prediction.

Response: The Reviewer suggested we could analyze the predictive ability of the HEART score by comparing it to the risk prediction provided by ECG and troponins alone. In our additional analyses we built a ‘simplified HEART score’, not evaluating all the five parameters but just the ECG and the level of troponin. Its discriminatory power was numerically worse (c-statistic 0.782; 95% CI, 0.653 – 0.911, p < 0.001) than the risk prediction capacity of HEART score (c-statistic
0.880; 95% CI, 0.807 – 0.950, p < 0.001). This data supports the value of using the HEART score in helping to make accurate management choices in the ED and underlines the value of clinical predictors in analyzing a very heterogeneous symptom, chest pain.

We did not include in our reviewed paper as much information as we provide in this answer to the Reviewers due to space constraints. However, if considered to be of importance, we will be happy to provide it either in the main manuscript or in the form of Supplementary material.

*What troponin method was used? I believe that this also is very important, since it is very unlikely that the HEART score would add anything beyond high-sensitivity cardiac troponins.*

Response: This is an excellent observation and we thank the Reviewer for the pertinent comment. During the period of time analyzed, our hospital was using conventional/non-high sensibility troponin I assays (cut-off for myocardial infarction diagnosis was 0.20 ng/mL). As we agree that moving to high-sensitivity troponin can have an important impact in chest pain management in the ED, we included it as an additional limitation in our manuscript (lines 332-335: “Furthermore, during the period of time analysed, the laboratory was using conventional troponin I assays, so we could not evaluate the potential impact of high-sensitivity troponin in chest pain management.”).

*Reference 4 and 16 are the same.*

Response: We thank the Reviewer for alerting us for this mistake of our reference manager software, which we promptly corrected.

*Legends to Figure 1. CPOD should be COPD.*

Response: We apologize for this error and we have corrected the legend of Figure 1 as suggested.
Referee 2:

The project described seems to represent honest work and was well performed. It deals with a large patient group and the topic is important. Apart from some minor misspellings and language errors, the paper is well written.

Response: We thank the Reviewer for the comment.

My main concern is the retrospective study design. The HEART score is meant to be used in real time in the ED. Several HEART score studies so far have been retrospective, but with the current state of knowledge this is not a good design. Unless patient records are extremely detailed, a HEART score calculated based on records is most likely different from one calculated in real time. History is often not extensively described in the records, and risk factors may be missing or wrong.

Response: We agree with the Reviewer regarding his concerns about the study, mainly because of its retrospective design, as we mentioned in the limitations section of the manuscript. The vast majority of records had a really complete description of the clinical history and it was possible to extract the information necessary for the performance of the “History” and “Risk factors for coronary heart disease” variables of the HEART score, although we recognize that it is an obvious limitation of a retrospective design. Regarding the risk factors of each patient, besides the information included in the record of the episode, we conducted an investigation through the common electronic health records information of our hospital in order to complete the data.

In addition, the perception of the history and the number of risk factors might influence the ECG interpretation.

Response: This is a fact, as the pre-test probability may impact the interpretation of the ECG, namely when analyzing subtle ST-deviation or T-wave abnormalities. However, they will be classified as “non-specific changes”.
And I don’t think that having two authors make the retrospective assessments
overcomes this – they both assess the same potentially incomplete or erroneous record.
Hence, as a reader, you would like to see either a prospective design or evidence that
retrospective HEART score calculation is as reliable as calculation in real time. No
such evidence is described in the paper. Is it exists, please insert it. Without it, the
conclusions can only be very vague, and the relevance of the results is limited. In
addition, due to missing data in the present study, 25% of the patients were not
included in the HEART score analysis.

Response: We are unaware of any prospective study using the HEART score and
we agree that it is an issue worthy of further studies. We also agree that the
proportion of patients not included in the HEART score analysis due to not having
all the five parameters available to complete the score is an important issue, but we
tried to mitigate this by comparing the characteristics of the patients with
incomplete datasets with patients with complete datasets, finding no statistically
significant differences, as we mentioned in the limitations section of the
manuscript.

The HEART score should be mentioned in the title - please insert.

Response: We thank the Reviewer for the suggestion; however, considering that
we reformulated the aims section of the manuscript, according to the comments of
Referee one, in order to include the Manchester triage system in chest pain risk
stratification analysis, we now believe that we should not restrict the title of the
manuscript solely to the role of HEART score. Nevertheless, if the Editor or the
Reviewers consider that we should change it, we are available to do it.

Line 72: The conclusion should not include a statement that is presented as background
further down (line 80). Rephrase.

Response: We thank the Reviewer for his comment and we have rephrased it in
the text as suggested (line 82-83: “Causes of chest pain range from musculoskeletal
chest pain to potentially life-threatening emergencies…”).
The ED cardiologist seemed to make the diagnoses used to group patients. I think the patients should be divided into ACS and non-ACS groups based on the final diagnosis of the index visit, including in-hospital stay. It is not always possible to determine the diagnosis in the ED. Who made the diagnoses in patients admitted to in-hospital care? Who made the diagnoses after discharge from the index visit but within 6 weeks? Why were the diagnoses not reviewed for accuracy by the authors? Please clarify in the text.

Response: We probably were not explicit enough regarding the description of the methodology. All ACS patients were assessed, diagnosed and admitted by the ED cardiologist consultant. However, every patient admitted to in-hospital care was reviewed by the authors of this manuscript to confirm the diagnosis (e.g., excluding any missed diagnosis of myocarditis). We have clarified it now in our methods section (lines 122-123: “Nevertheless, every patient admitted to in-hospital care was review by the authors to confirm the diagnosis.”).

Please state what clinical records were used. Only ALERT, or records from the hospital wards as well? Other records?

Who interpreted the ECGs? What were their qualifications? Please insert this.

Response: The five parameters of the HEART score were applied according to the information available in the clinical records. Therefore, the information about the history, age and troponin values was taken from electronic medical ALERT® records. The number of risk factors for coronary heart disease was calculated from the information in ALERT® records, but also from previous clinical episodes of the patients. The ECG’s were interpreted by the attending physician in the ED, specialist in internal medicine or in cardiology. All ECG’s of the admitted patients for ACS were reviewed by two cardiologists (the ED cardiologist and the Coronary Care Unit cardiologist). We have adjusted the text of the manuscript to be clearer (lines 141-142: “The ECG’s were interpreted by the attending physician in the ED, specialist in internal medicine or in cardiology.”).
Line 144: The follow up is not clearly described. Which patient records were scrutinized? From the same hospital, or from the whole of Portugal? Primary care? Please describe in the text.

Response: The 6-week follow-up of patients was conducted through the clinical records information of the hospital and through direct phone calls to the patients involved. We have rephrased it now in the text to make it clearer (lines 151-153: “A 6-week follow-up of all patients was conducted through the electronic health records information of the hospital and through direct phone calls to the patients involved.”).

Line 195: I would like to see a patient flow chart (tree) to account for all patients in the study. How many patients had ACS during the index visit/hospital stay? How many died or had unplanned revascularization after the index visit but within 6 weeks etc?

Response: In fact, this increases the manuscript readability. We added a new figure to the manuscript (figure 2), representing a flow diagram of all patients in the study, as represented below.

![Patient Flow Chart](image)

Line 330: The word “valid” should be omitted; the results do not reliably show the (relevant) validity. See above. I recommend a change to “…..the HEART score seems to be a useful tool for risk…..” And please insert that prospective studies are needed before clinical use.

Response: We thank the Reviewer for his comment and changes were made accordingly (lines 331-332: “Prospective studies would be useful to confirm the
prognostic value of HEART score.”; line 343: “Moreover, the HEART score seems to be a useful tool for risk stratification and decision making in acute chest pain.”.

Line 73: Change “is” to “seems to be”. See my general comments regarding study design above.

Response: We agree with the suggestion made by the Reviewer (line 74: “The HEART score seems to be an effective tool for risk stratification in the ED.”).

Line 94: “…the stratification of the risk of ACS in patients presenting to the ED with chest pain. One is the HEART score….”. In the following sentence, it is said that the HEART score predicts MACE. This seems illogical, and should be changed.

Response: The statements made were more ambiguous than intended and we have adjusted the text to be clearer (lines 96-97: “Other systems, more selective, are devoted to the risk stratification of suspected ACS in the ED. One is the HEART score…”).

Line 110: “imagiological” is a strange word – change into “imaging”.

Response: We have corrected the text as suggested (line 113).

Line 184-5: Please clarify who made the diagnoses shown in Figure 1.

Response: We have completed the text, accordingly to the response detailed above.

Line 214: Omit the word “good”.

Response: We agree with the suggested change (line 223).

Line 248: “excellent” should be changed into “good”, as in line 237.

Response: We agree with the suggested change (line 258).
Line 267: It was not a majority, it was 37%. Please change.

Response: We have adjusted the text to be clearer (lines 276-277: “Non-specific chest pain (mostly musculoskeletal pain) was the most frequent diagnosis, but with a proportion slightly lower than that reported in other studies…”).

Line 284-5: The main problem with a low priority is, in my opinion, not the time to ECG but that the entire workup, pharmaceutical therapy etc, are delayed. It is considered ok to attend to a green patient within 2 h, and in reality it often takes longer.

Response: The delay in the ED is a very important issue and it is good that we have the chance to discuss it. Although we agree that all the delay in the workup and therapy should be addressed, we have chosen to highlight the time taken to record the first ECG because the prompt diagnosis of ST segment elevation myocardial infarction (STEMI) is the key to a successful reperfusion therapy. Actually, as minimizing delays is associated with improved outcomes in this disease, the current European Society of Cardiology guidelines emphasizes the need to measure regularly the time delays in order to keep a good quality care in STEMI management.

All the authors thank you for the opportunity to resubmit our work. We have worked diligently to respond to all the concerns raised by the Reviewers and we hope you will find this version of the manuscript worthy of publication.

With best wishes,

Luís Leite