Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-24-823

Reviewer A

The study as presented presents inconsistencies and weaknesses that must be considered:

Introduction:

The study addresses the controversy in clinical practice regarding the value of ST-segment elevation in the aVR lead in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). The investigation focuses on the association between simultaneous ST segment elevation in leads aVR and III and angiographic findings and clinical outcomes.

Methodology:

The study is observational and included patients diagnosed with NSTE-ACS, specifically those with ST elevation in the aVR lead and absence of ST elevation in two other contiguous leads, between January 2018 and June. Demographic, clinical and angiographic data, as well as clinical outcomes, were collected using standardized forms.

Results:

The 157 patients included were divided into two groups based on the presence of ST elevation in lead III. Important notes include:

Similarities between groups in terms of average age and medical history.

Patients with ST elevation in lead III showed greater myocardial hypertrophy, higher levels of cardiac troponin T (cTnT) and creatinine kinase MB (CK-MB).

Patients without ST elevation in lead III had higher NT-proBNP levels.

Patients with ST elevation in lead III showed ST depression in multiple leads (especially I, aVL, V3-V6), a greater degree of ST depression, and a higher incidence of multivessel and left main lesions.

An increased risk of major adverse cardiovascular events (MACEs) was observed at 3 years in patients with ST elevation in lead III, although without a statistically significant difference between the groups.

Discussion and Critical Analysis:

Variability of Electrocardiographic Anomalies:

The electrocardiographic abnormalities observed, such as ST elevation in aVR and III, may have multiple origins. They may reflect severe myocardial ischemia but may also be influenced by other conditions such as ventricular hypertrophy, electrolyte disturbances or even technical variations in ECG recording.

Interpretation of these anomalies must be cautious, especially during an acute event such as myocardial infarction, where spurious changes may occur.

Reply: Thank you for your suggestion. We indeed take other conditions that may influence ECG into consideration when designing the study. Therefore, we excluded patients with tachycardia and serious medical conditions, such as pulmonary emboli, subarachnoid hemorrhage, aortic dissection, sepsis, hypoperfusion, shock, hypoxemia, and so on. Additionally, as you mentioned, in this study we identified more patients with myocardial hypertrophy in the group with ST-elevation in lead III. Patients with myocardial hypertrophy tended to have heart transposition (often clockwise transposition), contributing to ST-elevation in lead III. The myocardial hypertrophy in these patients resulted from long-term hypertension or other causes instead of hypertrophic cardiomyopathy, which could partially explain more severe coronary lesions in these cases (See page 8, Line 28-33).

Changes in the text: No changes in the text.

Relevance of MACEs:

Analysis of major adverse cardiovascular events (MACEs) showed an increased risk in patients with ST elevation in III, but the lack of statistical significance between groups suggests that these events may not be directly related to the initial ST elevation event. The absence of a significant difference between groups highlights the complexity of correlating specific electrocardiographic changes with long-term clinical outcomes, underlining the need for a multifaceted approach to risk stratification and patient management.

Reply: Thank you for your suggestion. We agreed with your opinion that lack of statistical significance indicated the need for a multifaceted approach to risk stratification and patient management (We have added in Page 9, Line 10-13). Besides, we considered lack of significance partially due to small sample size and short-term follow-up of this study. We are planning to design a larger sample investigation and longer-term follow-up in the future.

Changes in the text: We have added some sentences in Page 9, Line 18-21.

Importance of Angiographic Assessment:

The higher incidence of multivessel and left main trunk injuries in patients with ST III elevation points to the importance of detailed angiographic evaluation in these cases. The correlation between electrocardiographic changes and angiographic findings

reinforces the need for a comprehensive investigation to identify the extent of coronary disease and plan appropriate interventions.

Reply: Thank you for your suggestion. We have briefly described the angiographic and interventional characteristics in Table 3. All the interventions were operated by experienced operators according to guidelines. We agreed with your opinion that detailed angiographic evaluation is important, but in this study, we wanted to focus more on the predictive value of ECG before performing angiography, so we displayed detailed characteristics of ECG changes rather than angiography in the text.

Changes in the text: No changes in the text.

Conclusion:

The study suggests that simultaneous elevation of the ST segment in leads aVR and III may indicate more extensive and severe myocardial ischemia, with a potential impact on the prognosis of patients with NSTE-ACS. However, the variability and possible spurious origins of electrocardiographic abnormalities highlight the need for caution in interpreting these findings. Furthermore, analysis of MACEs demonstrates that long-term outcomes are not necessarily related to the initial electrocardiographic event, underlining the complexity of managing these patients and the importance of a comprehensive diagnostic and therapeutic approach.

Reply: Thank you for your suggestion. As we have responded to previous comments, we have modified our expressions in the Discussion.

Changes in the text: We have added some sentences in Page 9, Line 18-21.

Reviewer B

This is an interesting clinical study evaluating the basics of ACS diagnosis by the e.c.g, one of the first means available to the clinician, and inferring prognosis.

Several notes:

1. The authors states that "The value of ST elevation in lead augmented vector right (aVR) remains controversial in clinical practice" and later on describe how it is often neglected in clinical practice. While this may have been true in the past [Gorgels AP, Engelen DJ, Wellens HJ. Lead aVR, a mostly ignored but very valuable lead in clinical electrocardiography. J Am Coll Cardiol. 2001] current societal guidelines mention lead aVR as a high risk feature, including very recent guidelines published by the ESC on ACS in 2023. I would advise rephrasing this statement.

Reply: Thank you for your suggestion. We added “in the past” in this sentence. In Page 4, Line 7-16, we have also stated the critical importance of ST elevation in aVR in

previous publications and guidelines.
Changes in the text: We have modified our text as advised in Page 4, Line 7.

2. Methods-Although discussed later as possible mimickers of STE in aVR, exclusion of patients with "serious medical conditions" including tachycardia, hypo-perfusion, shock and hypoxemia may have severely biased the study population. Patients with NSTEMI and multi-vessel disease may present with a compensatory sinus tachycardia, shock, hypoxemia and thus may represent the "sicker patients" population which have been excluded from this paper. While there only 9 such patients (Figure 2), this is a small cohort.
Reply: Thank you for your suggestion. In the exclusion criteria, we referred to patients with sinus tachycardia, shock, hypoxemia not resulting from NSTEMI and multi-vessel disease. We have modified our expression here.
Changes in the text: We have modified our text as advised in Page 5, Line 9.

3. Clinical characteristics- As inferred from the text, the definition of NSTE-ACS was made without the use of high sensitivity troponin, which may have caused a bias towards missing patients with only mild elevation of Hs-TnT, whom would still be considered NSTE-ACS by current definitions.
Reply: Thank you for your suggestion. We used hs-TnT in clinical practice and in this study. We have modified our expression in the text.
Changes in the text: We have modified our text as advised in Page 6, Line 22 and Table 1.

4. Results- Is there data available of the previous PCI in the group of patients without STE in lead III which might help understand the statistically significant difference from the patients with STE in lead III? perhaps on an anatomical ground. This might be attached in the supplementary.
Reply: Thank you for your suggestion. Some patients underwent PCI in other hospitals, so it may be difficult to obtain the data in previous PCI. We will pay attention to this suggestion and try to improve our data in future studies.
Changes in the text: No changes in the text.

5. Table 1- three patients had moderate to severe AS. was NSTEACS their final diagnosis or angina as part of their valvular disease? As mentioned previously, while there are only 3 such patients, this is a small cohort which can easily be affected by such changes.

Reply: Thank you for your question. All the patients enrolled in this study underwent coronary angiography and the diagnosis was confirmed.
Changes in the text: No changes in the text.

6. Table 1 and methods- were patients defined as heart failure patients only with EF<50%? Were there any patients with Hfpef?

Reply: Thank you for your question. In this study, the patients were defined with heart failure as EF<50%. We checked the data and found no patient were diagnosed with HFpEF.
Changes in the text: No changes in the text.

7. Definitions- it would be advised to clarify the time frame used for emergent and elective PCI (Table 3) as there is variability in the literature and the current esc guidelines offer the terminology of emergent (as soon as possible) and early invasive (<24 hours).

Reply: Thank you for your suggestion. NSTEACS patients with extremely-high-risk and high-risk features would undergo emergent PCI (i.e., <24h) according to current guidelines. We have made some corrections in the text.
Changes in the text: We have modified our text as advised in Page 7, Line 26-27.

8. Additional information- if possible, it would help further clarify the interventions made in the PCI group: were multi-vessel disease patients subjected to multiple (staged?) PCI? How many were referred for surgery (which may have impacted survival trends).

Reply: Thank you for your suggestion. Multi-vessel PCI referred to those undergoing PCI in >=2 main coronary arteries (including complete revascularization in emergent PCI or staged PCI). 5 patients (3.6%) without ST-elevation in lead III and 1 patient (5.0%) with ST-elevation in lead III underwent coronary bypass graft surgery due to severe multi-vessel lesions (See Page 7, Line 22-24).
Changes in the text: No changes in the text.

Reviewer C

1. First, the title needs to indicate the comparisons between ST and non-ST elevation groups in terms of angiographic findings and clinical outcomes, as well as the clinical research design of this study, i.e., a comparative study.

Reply: Thank you for your suggestion. We agreed with your opinion, but we thought

that it might be too long as a title if we included all the information. Therefore, after several discussion, we finally decided not to change our title.
Changes in the text: No changes in the text.

2. Second, the abstract needs some revisions. The background needs to briefly specify the controversy and what the clinical significance of this study was in the background. The methods need to describe the inclusion criteria, assessment of baseline clinical characteristics, and measurements of angiographic findings and clinical outcomes. The results need to present the baseline comparability between the two groups and provide detailed figures and accurate P values to support the main findings. The conclusion needs comments for the clinical implications of the findings, not to repeat the main findings again.
Reply: Thank you for your suggestions. We have made some corrections in the abstract.
Changes in the text: We have modified our text as advised in Page 2, Line 13-30.

3. Third, in the introduction, I suggest the authors to specify the controversy, analyze the potential reasons of the controversy, and explain why the current comparative analysis would help address the controversy. Please also directly indicate the clinical significance of this study.
Reply: Thank you for your suggestions. We considered controversy due to heterogeneity of the study population and different management of these high-risk patients in different centers. Besides, the controversy may highlight the complexity of correlating ECG changes with long-term clinical outcomes. Simultaneous ST elevation in lead aVR and III in this study could add evidence to help assess the NSTEACS patients before angiography, compared to ST elevation in single lead aVR.
Changes in the text: We have modified our text as advised in Page 4, Line 22-34.

4. Fourth, in the methodology of the main text, a single-center, retrospective, observational study is not adequate to describe the clinical research of this study. Please further specify whether this was a cohort, cross-sectional, or comparative study. The authors need to describe the sample size estimation procedures, follow up procedures, and details of the assessment of angiographic findings and clinical outcomes. In statistics, please describe the procedures for assessing the baseline comparability between the two groups, and details of the statistical adjustment analysis. Please also specify the P value for statistical significance.
Reply: Thank you for your suggestions. This is a retrospective cohort study. We have made some corrections according to your suggestions.

Changes in the text: We have modified our text as advised in Page 5, Line 4 to Page 6, Line 4.

5. Finally, please consider to cite several related papers: 1. Farah A, Jeger RV. Drug coated balloons and bare metal stents in ST-elevation myocardial infarction: eternal life or return of the living dead? Cardiovasc Diagn Ther 2023;13(5):773-776. doi: 10.21037/cdt-2023-4. 2. Zhang D, Xing YL, Wang H, Wang S, Miao Y, Huang W, Zhang K, Li HW, Sun Y, Chen H. Invasive treatment strategy in patients aged 80 years or older with non-ST-elevation acute coronary syndromes: a retrospective cohort study. Cardiovasc Diagn Ther 2022;12(2):229-240. doi: 10.21037/cdt-21-650. 3.Wen J, Qiao J, Tang Y, Zhao Y, Yang Z, Wang L, Tao X, Zhou X, Xia L, Tang D, Huang L. Cardiac magnetic resonance imaging detection of intramyocardial hemorrhage in patients with ST-elevated myocardial infarction: comparison between susceptibility-weighted imaging and T1/T2 mapping techniques. Quant Imaging Med Surg 2024;14(1):476-488. doi: 10.21037/qims-23-591.

Reply: Thank you for your suggestions. These papers were well written, but we considered not closely related with this manuscript. We mainly focused on early assessment and risk-stratification of NSTEACS patients.

Changes in the text: No changes in the text.