December 12th, 2016

RESPONSE LETTER
World Journal of Cardiology

Manuscript Title: Accuracy of Gestalt Perception of Acute Chest Pain in Predicting Obstructive Coronary Artery Disease
Manuscript No.: (No. 30149)

Dear Dr. Fang-Fang Ji,

We are pleased to know that our manuscript was rated as potentially acceptable for publication in **the World Journal of Cardiology,** subject to adequate revision and response to the comments raised by the reviewers. It is with great satisfaction that we submit the revised version of the manuscript. The reviewers' comments were of great importance to improve the manuscript and we hope to have contemplated the suggestions. Please find below the response to each of these considerations. Additionally, according to instructions, all modifications have been highlighted in the revised version of the manuscript.

We would like to take this opportunity to express our sincere thanks to the reviewers who identified areas of our manuscript that needed corrections or modification. We would also like to thank you for allowing us to resubmit a revised copy of the manuscript.

We hope that the revised manuscript is considered worth of publishing in this prestigious Journal.

Sincerely,

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RESPONSE TO REVIEWER COMMENTS

Comments

- Reviewer 00506252

   The present study essentially supports that the elements of the chest pain history are only a little bit associated with increasing accuracy of diagnosis with CAD. Furthermore, It is very interested that there were poor agreement between the two cardiologists. The methods are sound, and the used statistics seem also sound. Minor Comments 1. Table A1: Pericardites----->Pericarditis

   Answer: We would like to thank reviewer **00506252** for the comments. The word "Pericarditis" has been edited in Table A1.

- Reviewer 00060494

   1. There are too many typing errors in this article. For example, Abstract, background: featuresin Abstract, method: cardiologistwho was blinded (blind) Abstract, results: wasassociated Introduction: acute chest pain lacks validation.[45] Introduction: 14 symptoms'characteristics obtained by remote Methods: Data collection was planned a priori Methods: Outcome data was collected by 3 other independent investigators (MC, FK, FF) and adjudicated by a forth investigator (LC). ----etc

   Answer: We would like to thank reviewer **005060494** for the comments.
   1. All identified typing errors have been corrected.

   2. In your method, "In case of a positive non-invasive test, patients had angiography for confirmation. A negative non-invasive test indicated absence of obstructive CAD and no further test was required." It may exist bias in the patients with negative non-invasive test which have the probability of false negative results.

   2. We believe it would be aggressive and ethically questionable to perform angiography in every patient after a negative non-invasive test. This is a limitation we recognize in our study; however it is lessened by the fact that all the cases of CAD were confirmed by angiography. Therefore, bias would be present only if a CAD case was considered as non-CAD, but not the contrary. Additionally, we do not believe that there were many patients in this situation, since those who had high pre-test probability underwent CAD. Thus, we also had many patients in which angiography also confirmed absence of disease.

   3. In your method, "Obstructive CAD was defined by a stenosis ≥70% on angiography." This is different from general CAD definition as the stenosis defined as ≥50%. And, this difference may be impact on your study results.

   3. We used a stenosis ≥70% on angiography due the fact that by doing so it is more probable that the symptom comes from CAD. In this case, using 50% would increase the subjectivity and doubt. By using the threshold of 70%, we

are including a population that has CAD of greater clinical relevance, and this therefore adds reliability to our conclusions.

- Reviewer 00186496

  I have no further comments on it.

  Answer: We would like to thank reviewer 00186496 for the comments.

- Reviewer 02446698

  In this investigation Authors deal with the problem of diagnostic value of the intuitive procedure of assembling clinical information called "gestalt", that represents a global vision of clinical features. In the study the accuracy of the gestalt concept in the clinical judgement of acute chest pain is compared with the presence or absence of obstructive coronary artery disease (CAD) demonstrated by objective instrumental techniques. I have some comments and observations: 1) the group of doctors formulating the judgements had no access to very important characteristics of the clinical and social context (eg family and personal history, lifestyle and other risk factors, etc) that are usually available to the clinicians performing a diagnosis. This condition may explain in part the unsatisfactory results of the gestalt approach: in fact gestalt was not complete. Thus I am not surprised that the characteristics of chest pain taken alone had a low predictivity for coronary obstruction.

  Answer: We would like to thank reviewer 02446698 for the comments and insightful suggestions.

  1. We agree with the reviewer's point that chest pain characteristics alone would be most likely to show a low predictive diagnostic value. However, despite this impression, it is still highly common to notice an overvaluing of these subjective data during daily clinical practice. The objective of our study was therefore to question this paradigm and to evaluate exclusively the chest pain characteristics. We have divided the components of gestalt. The study does not conclude that *general* clinical judgment is inaccurate, but one of its components (that was evaluated separately). Thus, when using his/her general gestalt, the physician should rely less on pain characteristics. We have modified our introduction in order to clarify better these aspects, by adding the following sentence: "*Since gestalt accuracy depends on chest pain characteristics, and knowing that these findings have a broad and variable spectrum, we focused our analysis exclusively on clarifying the reliability of this component*" (paragraph 2, line 2) This information is reinforced in the discussion (paragraph 2, line 2: "*Thus, our methods were designed to evaluate accuracy of clinical judgment that comes specifically from chest pain characteristics, as opposed to the entire clinical presentation.*") and (paragraph 7, line 2: "*Firstly, our findings do not undermine the value of the history as a whole, because our analysis only refers to chest pain characteristics*").

  2) A valuable observation seems to be that atypical chest pain has about the same diagnostic probability for coronary obstruction as typical chest pain.

This concept may have important practical consequences that should be discussed.

Answer: 2. We agree that the similarity found between typical and atypical pain in their diagnostic probability of CAD should be further discussed. This finding reinforces the demand of physicians to develop a more probabilistic method of thinking when approaching the patient with acute chest pain, relying less on the typicality of pain characteristics and gathering other clinical information that might have a better diagnostic reliability. We have added a further comment on the practical implications of these findings, since the fact that typicality of pain did not show significant differences on predicting CAD probability may influence initial decision-making during the clinical management of patients (paragraph 7, line 8: *"The fact that typicality of pain did not show significant differences on predicting CAD probability has important practical implications, since decision-making during the clinical management of patients can be initially guided by these subjective classifications. The overvaluing of the current categorization may be misleading, resulting in under or overdiagnosis of CAD and mismanagement of cases").*

3) Quotations 7 and 8, related to the comparison of established risk scores with gestalt diagnosis is misleading: first the Heart Score did not show better predictability for major cardiac events than gestalt, as did in contrary the GRACE score for mortality; and second both scores were not only clinical but included laboratory or instrumental data.

Answer: 3. Authors have reviewed quotations 7 and 8. We agree with the reviewer that indeed the HEART score showed similar diagnostic accuracy when compared to gestalt. In order to reduce potential confusing, these quotations have been removed from the manuscript.

4) Authors conclude that doctors should be cautious in evaluating the characteristic of chest pain, a point that must be accepted, and advise clinicians to redirect their focus to validated predictors. Could Authors indicate which are the validated predictors of major cardiac events, except for mortality?

Answer: 4. This is an important question, and it is the message that we intend to address: this model does not yet exist. Our data suggests that it should be developed and compared to the complete clinical judgment (*gestalt*). We suggest that this investigation should be taken further. Since the clinical judgment of pain features is inaccurate, we then need to know *what* is indeed accurate. This can be useful both to modify an existing score and or/ guide intuitive judgment. Consequently, it would become an educated intuitive judgment – an educated guess. The final conclusion sentence has been modified in order to make this point clearer, now stating that *"Physicians should be cautious when relying on chest pain characteristics and investigators should redirect their focus to **identify** validated predictors"* (conclusion paragraph, line 3).