**Response to Reviewer Comments**

**Reviewer 1:**

1. The introduction section is well written. If the authors describe the necessity of ML algorithms and research trends in more detail in the introduction section, it can help readers understand.

   **Response:** We have included another recently published study both in the introduction and discussion. This study was published in May-2022 by Doudesis D et al. in "The Lancet – Digital Health". It highlights the increasing momentum of using machine learning model for stratification of chest pain in specific and other medical problems in general.

2. page 16: In my opinion, "Limitations" should be combined into the last paragraph of the discussion section rather than splitting the sections apart.

   **Response:** Limitations have been combined in to discussion now.

**Reviewer 2:**

1. The abstract is very lengthy and should be shortened.

   **Response:** According to the World Journal of Cardiology guidelines for authors (https://www.wjgnet.com/bpg/GerInfo/210), the total word count of the abstract should not be less than 350 words. In addition, background should be no more than 100 words, aim should be no more than 20 words, methods should be no less than 80 words, results should be no less than 120 words and discussion should be no more than 30 words. These journal guidelines provide liberty to the authors to be a little bit more elaborate in their methods and results section in their abstracts, if need be. In summary, we (the authors) didn't violate the journal guidelines for the abstract. However, to respect the recommendation provided, the word count of the abstract has been reduced to 394 from 439.

2. The description of introduction part is not clear. Content related with generic background should be reduced.

   **Response:** This comment is very broad and none specific (no paragraph/sentence highlighted or any specific example provided by the reviewer). We (the authors) will provide the breakdown of each paragraph below, in an attempt to address any concerns.

- 1st Paragraph: Healthcare costs are significantly high in the United States. 1st paragraph not only highlights this fact but also uses it as the basis for why we need better stratification tools (including for chest pain patients). The idea is to reduce healthcare costs without affecting the quality of healthcare through better stratification/triage. In summary, first paragraph is about "Why is this study needed?".
- 2nd Paragraph: The 2nd paragraph focuses on the current recommendations for patients who present with chest pain to the hospital, what stratification tools are currently at our disposal to follow these recommendations and what are the pros and cons of these stratification tools. In our opinion, it is important to include the generic content in this paragraph, so that the readers know about the present well. Else, how will the readers know that new idea is better than the present way of stratification and should be adopted? In summary, 2nd paragraph is about the "present" and readers should know it well before making any comparisons to it.
- 3rd Paragraph: This paragraph highlights new trends/ideas and gives insight about the feasibility of using machine learning models in healthcare. Point being that machine learning models have been used to address some medical problems. Then why not use it for chest pain stratification as well. 3rd paragraph also provides reference to some studies which have already attempted to create machine learning models for chest pain stratification but have important limitations. In summary, 3rd paragraph is about "new techniques / stratification methods", which can be better than the "present stratification tools"
- 4th Paragraph: This paragraph highlights some of the important limitations/challenges of the currently used stratification tools as well as new trends. Given these challenges, 4th

paragraph provides the ideas for potential solutions and lay the foundation for the methodology of our study.

- 5th Paragraph: After highlighting why is this study needed (1st paragraph), what is currently being done (2nd paragraph), what is new on the horizon (3rd paragraph), what are the limitations of the present and new trends (first half of the 4th paragraph), second half of the 4th paragraph and the 5th paragraph then summarizes what we planned to address these limitations via the new idea (of using machine learning models for chest pain stratification) and what were our specific goals/aims.

3. The originality of the study should be emphasized.
4. The novelty/originality shall be further justified that the manuscript contains sufficient contributions to the new body of knowledge. The knowledge gap needs to be clearly addressed in the Introduction.

   **Response to comment 3 & 4:** The **originality of the study** is well documented in the discussion section. This is the **first study, to our knowledge, that has used machine learning model for the risk stratification of abnormal cardiac stress test.** The justification for using cardiac stress test has been well documented too, both in introduction as well as discussion. In addition, this study focused primarily on patients with normal troponins. While majority of the studies have included both normal and abnormal troponins.

   **"Low positive predictive value"** of the currently used stratification tools for the stratification of chest pain patients is **"the knowledge gap"**. We aimed to cover this knowledge gap by improving the positive predictive value in a newly developed stratification tool using a machine learning model, while simultaneously aimed to maintain the recommended negative predictive value of 99%. It has been mentioned extensively both in the introduction and discussion. We were not able to achieve the recommended negative predictive value but we certainly improved the positive predictive value.

5. Literature survey is not sufficient to present the most updated for further justification of the originality of the manuscript. You should carry out a thorough literature survey of papers published in a range of top medical journals to fully appreciate the latest findings and key challenges relating to the topic addressed in your manuscript and to allow you to present your contribution more clearly to the pool of existing knowledge

   **Response:** Doudesis D et al. have recently published a study in "The Lancet – Digital Health" for risk stratification of patients who present with chest pain, using gradient boosting as their machine learning model. This study was published in May-2022. We have included this study in our introduction and discussion now. The link for this study is given below.

   (https://www.thelancet.com/journals/landig/article/PIIS2589-7500(22)00025-5/fulltext)

   We are not aware of any additional publications in 2021 or 2022, related to use of machine learning for stratification of patients with chest pain, in reputable journals such as Lancet, New England Journal of Medicine, JAMA, Annuals of Internal Medicine, The American Journal of Cardiology, etc. The concept of using machine learning model for stratification of patient who present with chest pain is relatively new and is currently gaining momentum.

6. A comparative analysis is missing from the manuscript. The authors should compare their proposed ML model performance with the related literature contributions. It is very hard to prove that the presented method has obtain an improvement with no comparison with existing's models in the literature.

   **Response:** 2nd and 3rd paragraph in the discussion section provides a direct comparison of our model with the currently used stratification tools. 5th paragraph in the discussion section provides a direct comparison of our model with another published study that used machine learning algorithms and have similarity to our study.

7. Lastly, Binomial regression (BR), random forest, and XGboost have been widely used in X, Y and Z field. It is not clear in this case, why a new method is even needed for risk identification of patients with chest pain.

   **Response:** It been highlighted both in the introduction as well as discussion that we want to develop a prediction model that risk stratify only patients with normal troponins and then risk stratify based on the probability of abnormal cardiac stress test. To our knowledge, this is the first study ever to undertake this challenge. The reasons behind using cardiac stress test and only normal troponins have been discussed in the manuscript.

**Revision reviewer:**

The authors have addressed all my concerns. This paper can be accepted it.

**Response:** Thanks for your comments.